CASE AUTH/3503/4/21

COMPLAINANT v LEO

Due to the length of this case and the number of matters considered, a short summary has been provided and readers are encouraged to view the numbered Points in the full report for details.

This case was in relation to a promotional website for Kyntheum (brodalumab), used in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The case involved 102 Points (and an additional overall Point) which covered numerous matters across the website, mostly in relation to misleading, unsubstantiated and/or exaggerated claims. Some Points included rulings of multiple clauses. This case was considered under the 2019 Code.

The Panel ruled breaches of the Code at Points 8, 13, 14, 17, 20, 21, 24, 28, 35, 55, 64, 65, 66, 67, 68, 69, 72, 73, 75, 77, 79, 80, 81, 85, 86, 87, 92 and 101. The Panel ruled breaches of Clause 2 (a sign of particular censure) at Points 35, 64, 65 and 92, which included matters related to safety information.

Leo accepted many of the Panel's rulings of breaches of the Code including all the Panel's rulings of breaches of Clause 2. Leo appealed the Panel rulings at Points 13, 14, 55, 66, 67, 73, 79, 80, 85, 87 and 101. The complainant became non-contactable and was therefore unable to appeal any of the Panel's rulings of no breaches of the Code.

Leo's appeal was successful at Points 55 and 101 and was partially successful at Point 85. Leo's appeal at Points 13, 14, 66, 67, 73, 79, 80 and 87 was unsuccessful. The details of each Point, including the appeal, appear within the full report.

An anonymous complainant, who was contactable initially but then became uncontactable, complained about Kyntheum on the Leo website uk.dermaworld.eu. The complainant alleged that on this website, aimed at UK health professionals, there were numerous errors and Code issues.

Background

Leo stated that it was concerned to receive this complaint, which it believed to be part of a series of complaints from the same anonymous complainant.

Whilst Leo submitted that most of the allegations made by the complainant were unfounded, it accepted that the complainant had raised some points that should be addressed.

Leo responded with reference to the 2019 Code, as this was the Code in place at the time of the complaint.

DermaWorld website

Leo submitted that the website was produced by Leo UK/Ireland as an online resource for promotional material relating to the Leo dermatology portfolio. The content of the website was

targeted towards health professionals with an interest in dermatology, both in primary and secondary care. Health professionals who agreed to receive such communications from Leo were directed towards the website through promotional emails and in promotional calls.

Leo stated that it took its commitment to Code compliance very seriously and had a generally robust approval process for all relevant material and activities.

The complainant referred to specific points which are numbered 1 to 102 below.

Leo submitted, in response to a request for further information, that there was a number of discrepancies in relation to certification of the website at issue which it was investigating. It was difficult for the Authority to know exactly what content was live contemporaneous to the complaint. The Panel made its rulings in relation to the materials provided by Leo with the corresponding material reference numbers cited by the complainant. The only exception was at Points 10 and 13 (please see Leo's response at Point 13 in this regard).

1 'Treatments' section of the website (MAT-27513 V2 September 2020)

COMPLAINT

The complainant stated that in the 'Treatments' section of the website there was a pack shot of Kyntheum, two syringes, the brand name, active name and an indication 'A biologic treatment for moderate to severe plaque psoriasis in adults' with the summary of product characteristics (SPC) acting as a reference. The SPC indication stated 'A biological treatment for moderate to severe plaque psoriasis in adults patients who are candidates for systemic therapy'. The complainant alleged that shortening or reducing the indication in the claim did not reflect the SPC and was therefore inaccurate and misleading. The consequence of which impacted patient safety.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 3.2 and 9.1.

RESPONSE

Leo did not agree that this information was in breach of the Code. The text 'A biological treatment for moderate to severe plaque psoriasis in adults' was consistent with the indication in the Kyntheum SPC which also included the words 'who are candidates for systemic therapy'.

As described by the complainant, the statement appeared immediately under an image of a pack shot and syringes. The pack shot stated 'Kyntheum 210mg Solution for injection in pre-filled syringe'. The syringes were positioned close to the pack and had labels showing a flash of the same colour branding used on the pack; they were therefore clearly identifiable as Kyntheum. There were needles visible through the needle caps of these syringes. It would therefore be obvious to any health professional that Kyntheum was an injectable (ie systemic) treatment and would therefore only be used in patients who were suitable for systemic treatment.

Leo submitted that the statement reflected the licensed indication and was not inconsistent with the SPC; the text did not present any safety issue and the complainant had identified none.

Presenting this information did not demonstrate any failure to maintain high standards and Leo denied breaches of Clauses 2, 3.2 and 9.1.

PANEL RULING

The Panel noted that Section 4.1, therapeutic indications, of the Kyntheum (brodalumab) SPC stated that Kyntheum was indicated for the treatment of moderate to severe plaque psoriasis in adult patients who were candidates for systemic therapy.

The Panel noted that the SPC stated that Kyntheum was intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

The Panel noted Leo's submission that the statement at issue, 'A biologic treatment for moderate to severe plaque psoriasis in adults', appeared immediately beneath an image of a pack shot and syringes with labels showing a flash of the same colour branding as used on the pack and with needles visible through the needle caps, and that it would be obvious to any health professional that Kyntheum was an injectable and therefore would only be used in patients who were suitable for systemic treatment.

However, the Panel noted that Leo had provided a low resolution black and white PDF of the webpage in question. Nevertheless, the Panel considered that the image of the Kyntheum pack shot alongside syringes with needles, above the statement 'A biologic treatment for moderate to severe plaque psoriasis in adults', would indicate to a physician experienced in the diagnosis and treatment of psoriasis that it was only for patients who were candidates for systemic therapy. The Panel considered that the complainant had not established that this statement, in the context of the webpage, was inconsistent with the SPC and no breach of Clause 3.2 was ruled. Nor did the Panel consider that the complainant had established that the statement in the context of the webpage was inaccurate, misleading or impacted patient safety as alleged and the Panel therefore ruled no breach of Clauses 9.1 and 2.

2 Prescribing Information

COMPLAINT

The complainant stated that on the Kyntheum 'Home', 'Mode of Action', 'Speed of onset', 'Efficacy', 'QOL', 'Dosing', 'Safety', 'Patient Support' and 'Resources' tabs in the Kyntheum treatment section, there was a bar at the top of the page which stated 'Kyntheum Prescribing Information'. On the 'Kyntheum at a glance' tab, there was a bar at the top of the page which stated, 'Prescribing Information'. According to the Code, there needed to be a clear and prominent statement as to where to find the prescribing information, for example, 'Click here for the Kyntheum Prescribing Information'. The complainant alleged that this bar and statement did not meet the Code requirements. As the reader scrolled down through the mass of promotional material on this page, the bar at the top did not adjust to the screen view, was therefore not visible and was out of sight when reading promotional material.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.6.

RESPONSE

Leo did not agree that the link to Kyntheum prescribing information was in breach of the Code. On all the Kyntheum pages of the website there was a dark orange band immediately under the navigation section at the top of the page. This dark orange band provided a prominent visual contrast to the beige colour of the navigation section. On the left-hand side of this band was the text Kyntheum prescribing information, followed by a small arrow (→), all in white. The text was in capitals and was larger than the navigation headings. Hovering over this text changed the cursor in the conventional manner to indicate that it was an active link. Clicking on this text opened a page with the UK prescribing information on it. It was not possible to navigate to any Kyntheum page without seeing this dark orange band and the text linking to the prescribing information as it was at the top of the initial view of each page.

Clause 4.6 stated that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the prescribing information could be found. Leo submitted that the presentation, positioning and wording of the link on the Kyntheum pages was clear and prominent and it denied a breach of Clause 4.6 of the Code.

PANEL RULING

The Panel noted that on the webpages at issue, there was a dark orange band with the white text 'KYNTHEUM PRESCRIBING INFORMATION' followed by an arrow to its right. The Panel noted Leo's submission that: this band was on all of the Kyntheum webpages immediately beneath the navigation headings, its typeface was larger than the navigation headings, hovering over the text changed the cursor to indicate it was an active link and clicking on this text opened a page with the UK prescribing information on it.

The Panel considered, on the evidence before it, that the complainant had not established that the requirements of Clause 4.6 had not been met as alleged and it therefore ruled no breach of Clause 4.6 in relation to each of the webpages cited by the complainant.

Home Tab (August 2020 UK/IE MAT-30813 V2)

3 Picture of an apparently naked man

COMPLAINT

The complainant alleged that on the Kyntheum homepage, there was a picture of an apparently naked man sitting on an underground train seat between other passengers holding an A3 newspaper which covered his upper thigh to mid chest. This image was using nakedness in a social setting to attract attention and was distasteful and did not hold medicines or a health professional audience in special standing.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 9.1 and 9.2.

RESPONSE

Leo did not agree that the image was in breach of the Code. The description provided by the complainant was not an accurate representation of the image on the website. The man was visible only from the waist up, so it was not possible to conclude that he was naked, only that his chest was bare. The newspaper was standard broadsheet size, so considerably bigger than A3.

Leo submitted that the complainant appeared to have drawn on comments made by the PMCPA during consideration of Case AUTH/2982/10/17 (Member of the public vs LEO Pharma). During its consideration of that case the Panel noted that one of the items at issue included 'an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest'. The Panel considered that the subject's nakedness in a social setting was designed to draw attention to the material, queried whether this complied with the supplementary information to Clause 9.1 and requested that Leo Pharma's attention be drawn to this matter.

At the time of the previous complaint, Kyntheum was not licensed. The imagery was used in internal communication (and clearly marked 'For internal use only'). Leo gave considerable thought to the subsequent use of this imagery in promotion and considered that a cropped version of the image would eliminate the concern about nakedness whilst still expressing the message of the campaign – that skin clear of psoriasis improves confidence, potentially giving the confidence for a man to bare his chest in a social setting. In this context, Leo Pharma believed that the link between clear skin (both for psoriasis and other chronic inflammatory skin conditions) and confidence was well established and widely recognised.

Leo stated that the Panel had acknowledged in Case AUTH/2982/10/17 that it was acceptable to show bare skin when advertising prescription medicines so long as the image was relevant and complied with the Code (ie recognised the special nature of medicines and the professional audience, and was not for the purpose of attracting attention to the material), and that the quality and appearance of a patient's skin was relevant to the product. The PMCPA had previously decided that improving the confidence of psoriasis patients could be justification for an advertising campaign which showed an individual who was undressed in a social setting (Case AUTH/2304/3/10, Doctor v Forest Laboratories). Plaque psoriasis could occur anywhere on the body, so an image of a partially undressed individual was directly relevant to the disease and contributed to the overall message of clearance improving confidence.

Leo submitted that the image presented a man with the confidence to expose his skin in public following clearance of his psoriasis. The image was not sexual and the approach was justified in the context of the condition and treatment under consideration. Leo considered this recognised the special nature of medicines and the professional standing of the audience, was not likely to cause serious or widespread offence, and did not fail to maintain high standards. Leo denied breaches of Clauses 9.1 and 9.2.

PANEL RULING

Clause 9.1 of the Code stated that high standards must be maintained at all times. Clause 9.2 stated that all material and activities must recognise the special nature of medicines and the professional standing of the audience to which they are directed and must not be likely to cause offence. The supplementary information to Clauses 9.1 and 9.2 (suitability and taste), stated, *inter alia*, that the display of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose was an unacceptable style of promotion.

The Panel noted that the man in the image was bare chested, sitting on an underground train, in between two fully clothed individuals; the female to his right was wearing earphones and was looking straight ahead, whilst the male to his left appeared to be showing him something on a

mobile phone to which they both appeared to be smiling at. It was impossible to conclude that the bare chested man was naked as the image was cropped from the waist up. Furthermore, he was reading a newspaper, which covered his chest from the armpit down. The claim 'Kyntheum confidence starts with clearance' appeared twice: to the right of the image and below it.

In the Panel's view, given the indication of the medicine, it was not necessarily unacceptable to show bare skin in advertising material so long as the image was relevant, complied with the Code, recognised the special nature of medicines and the professional audience, was not for the purpose of attracting attention to the material, and that the quality and appearance of the patient's skin was relevant to the product.

In the Panel's view, whilst it would be unusual for a man to be bare chested on a train, and therefore the image might attract attention in that regard, the image did not portray one of a sexual nature and was relevant to the therapeutic area. The theme of the advertisement was improving the confidence of psoriasis patients. The Panel considered that the image was unlikely to offend the majority of the intended audience of health professionals, particularly given Kyntheum's indication and that plaque psoriasis could affect the chest.

Whilst noting the complainant's views, the Panel did not consider that the image failed to meet the requirements of Clauses 9.1 or 9.2 as alleged, and no breach of Clauses 9.1 and 9.2 were ruled.

4 Claims 'Confidence Starts With Clearance' and 'Kyntheum confidence starts with clearance'

COMPLAINT

The complainant stated that beside the image of the naked man (see Point 3), there was a claim 'Confidence Starts With Clearance' and under this image was a claim 'Kyntheum confidence starts with clearance'. Both of these claims were unreferenced.

The complainant alleged that these statements were incomplete so it was impossible to know if they could be verified or not; he/she had been unable to locate any studies in which Kyntheum provided 100% clearance as the word 'clearance' would imply, with a change in confidence to emerge in this study population as a result.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that the claim was in breach of the Code. The Code required that when promotional material referred to published studies, clear references must be given (Clause 7.6). This claim did not refer to published studies so no reference was required.

Leo submitted that the claim '[Kyntheum] confidence starts with clearance' related to the effect of skin clearance on quality of life. Quality of life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provides a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the

questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence. A paper by Warren *et al* (2021) analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI (Psoriasis Area Severity Index) response level and DLQI 0/1 achievement (P<0.0001).

Leo stated that the meaning of 'clearance' in the context of psoriasis was not widely understood to mean 100% clearance. The dermatology healthcare community and clinical research studies specifically referred to Complete Skin Clearance (CSC) if all lesions were resolved. It was accepted that below CSC, there were varying degrees of clearance, defined as 'partial clearance' – this might be a reduction in lesions overall, or on a particular part of the body. In any event and for completeness, there were data to support complete clearance of psoriasis following treatment with Kyntheum. This was presented in the graph of PASI responses at 12 weeks vs ustekinumab (Lebwohl M *et al* 2015) in the AMAGINE 2 and AMAGINE 3 analysis which showed that 37-44% of patients on Kyntheum achieved PASI 100.

Leo submitted that the claim was therefore substantiable, not misleading and references were not required and it denied a breach of Clauses 7.2, 7.4 and 7.6.

PANEL RULING

Clause 7.6 stated that when promotional material referred to published studies, clear references must be given. In the Panel's view, the claims in question did not refer to a published study and the Panel therefore ruled no breach of Clause 7.6.

Nonetheless, Clause 7.4 required that any claim must be capable of substantiation.

Clause 7.2 stated, *inter alia*, that claims must be accurate, balanced, fair, objective and unambiguous and must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

The Panel noted Leo's submission that the meaning of 'clearance' in the context of psoriasis was not widely understood to mean 100% clearance; the dermatology healthcare community and clinical research studies specifically referred to Complete Skin Clearance (CSC) if all lesions were resolved and it was accepted that below CSC, there were varying degrees of clearance, defined as 'partial clearance' – this might be a reduction in lesions overall, or on a particular part of the body. In this regard, the Panel noted that the image of the man described at Point 3 appeared to illustrate complete skin clearance on the face, chest and arms.

The Panel noted that Lebwohl *et al* (2015) investigated brodalumab vs ustekinumab in two Phase III, randomized, double-blind, placebo controlled and active comparator-controlled, parallel-group studies (AMAGINE-2; n =1831 and AMAGINE-3; n=1881). The primary aims were to evaluate the superiority of brodalumab over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75) and a static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin), as well as the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100).

Lebowohl *et al* stated that at week 12, the PASI 75 response rates were significantly higher with brodalumab (210mg every 2 weeks) than with placebo (86% vs. 8% [AMAGINE-2] and 85% vs. 6% [AMAGINE-3]; both P<0.001). The rates of sPGA scores of 0 or 1 at week 12 were also significantly higher with brodalumab 210mg than placebo (79% vs 4% [AMAGINE-2] and 80% vs 4% [AMAGINE-3]; both P<0.001). The week 12 PASI 100 response rates were significantly higher with brodalumab 210mg than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001).

The Panel noted the complainant's very narrow allegation that he/she had been unable to locate any studies in which Kyntheum provided '100% clearance' as the word 'clearance' would imply, with a change in confidence to emerge. In this regard, the Panel noted that in the AMAGINE 2 and AMAGINE 3 Phase III studies, 37-44% of patients administered Kyntheum 210mg every 2 weeks achieved PASI 100 at week 12.

Furthermore, the SPC gave pooled PASI 100 results from AMAGINE-2 and AMAGINE 3 which showed that 41.6% and 51% of patients administered Kyntheum 210mg every 2 weeks achieved PASI 100 at weeks 12 and 52, respectively.

The Panel further noted Leo's submission that Warren *et al* (2021) analysed the results of the AMAGINE-2 and AMAGINE-3 studies and demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (with 0 being no impact on patient's life and 30 being an extremely large effect on patient's life; P<0.0001). The Panel noted Leo's further submission that although none of the questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence.

Based on the complainant's very narrow allegation that he/she had been unable to locate any studies in which Kyntheum provided 100% clearance with a change in confidence to emerge, the Panel considered that the complainant had not established that the claims 'confidence starts with clearance' and 'Kyntheum confidence starts with clearance', were misleading or incapable of substantiation as alleged and the Panel ruled no breach of Clauses 7.2 and 7.4 in that regard.

5 Claim of a simple induction and dosing schedule

COMPLAINT

On the homepage for Kyntheum, was a series of images and buttons called 'Learn more'.

One such image was a graphic of a syringe and the text under this read 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0,1 and 2 followed by 210mg every 2 weeks)'. The reference for this promotional claim was listed as Reference 1, the Kyntheum SPC. The complainant alleged that the SPC did not support this claim of a simple induction and dosing schedule ('simple' was a word which was not in the SPC); the reference was incorrect and therefore misleading.

The complainant alleged that this claim was contrary to the SPC which required 'after proper training in subcutaneous injection technique, patients may self inject Kyntheum when deemed appropriate by a physician'.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.4.

RESPONSE

Leo did not agree that the statement 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0,1 and 2 followed by 210mg every 2 weeks)' was in breach of the Code. The statement was an accurate representation of the dosing regimen in the SPC. The dose strength and frequency of Kyntheum were the same for all patients. There was no requirement to adjust the dose on the basis of weight or age. The regimen (weekly for 2 weeks, then fortnightly) was simple.

Leo submitted that the statement was specifically about the dosing schedule, not about the route of delivery. The need for injection training was not relevant; it did not mean that the dosing schedule was not simple. The statement was not inconsistent with the Kyntheum SPC, was not misleading and was capable of substantiation. Leo denied breaches of Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel noted that Section 4.2 of the Kyntheum SPC (Posology and method of administration) stated, *inter alia*:

> 'Method of administration
> Kyntheum is administered by subcutaneous injection. Each pre-filled syringe is for single use only. Kyntheum should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. The pre-filled syringe must not be shaken.
>
> After proper training in subcutaneous injection technique, patients may self-inject Kyntheum when deemed appropriate by a physician. Patients should be instructed to inject the full amount of Kyntheum according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.'

The Panel noted Leo's submission that the claim 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0, 1 and 2 followed by 210 mg every 2 weeks)' was specifically about the dosing schedule and not about the route of delivery.

The Panel noted that Section 4.2 of the SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.'

The Panel noted Leo's submission that the dose strength and frequency of Kyntheum was the same for all patients and that there was no requirement to adjust the dose on the basis of weight or age.

The Panel noted that the claim 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0,1 and 2 followed by 210mg every 2 weeks)' was all in the same size, style and colour typeface.

In the Panel's view, the claim at issue referred to the dosing of Kyntheum and not the method of administration. In that regard, the Panel considered that the complainant had not established that the claim 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0,1 and 2 followed by 210mg every 2 weeks)' was inconsistent with the SPC, misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of Clauses 3.2, 7.2 and 7.4.

6 Claim 'Clearance rates sustained through to 2 years in an observed data analysis of PASI 75, 90 and 100 (n=90 at 120 weeks, no p values calculated)'

COMPLAINT

A graphic of a calendar alongside the claim 'Clearance rates sustained through to 2 years in an observed data analysis of PASI 75, 90 and 100 (n=90 at 120 weeks), no p value calculated'. The complainant alleged that the SPC only recommended treatment beyond 16 weeks in some patients with initial partial response who might subsequently improve. The SPC for Kyntheum only reported data points to 52 weeks. The lack of information on when to continue treatment beyond 16 weeks and the promotion of clearance rates beyond 52 weeks was off label and the lack of statistical analysis of the data or inclusion of study design detail presented a misleading, incomplete and inaccurate picture of the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not agree that the presentation of data relating to clearance rates after 2 years of treatment was in breach of the Code.

Section 4.2 of the Kyntheum SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
> Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'

Leo stated that the complainant had misinterpreted this section of the SPC. There was no limit on the duration of use of Kyntheum. Discontinuation after 12-16 weeks was only recommended for those who had not responded to treatment. The guidance about continuation in patients with initial partial response was included to indicate that some of these patients might achieve better results with longer treatment. It did not mean that this was the only patient group that could continue treatment beyond 16 weeks.

Leo stated that Section 5.1 of the SPC described the use of Kyntheum as maintenance treatment up to 52 weeks as this was the analysis presented in the submission for marketing

authorisation. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for longer periods was not inconsistent with the SPC.

Leo submitted that the graph was an accurate representation of the data from a study by Puig *et al* (2020) which was designed to evaluate the efficacy and safety of brodalumab through 120 weeks of treatment in the AMAGINE-2 trial. The study showed that clearance rates were sustained across the long term extension. 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100. The web page clearly stated that statistical significance was not provided. There was no requirement to include details of the study design as long as the material was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and not misleading. The graph identified by the complainant was not misleading and details of trial design were not required for readers to form their own view of the data presented.

Leo submitted that the statement was not inconsistent with the SPC and was not misleading and it denied breaches of Clauses 3.2 and 7.2.

PANEL RULING

Section 4.2 of the Kyntheum SPC stated:

> 'Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'

The Panel noted Leo's submission that there was no limit on the duration of use of Kyntheum and that the SPC's reference to discontinuation after 12-16 weeks was only recommended for those who had shown no response to treatment. Leo submitted that the guidance about continuation in patients with initial partial response was included in the SPC to indicate that some of these patients might achieve better results with longer treatment; it did not mean that this was the only patient group that could continue treatment beyond 16 weeks.

The Panel noted that the Kyntheum SPC referred to three Phase 3 studies (AMAGINE-1, AMAGINE-2 and AMAGINE 3) and stated that all three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension. The Panel noted that the SPC only reported results up to week 52.

The Panel considered that companies might be able to make claims based on data with a longer time-period of observation than that cited in the SPC so long as the promotion was not inconsistent with the particulars listed in the SPC and it complied with the Code.

In the Panel's view, as the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, the complainant had not established that the promotion of clearance rates beyond 52 weeks was inconsistent with the SPC, as alleged, and the Panel ruled no breach of Clause 3.2.

The Panel noted Leo's submission that the claim 'Clearance rates sustained through to 2 years in an observed data analysis of PASI 75, 90 and 100 (n=90 at 120 weeks, no p values calculated)' was referenced to and substantiated by Puig *et al* (2020), which evaluated the efficacy and safety of brodalumab through 120 weeks in the AMAGINE-2 trial. The authors

stated that of patients who received brodalumab 210mg every 2 weeks, 84.4%, 75.6%, and 61.1% achieved 75%, 90%, and 100% improvement from baseline in PASI at 120 weeks, respectively. The Panel noted that Puig *et al* concluded that brodalumab showed sustained skin clearance through 120 weeks.

The Panel noted that the claim 'Clearance rates sustained through to 2 years in an observed data analysis of PASI 75, 90 and 100 (n=90 at 120 weeks), no p values calculated' was all in the same size, style and colour typeface. In the Panel's view, whilst it would have been helpful to have given more of the study detail, for example, that data included an open-label extension phase, the complainant had not established that the claim in the context of the webpage was misleading as alleged and no breach of Clause 7.2 was ruled.

7 Claim 'The efficacy of Kyntheum has been shown to be unaffected by previous biologic use'

COMPLAINT

A graphic of two arrows with the claim 'The efficacy of Kyntheum has been shown to be unaffected by previous biologic use' and a reference by Papp 2018 was cited. For a product with a black triangle, the complainant alleged that statements like this could not be made as there was not enough evidence to support this; 0.3% of patients at baseline had anti-brodalumab antibodies according to the SPC, indicating that immunogenicity might be an issue in all patients, including those who had received previous biologics. The complainant stated that Leo could not exclude this possible safety issue.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.4 and 9.1.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The statement described the findings of Papp *et al* (2018) who analysed the results of two large phase III studies in order to investigate the impact of previous biologic exposure on the efficacy and safety of brodalumab and ustekinumab. 1,236 patients were on brodalumab 210mg every two weeks; 902 were biologic naïve and 334 had previous exposure to biologics. Efficacy in the two groups was statistically equivalent: 40.9% and 39.5% of biologic-naive and -experienced patients achieved PASI 100 at week 12.

In addition, Section 5.1 of the SPC stated that examination of various patient subgroups across the three phase trials, including use of prior biologics and biologic failures, failed to identify differences in response in all key endpoints.

Leo submitted that the statement was an accurate representation of the AMAGINE study findings (Lebwohl *et al* (2015) and was in line with similar information in the SPC. It had no safety implications and was not at odds with either the black triangle status of Kyntheum, or with the SPC statement about incidence of anti-brodalumab antibodies at baseline. Presenting this information did not demonstrate any failure to maintain high standards. Leo denied breaches of Clauses 2, 7.4 and 9.1.

PANEL RULING

The Panel noted that Section 4.8 of the SPC current at the time of the complaint stated:

> *'Immunogenicity*
> Antibodies to brodalumab developed in 2.2% (88/3935) of patients treated with Kyntheum for up to 52 weeks in psoriasis clinical trials (0.3% of the patients had anti-brodalumab antibodies at baseline). Of these patients, none had neutralising antibodies.
>
> No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with anti-brodalumab antibody development.'

The Panel noted that Section 5.1 of the SPC stated, *inter alia*, that the efficacy and safety of Kyntheum was assessed in 4373 adult plaque psoriasis patients across three multinational, randomised, double-blind, phase 3, placebo-controlled clinical trials (AMAGINE-1, AMAGINE-2, and AMAGINE-3) and that in these studies, approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC further stated in Section 5.1:

> 'In all three clinical trials, examination of age, gender, race, use of prior systemic or photo therapy, use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.'

The Panel noted that Papp *et al* (2018) evaluated the impact of previous biologic use on the efficacy and safety of brodalumab in an integrated analysis of AMAGINE-2 and AMAGINE-3. The authors concluded that the efficacy of brodalumab 210mg every 2 weeks was similar regardless of prior biological therapy (P = 0.31, 0.32 and 0.64 for PASI 75, 90 and 100, respectively). The study authors also stated that the safety results for brodalumab were similar in patients who had previous exposure to biologics versus those who were biologic naive.

The Panel considered that the complainant had not established that the claim 'The efficacy of Kyntheum has been shown to be unaffected by previous biologic use' could not be substantiated or was a patient safety issue as alleged and no breach of Clauses 7.4, 9.1 and 2 were ruled.

8 Claim '25% of patients (n=1,236) reached PASI 75 at 2.1 weeks (vs 4.8 weeks for ustekinumab (n=613; p<0.001).'

COMPLAINT

A picture of a clock was presented with a statement '25% of patients (n=1,236) reached PASI 75 at 2.1 weeks (vs 4.8 weeks for ustekinumab (n=613; p<0.001)'. The complainant alleged that this claim represented cherry picking; the primary endpoint for these studies was at 12 weeks and the results were a pooled analysis of two separate studies. This was not clear to the reader of the statement and therefore the claim was misleading.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that this claim was in breach of the Code. The statement of 25% of patients reaching PASI 75 at 2.1 weeks was an accurate reflection of the findings of a published peer reviewed analysis (Blauvelt *et al* (2017)). The Blauvelt paper described a *post hoc* statistical analysis of pooled data from two large phase 3 studies of brodalumab versus ustekinumab, in which PASI assessments were conducted at weeks 1, 2, 4, 6, 8, 10 and 12. The allegation mentions 'cherry-picking' – however, the statistical analysis involved a well-established and reliable statistical technique – the Bootstrap Technique - which estimated quantities about a population by averaging estimates from multiple smaller data samples taken from within a larger data set. In this analysis the Bootstrap Technique was used to calculate the time point at which 25% of each treatment group achieved PASI 75. In essence, the Bootstrap Technique was specifically used to avoid cherry-picking data by providing a reliable estimate for a population. Leo submitted that a claim was not misleading simply because details of the analysis had not been provided. In this case the data presented were fair and accurate and the absence of further detail was not misleading. The analysis was consistent with the AMAGINE study outcomes (Lebwohl *et al* 2015) which showed significantly greater proportions achieving PASI 75 at all time points versus ustekinumab, and therefore could not be considered to be cherry picking. The statement was an accurate and balanced representation of the study findings using an appropriate analysis and Leo denied a breach of Clause 7.2.

PANEL RULING

The Panel noted Leo's submission that Blauvelt *et al* described a *post hoc* statistical analysis of pooled data from two large phase 3 studies of brodalumab versus ustekinumab, in which PASI assessments were conducted at weeks 1, 2, 4, 6, 8, 10 and 12 and that the statistical analysis involved the Bootstrap Technique which was used to calculate the time point at which 25% of each treatment group achieved PASI 75.

The Panel noted that the authors stated that estimated times for 25% of patients to achieve PASI 75 were 2.1 (95% confidence interval [CI], 2.0-2.3) weeks for brodalumab and 4.8 (95% CI, 4.5-5.1) weeks for ustekinumab. The figure in the article indicated a p-value of <0.001 versus ustekinumab.

The Panel noted that Section 5.1 of the SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%). The Panel noted that the claim at issue, based on a *post hoc* analysis, stated '25% of patients (n=1,236) reached PASI 75 at 2.1 weeks (vs 4.8 weeks for ustekinumab (n=613; p<0.001)'.

The Panel considered that the use of *post hoc* analyses in promotional material was not necessarily unacceptable, however, this should be made clear to the reader and care must be taken to ensure that such claims are not misleading. The Panel noted that the claim, which appeared before any other clinical trial claims on the webpage in question (the homepage), including before any of the primary endpoint results, did not refer to it being a *post hoc* analysis. The Panel considered, on the balance of probabilities, that readers would assume that the claim in question related to a prespecified endpoint which was not so. The Panel considered that the reader had not been given sufficient information to put the claim into context and form his/her own opinion of the therapeutic value of the medicine and thus a breach of Clause 7.2 was ruled.

9 Claim '41.6% of patients (n=339) achieved PASI 100 at 12 weeks (vs 20.7% for ustekinumab; n = 590, p<0.001)'

COMPLAINT

A graphic stating 'PASI 100' was listed with the statement '41.6% of patients (n=339) achieved PASI 100 at 12 weeks (vs 20.7% for ustekinumab; n = 590, p<0.001)'.
This claim was from a pooled analysis of trials, run post trial by the company and was not a primary endpoint of the study. The complainant alleged that this was not clear to the reader and therefore the claim was misleading.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that this claim was in breach of the Code. The statement was an accurate reflection of the findings of a pooled analysis of two identical clinical trials by Lebwohl *et al* (2015). This information was also presented in Section 5.1 of the SPC. There was no Code requirement to define the nature of the analysis on which statements were based, provided the information was not misleading without those details. The Lebwohl analysis looked at patients in the AMAGINE-2 and AMAGINE-3 phase 3 studies who were randomised to receive either brodalumab 210mg, brodalumab 140mg, ustekinumab or placebo. As demonstrated in Section 5.1 of the SPC (Figure 1), the 12 week results for the licensed 210mg dose of brodalumab vs ustekinumab were accurately reflected in the graphic.

Leo submitted that the findings were consistent with the individual study outcomes which showed 272 out of 612 patients (44%) in AMAGINE-2 and 229 out of 624 patients (37%) in AMAGINE-3 on brodalumab 210mg reaching PASI 100 at 12 weeks compared to 65 out of 300 (22%, AMAGINE-2) and 58 out of 313 (19%, AMAGINE-3) patients on ustekinumab.

The primary endpoints (PASI 75 at 12 weeks) for both studies were also met and were statistically significant. As such, the statement was an accurate representation of the study and was not misleading. Leo denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that Lebwohl *et al* (2015) investigated brodalumab vs ustekinumab in two Phase III, randomized, double-blind, placebo controlled and active comparator-controlled, parallel-group studies (AMAGINE-2; n =1831 and AMAGINE-3; n=1881). The primary aims were to evaluate the superiority of brodalumab over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75) and a static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin), as well as the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100).

Lebowohl *et al* stated that at week 12, the PASI 75 response rates were significantly higher with brodalumab (210mg every 2 weeks) than with placebo (86% vs. 8% [AMAGINE-2] and 85% vs. 6% [AMAGINE-3]; both P<0.001). The rates of sPGA scores of 0 or 1 at week 12 were also significantly higher with brodalumab 210mg than placebo (79% vs 4% [AMAGINE-2] and 80% vs 4% [AMAGINE-3]; both P<0.001). The week 12 PASI 100 response rates were significantly higher with brodalumab 210mg than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001).

The Panel noted that Section 5.1 of the SPC presented the pooled results from AMAGINE-2 and AMAGINE-3 in relation to PASI 100 in graphical form with results which showed that 41.6% of patients administered Kyntheum 210mg every 2 weeks (N=339) achieved PASI 100 at 12 weeks (vs 20.7% for ustekinumab; N = 590).

The Panel noted the complainant's very narrow allegation that this claim was from a pooled analysis of trials, run post hoc by the company and was not a primary endpoint of the study which was not made clear on the webpage. The Panel noted that the superiority of brodalumab over ustekinumab at week 12 with respect to PASI 100 was a primary endpoint in both AMAGINE-2 and AMAGINE 3, which the SPC stated were identical placebo- and ustekinumab-controlled trials, and where the SPC gave the pooled results from the two studies for PASI 100.

Whilst it would have been helpful to have included more details, including that the claim was based on a pooled analysis, the Panel considered, on balance, noting its comments above, that the complainant had not established that the claim in question was misleading, and no breach of Clause 7.2 was ruled in that regard.

10 Statement 'What does clearance look like?'

COMPLAINT

On the Kyntheum homepage was a question 'What does clearance look like?'. The complainant alleged that this product did not provide complete clearance as the statement would imply and was therefore false and misleading.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The statement was not a product claim, it was a question about how clinicians assessed clearance and what PASI 75, 90 and 100 responses actually looked like. As explained in Leo's response to Point 4 above, 'clearance' in the context of psoriasis and other inflammatory skin conditions did not necessarily mean complete clearance, which was specifically referred to as 'Complete Skin Clearance (CSC)' in the dermatology field. Instead, health professionals and dermatology studies referred to levels of clearance, most commonly assessed by measures such as the Psoriasis Area and Severity Index (PASI). Directly below the statement 'What does clearance look like?' were a set of images, representing PASI 75 (an improvement in the PASI score of 75% from baseline), PASI 90 (an improvement of 90%) and PASI 100 (an improvement of 100%). As such, these represent different levels of clearance in a visual way.

Leo submitted that given this context, the statement 'What does clearance look like?' clearly referred to the assessment of clearance and the different degrees of clearance, based on PASI 75, 90 and 100, and was not a claim about Kyntheum or any other product. In these circumstances the question 'What does clearance look like?' was not in breach of the Code. Leo denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that below the claim 'What does clearance look like?' were four sets of images from what appeared to be four different patients which the reader could scroll through.

Set 1 showed an image of a patient's forehead with plaque psoriasis at baseline and then after 4 weeks where it was stated that the patient had achieved PASI 100 followed by an image after 14 months with the claim 'sustained clearance'. Below these three pictures of the patient's forehead was the statement:

> 'Global clinical experience images of a patient treated with Kyntheum. Images provided by [named doctor], [place of work], [location] and originally published by [publisher]. Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience *may* vary from patient to patient.'

Set 2 showed an image of a patient's legs with plaque psoriasis at baseline and then after 4 weeks of treatment and it was stated that the patient had achieved PASI 75. The third set of pictures showed a pair of legs at baseline, after 4 weeks and at 12 weeks where it was stated that the patient had achieved PASI 90. The fourth set of images showed a torso at baseline, after 4 weeks and at 12 weeks where it was stated that the patient had achieved PASI 100. Beneath image sets 2 to 4 was the statement:

> 'These images are a representative patient response from the AMAGINE-2 study. Clinical imagery not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient.'

The Panel disagreed with Leo's submission that the statement 'What does clearance look like' was not a claim for Kyntheum. The statement was placed on a Kyntheum promotional website directly above images of patients before and after being treated with Kyntheum and as such it was clearly a claim for Kyntheum.

The Panel further noted Leo's submission that 'clearance' in the context of psoriasis and other inflammatory skin conditions did not necessarily mean complete clearance; health professionals and dermatology studies referred to levels of clearance, most commonly assessed by measures such as the Psoriasis Area and Severity Index (PASI).

The Panel considered that the four sets of images which could be seen below the claim 'What does clearance look like' were sufficiently clear as to what each meant by the term 'clearance' as each set was clearly labelled with PASI 75, PASI 90 or PASI 100 and therefore the Panel did not consider that the claim 'What does clearance look like' was misleading as alleged and no breach of Clause 7.2 was ruled.

11 Image of a patient at 4 weeks with the statement 'PASI 75'

COMPLAINT

One image was a patient at 4 weeks and stated 'PASI 75'. The trial outcome assessments were not completed at 4 weeks or reported in the SPC. The results in the SPC of PASI 75 at 12 weeks would suggest this experience of achieving PASI 75 at 4 weeks was not typical. The complainant alleged that this misrepresented the efficacy of the product and cherry picked isolated case studies.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo did not agree that this information was in breach of the Code. While the week 4 data were not reported in the SPC and were not reported in detail in the main body of the referenced paper (Lebwohl *et al* 2015), the supplementary appendix for Lebwohl *et al* demonstrated that the median time to response, based on Kaplan-Meier analysis was 4.1 weeks in both AMAGINE-2 and AMAGINE-3, both with a p-value of <0.001 vs both placebo and ustekinumab.

The image was therefore based on a published analysis of data from two clinical trials, rather than isolated case studies as alleged by the complainant. Such data were representative of the median response in the Phase III studies (Lebwohl M *et al* 2015) and therefore 'typical'. In these circumstances, Leo submitted that the image was accurate and not misleading as required by Clause 7.2 of the Code. The image did not exaggerate the properties of Kyntheum or imply that it had special properties which could not be substantiated, consistent with clause 7.10.

PANEL RULING

The Panel considered that the allegation in question appeared to be in relation to the second set of images as described at Point 10 above.

The Panel noted Leo's submission that while week 4 data were not reported in the SPC, nor detailed in the main body of the referenced paper (Lebwohl *et al* 2015), the supplementary appendix for Lebwohl *et al* demonstrated that the median time to response (PASI 75 response), based on Kaplan-Meier analysis was 4.1 weeks (for the brodalumab 210mg dose) in AMAGINE-2 and AMAGINE-3; both with a p-value <0.001 vs both placebo and ustekinumab.

The Panel noted Leo's submission that the images in question were representative of the median response in the Phase III studies and therefore 'typical'.

The Panel considered that the complainant had not established that the PASI 75 images in question misrepresented the efficacy of Kyntheum or exaggerated its properties and no breach of Clauses 7.2 and 7.10 were ruled.

12 Images of a patient's legs at baseline, after 4 weeks and PASI 90 at 12 weeks

COMPLAINT

Another set of images showed a patient's legs at baseline, after 4 weeks and PASI 90 at 12 weeks. The complainant alleged that there was no clinical assessment or measurement of the condition included for 4 weeks, and therefore the information was incomplete. Under the image was a statement 'These images are a representative patient response from the AMAGINE-2 study'. In the Kyntheum SPC, there was no reported efficacy outcome of PASI 90 at 12 weeks. AMAGINE-2 and AMAGINE-3 were reported in the SPC as 86% of patients achieving PASI 75 at week 12. This would suggest that these images were not a typical patient response from AMAGINE-2, as claimed by Leo. This misrepresented the efficacy of the product and cherry picked isolated case studies.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo stated that it disagreed that the identified images breach Clauses 3.2, 7.2 or 7.10 of the Code. The complainant had quoted only part of the statement under the set of images. The complete text stated 'These images *a*re a representative patient response from the AMAGINE-2 study. Clinical imagery not claimed to represent the typical patient response to Kyntheum. Individual response and experience *may* vary from patient to patient'. Consistent with this statement, the week 4 image was provided as a representative patient response, to illustrate how the skin improved over time, and not to specify a particular clinical assessment/measurement endpoint. This was clearly explained in the text.

With regards to the PASI 90 result at 12 weeks, although this was not documented in the main text of the referenced paper (Lebwohl M *et al 2015)*, the supplementary appendix provided PASI 90 responses up to 12 weeks. In the graphs, 70% of patients in AMAGINE-2 and 69% of patients in AMAGINE-3 on brodalumab 210mg achieved PASI 90 at 12 weeks. Leo therefore believed that the images provided a representative patient response from the AMAGINE-2 study, without exaggeration of benefits.

In summary therefore, Leo submitted that the images were intended, as stated explicitly in the text, to show the appearance of a representative patient response from the AMAGINE-2 study, rather than clinical assessments or measurement. The text also made clear that the images were not claimed to show a typical patient response, in circumstances where this could vary from patient to patient (emphasis in original). Leo denied that the images with the associated text breached Clauses 7.2 or 7.10 of the Code.

PANEL RULING

The Panel considered that the allegation in question appeared to be in relation to the third set of images as described at Point 10 above.

The Panel considered that health professionals experienced in the treatment of psoriasis would likely accept that individual response and experience may vary from patient to patient, however, it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties. Use of the disclaimer '…not claimed to represent the typical patient…' would not mitigate against any misleading impression that might be given regarding the response to a medicine.

The Panel noted Leo's submission that PASI 90 results at 12 weeks, although not documented in the main text of the referenced paper (Lebwohl M *et al* 2015), were provided in the supplementary appendix. The Panel noted that the results in the supplementary appendix were provided in graphical form and showed that 70% of patients in AMAGINE-2 and 69% of patients in AMAGINE-3 on brodalumab 210mg achieved PASI 90 at 12 weeks.

The Panel considered that the complainant had not established that the PASI 90 images in question misrepresented the efficacy of Kyntheum or exaggerated its properties and no breach of Clauses 7.2 and 7.10 were ruled.

13 Images of a female's forehead at baseline, and images of PASI 100 after 4 weeks and sustained clearance after 14 months

COMPLAINT

Another set of images showed a female's forehead at baseline, and images of PASI 100 after 4 weeks and sustained clearance after 14 months. The complainant alleged that, again, the use of these images was cherry picking; in a pooled analysis only 41.6% of patients achieved PASI 100 at 12 weeks - therefore this effect at 4 weeks was not typical. The SPC did not report any data beyond 52 weeks and the claim of sustained clearance after 14 months was off label and without context; did the patient continue on Kyntheum or how long was their therapy? etc. This misrepresented the efficacy of the product and cherry picked isolated case studies.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.10.

RESPONSE

Leo stated that it disagreed that the identified images breached Clauses 3.2, 7.2 or 7.10 of the Code.

The complainant alleged that a reference to sustained clearance after 14 months was off-label. However, the SPC for Kyntheum did not limit the duration of treatment. As stated in the response to 6 above, Section 5.1 of the SPC described use of Kyntheum in the AMAGINE-1, AMAGINE-2 and AMAGINE-3 clinical trials up to 52 weeks, as this was the analysis presented in the submission for marketing authorisation and also referenced the long term extension study. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for periods beyond 52 weeks was not inconsistent with the SPC. Leo stated that it did not therefore accept that there had been any breach of Clause 3.2.

Leo stated that the images were presented with text stating 'Global clinical experience images of a patient treated with Kyntheum. Images provided by [named doctor], [place of work], [location]and originally published by [publisher]. Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience *may* vary from patient to patient'. It was therefore clear to any reader that, while PASI 100 might be achieved at week 4, the images presented were not intended to represent a typical patient The images were therefore consistent with the requirements of Clauses 7.2 and 7.10,

Unfortunately, in this instance, there had been an error in the process of uploading this particular section of the website onto the internet. Despite a thorough briefing of the external agency by Leo Pharma, the reviewed and approved document on its approval system (PromoMats) did not include the forehead images or associated data and was signed off without them.

It had since come to light that the upload to PromoMats did not include the forehead images in error – the intention from the job originator had always been to include the images but they were omitted from the 'screen captures' when generating the PDF for approval, with the result that the review team and final signatory did not see the forehead images in the approval system.

Leo stated that it accepted that there had therefore been a breach of Clause 14.1 through the actions of a third party agency. Leo had thoroughly debriefed the agency as soon as it was made aware of this issue and had also implemented an additional 'live final form' review stage for all online material, in which a signatory would check all uploaded material on the day of upload to ensure it was identical to the signed off and approved material. This was in addition to the usual final form certification which took place on the 'pre-live' loading site just before material was uploaded to the web.

Leo therefore agreed that a breach of Clause 14.1 had occurred in this instance, as Leo had inadvertently used material that had not been certified.

Following a request for further information, Leo provided a copy of the webpage which it stated would have been seen by the complainant (March 2020 UK/IE/MAT-30813), including the images of the female's forehead. Leo stated that it was currently investigating the circumstances around the approval of the material in this case. The pre-live version of the website, which was viewed and approved by the signatory, did include the forehead images, although the PDF version of the website in Leo's approval system did not. Leo stated that it did not yet feel that it had sufficient clarity to make a voluntary admission or to confirm or deny a breach of Clause 14.1 and that it would make this decision once it had clarified the situation.

PANEL RULING

The Panel noted that the allegation in question appeared to be in relation to an image of a patient's forehead with plaque psoriasis at baseline and then after 4 weeks where it was stated that the patient had achieved PASI 100 followed by an image after 14 months with the claim 'sustained clearance'. Below these three pictures of the patient's forehead was the statement:

> 'Global clinical experience images of a patient treated with Kyntheum. Images provided by [named doctor], [place of work], [location]and originally published by [publisher]. Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient.'

The Panel noted Leo's submission that the material certified in the company's electronic approval system did not include the images in question in error; the intention from the job bag originator was to include those images.

In relation to the allegation regarding presenting PASI 100 data at 4 weeks, the Panel noted that the supplementary appendix to Lebwohl *et al* (2015) contained figures showing PASI 100 response rates over time. It appeared to the Panel that at week 4, the graphs showed that the PASI 100 response rate in AMAGINE-2 and AMAGINE-3, for patients on brodalumab 210mg, was just over 10% and just under 10%, respectively. Although the Panel could not estimate the exact percentages from the graph, it was clear that PASI 100 at week 4 was not a typical response to Kyntheum for the majority of patients. The Panel noted that the images at issue portrayed complete clearance (PASI 100) after 4 weeks, with sustained clearance after 14 months.

The Panel noted Leo's submission that the images presented were not intended to represent a typical patient. However, the Panel noted that it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's

properties. Use of the disclaimer 'Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient' would not mitigate against any misleading impression that might be given regarding the response to a medicine.

In the Panel's view, the material placed undue emphasis on a positive response that would not be expected in the vast majority of patients treated with Kyntheum and the statement below it 'Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient' did not negate the misleading impression given. The Panel considered that the images exaggerated Kyntheum's properties and were misleading in that regard and ruled breaches of Clauses 7.10 and 7.2.

Regarding the allegation that an image of sustained clearance after 14 months was off-label, the Panel considered that its comments at Point 6 were also relevant here. Whilst the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, the complainant had not established that the promotion of sustained clearance after 14 months of Kyntheum treatment was inconsistent with the particulars listed in the SPC as alleged and the Panel therefore ruled no breach of Clause 3.2 based on the narrow allegation.

In relation to the allegation that there was insufficient context regarding length of time the patient in question had continued on Kyntheum, the Panel noted, from the statement beneath the images, that the patient in set 1, unlike the patients in sets 2 to 4, did not appear to have been from the AMAGINE-2 study. The Panel considered that it was not clear from the webpage if the patient in the image had continued on Kyntheum for 14 months or had discontinued the medicine following achievement of PASI 100 at 4 weeks. Therefore, in the Panel's view, the material was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and a breach of Clause 7.2 was ruled in that regard.

APPEAL BY LEO

Leo submitted that the dissemination of images showing the effects of treatment was central to any communication of information regarding dermatology treatments. The images which were the subject of allegation 13, represented the forehead, which formed part of the scalp.

Leo submitted that a poster by Philipp *et al*, presented at the EADV Conference 12-16 September 2018, provided an analysis of data from AMAGINE-1 which demonstrated improvements in scalp psoriasis in patients with moderate to severe scalp psoriasis treated with brodalumab relative to placebo, considered in clinical subgroups. These data showed that 35-55% of patients achieved 100% clearance at 4 weeks, depending on the relevant clinical subgroup.

As noted by the Panel, the images were provided with text which explained the images:

> 'Global clinical experience images of a patient treated with Kyntheum. Images provided by [named doctor], [place of work], [location] and originally published by [publisher]. Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient.'

Leo submitted that the publication was Pinter A *et al*. Brodalumab for the treatment of moderate to severe psoriasis: case series and literature review. Clinical, Cosmetic and Investigational Dermatology 2019; 12:509-517. The authors published this paper in response to criticism that clinical trials of biologics for the treatment of moderate to severe psoriasis were not necessarily representative of patients seen in daily clinical practice. The authors stated that the reporting of case studies from real-world clinical practice, such as those presented, could help to address that criticism. The images shown on the website represented Case 1 from the Pinter paper and the text confirmed that the patient continued on treatment 14 months after commencing on Kyntheum:

> 'By August 2018, after almost 1 year of treatment, the PASI score, DLQI score … and BSA coverage were all zero, and these outcomes were maintained at the last follow-up (14 months after starting brodalumab…).'

Leo submitted that the text on the website therefore provided context for the images and explained what they represented, namely that they were 'illustrative' of the outcome which could be achieved following brodalumab treatment, based on the actual clinical experience of a single psoriasis patient. The images did not exaggerate the benefits obtained by that patient (which were consistent with up to 55% of patients from AMAGINE-1) and stated expressly that the outcome shown was not intended to reflect a 'typical' patient response.

Leo disagreed with the Panel's view of the overall impression created by the images and the two sentences referenced above (described by the Panel as a 'disclaimer'). These should be considered together, where they provide a single message. The fact that a patient obtained the outcome shown in circumstances where this was not stated to represent a typical response, but nevertheless reflected the outcomes seen in up to 55% of patients in AMAGINE-1, was not misleading and there was no breach of Clauses 7.2 and/or 7.10.

APPEAL BOARD RULING

The Appeal Board noted that the image was of a patient's forehead with plaque psoriasis at baseline and then after 4 weeks where it was stated that the patient had achieved PASI 100 followed by an image after 14 months with the claim 'sustained clearance'. Below these three pictures of the patient's forehead was the statement 'Global clinical experience images of a patient treated with Kyntheum. Images provided by [named doctor], [place of work], [location] and originally published by [publisher]. Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient.'

The Appeal Board noted from Lebwohl *et al* (2015) that at week 4, graphs showed that the PASI 100 response rate in AMAGINE-2 and AMAGINE-3, for patients on brodalumab 210mg, was just over 10% and just under 10%, respectively.

The Appeal Board noted Leo's submission that a poster by Philipp *et al* provided an analysis from AMAGINE-1 which showed that in a subgroup of patients with moderate to severe scalp psoriasis, 35-55% achieved 100% clearance at week 4. However, the Appeal Board noted that this was a *post hoc* analysis of a subgroup of patients in one study and that the figure in section 5.1 of the Kyntheum SPC clearly showed that at week 4 the PASI 100 response rate in the pooled AMAGINE-2 and AMAGINE-3 studies was around 10%.

The Appeal Board considered that it was clear based on the clinical data that PASI 100 at week 4 was not a typical response to Kyntheum for the majority of patients.

The Appeal Board noted that it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties. Use of the statement 'Illustrative clinical case not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient' would not mitigate against any misleading impression that might be given regarding the response to a medicine.

The Appeal Board considered that PASI 100 at week 4 would not be expected in the majority of patients treated with Kyntheum. The Appeal Board considered that the images exaggerated Kyntheum's properties and were misleading in that regard and it upheld the Panel's ruling of breaches of Clauses 7.10 and 7.2. The appeal on this point was not successful.

The Appeal Board noted Leo's submission that the image shown on the website was from Pinter *et al* and text in that paper confirmed that the patient continued on Kyntheum for 14 months after commencing treatment. However, the Appeal Board noted that the text in the paper highlighted by Leo was not on the webpage at issue. The Appeal Board considered that it was not clear from the webpage whether the patient in the image had continued on Kyntheum for 14 months or had discontinued the medicine following achievement of PASI 100 at 4 weeks. The Appeal Board considered that the material was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was not successful.

14 Images of a male torso at baseline, after 4 weeks and PASI 100 at 12 weeks

COMPLAINT

Another set of images showed a male torso at baseline, after 4 weeks and PASI 100 at 12 weeks. Under the image was a statement 'These images are a representative patient response from the AMAGINE-2 study'. AMAGINE-2 and AMAGINE-3 pooled analysis results were reported in the SPC as 41.6% of patients achieving PASI 100 at week 12. The complainant alleged that this would suggest that these images were not a representative patient response from AMAGINE-2, as claimed by Leo.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo stated that it did not agree that this page of the website was in breach of the Code.

The complainant had quoted only part of the statement associated with this set of images. The complete text stated 'These images are a representative patient response from the AMAGINE-2 study. Clinical imagery not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient'.

As expected, fewer patients achieved PASI 100 (complete skin clearance) in the AMAGINE2 or 3 clinical trials than PASI 90 or PASI 75. However, as mentioned by the complainant, 41.6% of patients in the pooled analysis achieved PASI 100 at week 12 (Lebwohl M *et al* 2015). This was a significant proportion of the total patient population in the AMAGINE-2 and AMAGINE-3 studies, and the findings were consistent with the individual study outcome which showed 272 out of 612 patients (44%) in AMAGINE-2 and 229 out of 624 patients (37%) in AMAGINE-3 on brodalumab 210mg reaching PASI 100 at 12 weeks.

Leo submitted that it therefore believed the images presented were representative of the response that could be expected by over 40% of patients on Kyntheum, while as clearly stated, Leo did not claim that these images represented a typical patient response. In these circumstances, the images and the associated statement were not inaccurate or misleading and did not exaggerate the properties of the product. Leo denied a breach of Clauses 7.2 or 7.10.

PANEL RULING

The Panel considered that the allegation in question appeared to be in relation to the fourth set of images as described at Point 10 above.

Beneath the images was the statement:

> 'These images are a representative patient response from the AMAGINE-2 study. Clinical imagery not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient.'

However, the Panel noted that it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties. Use of the disclaimer '…clinical imagery not claimed to represent the typical patient response to Kyntheum…' would not mitigate against any misleading impression that might be given regarding the response to Kyntheum.

The Panel noted that Section 5.1 of the SPC presented the pooled results from AMAGINE-2 and AMAGINE-3 in relation to PASI 100 in graphical form with results which showed that 41.6% of patients administered Kyntheum 210mg every 2 weeks (N=339) achieved PASI 100 at 12 weeks (vs 20.7% for ustekinumab; N = 590).

In relation to the individual trials, Lebowohl *et al* stated that the week 12 PASI 100 response rates were significantly higher with 210mg of brodalumab than with ustekinumab in AMAGINE-2 (44% vs. 22%) and AMAGINE-3 (37% vs. 19%), respectively; both P<0.001).

The Panel considered that the statement 'representative patient response' would likely imply to the audience that it was the typical result seen in that study.

The Panel noted that 44% of patients administered Kyntheum 210mg achieved PASI 100 at 12 weeks in AMAGINE-2, therefore, the majority of patients in that study did not achieve the level of response depicted in the images in question. Thus, in the Panel's view, the images in question were not typical of a patient response from the AMAGINE-2 study and placed undue emphasis on an outcome that would not be expected in the majority of patients treated with Kyntheum at 12 weeks; the statement below it 'clinical imagery not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from

patient to patient' did not negate the misleading impression given. The Panel considered that the images exaggerated Kyntheum's properties and were misleading in that regard and ruled breaches of Clauses 7.10 and 7.2.

APPEAL BY LEO

Leo submitted that use of the phrase 'a representative patient response from AMAGINE-2' meant that the images illustrated an example of a response seen in that study, rather than indicating that the majority of patients would experience that response. This was confirmed by the subsequent sentence which qualified the term 'representative' by stating explicitly that the images were not intended to reflect a 'typical' patient response.

Leo disagreed with the Panel's view of the overall impression created by the images and the two sentences referenced above (described by the Panel as a 'disclaimer'). These should be considered together, where they provide a single message. The pooled analysis quoted in the SPC for Kyntheum (provided), which reported that 41.6% of patients achieved PASI 100 at week 12, was consistent with the fact that the images were representative of a substantial proportion of outcomes from the AMAGINE studies.

In the above circumstances, Leo submitted that the images were neither misleading nor exaggerated the properties of Kyntheum in breach of Clauses 7.2 and 7.10 of the Code.

APPEAL BOARD RULING

The Appeal Board noted the images in question showed a male torso at baseline, after 4 weeks and at 12 weeks where it was stated that the patient had achieved PASI100. Beneath the images was the statement 'These images are a representative patient response from the AMAGINE-2 study. Clinical imagery not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient.'

However, the Appeal Board noted that it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties. Use of the disclaimer '…clinical imagery not claimed to represent the typical patient response to Kyntheum…' would not mitigate against any misleading impression that might be given regarding the response to Kyntheum.

The Appeal Board considered that the statement 'representative patient response' would imply to the audience that it was the typical result seen in that study which was not the case as only 44% of patients in AMAGINE-2 administered Kyntheum 210mg achieved PASI 100 at 12 weeks. The Appeal Board further noted that section 5.1 of the SPC presented the pooled results from AMAGINE-2 and AMAGINE-3 which showed that 41.6% of patients administered Kyntheum 210mg achieved PASI 100 at 12 weeks. Thus, in the Appeal Board's view, the images in question placed undue emphasis on an outcome that would not be expected in the majority of patients treated with Kyntheum at 12 weeks. The Appeal Board considered that the images exaggerated Kyntheum's properties and were misleading in that regard and it upheld the Panel's ruling of breaches of Clauses 7.10 and 7.2. The appeal on this point was not successful.

15 Black triangle

COMPLAINT

A black triangle had not been included next to the first mention of the product on this page as it should for digital material. The first mention of Kyntheum which was part of this section was the 'Kyntheum Prescribing Information' but no black triangle had been included.
When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo stated that it did not agree that this page of the website was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. The black triangle was present on the page adjacent to the first mention of the product. Leo denied a breach of Clause 4.10.

PANEL RULING

The Panel noted that the supplementary information to Clause 4.10 stated that in digital communications the black triangle symbol should be located adjacent to the first mention of the product as this was likely to be considered the most prominent display of the name of the product.

The Panel noted Leo's submission that the black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar and that this came above the mention of the Kyntheum prescribing information.

The Panel considered that the name of the product in the navigation bar was the first mention of the product on the webpage but not the most prominent display; the most prominent display of the name of the product was within the headline claim 'Kyntheum (brodalumab) confidence starts with clearance' where a black triangle had also been used.

Given that the black triangle symbol was located both adjacent to the first mention of Kyntheum and next to the most prominent mention of Kyntheum, on the webpage in question, the Panel considered that the requirements of Clause 4.10 had been met and no breach of Clause 4.10 was ruled.

Mode of Action Tab (MAT-39266 Nov 2020)

16 Claim 'Kyntheum is the first biologic that selectively targets the pro inflammatory IL-17 receptor subunit A'

COMPLAINT

On the mode of action page, a claim was made 'Kyntheum is the first biologic that selectively targets the pro inflammatory IL-17 receptor subunit A'. Two references were used to support this claim, including the Kyntheum SPC. The Kyntheum SPC did not support 'first'.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that this claim was in breach of the Code. There were two elements to the claim for Kyntheum: that it selectively targeted the pro inflammatory IL-17 receptor subunit A, and that it was the first biologic to do so. The SPC had been used to support the mode of action. It said 'Brodalumab is a recombinant fully human monoclonal immunoglobulin IgG2 antibody that binds with high affinity to human IL-17RA …'. A paper by Baker & Isaacs (2018) provided an overview of biologics targeted against elements of the T-helper 17/interleukin-17 and tumour necrosis factor axes, demonstrating that brodalumab was, at the time of publication, the only therapy targeting the IL17 receptor and therefore, by definition, 'the first'. At the time of responding to this complaint, brodalumab remained the only biologic to selectively target the IL-17 receptor subunit A, so the claim was still valid. Use of the SPC as the primary reference for this claim was not misleading. Leo denied a breach of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted Leo's submission that there were two elements to the claim at issue: the SPC was used to support the claim that Kyntheum was a biologic that selectively targeted the pro inflammatory IL-17 receptor subunit A and a paper by Baker & Isaacs (2018) supported that brodalumab was, at the time of publication, the only therapy targeting the IL-17 receptor and was therefore used to substantiate the reference to it being 'the first'. The Panel further noted Leo's submission that at the time of responding to this complaint, brodalumab remained the only biologic to selectively target the IL-17 receptor subunit A.

The Panel made its rulings based on the evidence provided by both parties and considered that the complainant had not established that the claim was misleading as alleged and no breach of Clause 7.2 was ruled.

17 Black triangle

COMPLAINT

The black triangle for Kyntheum had not been included next to the brand name anywhere on the 'Mode of Action' page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. Leo stated that the black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. The black triangle was present on the page adjacent to the first mention of the product. Leo denied a breach of Clause 4.10.

PANEL RULING

The Panel noted that following its request for further information, Leo provided a PDF of the webpage at issue (MAT-39266 Nov 2020) on which there did not appear to be a black triangle next to any mention of the product. The Panel made its rulings based on the evidence provided by both parties.

The Panel did not know how exactly a busy health professional would likely navigate the website in question or how each webpage could be accessed; in the Panel's view, it was prudent that each webpage was not misleading when read in isolation.

Contrary to Leo's submission, the Panel noted there was no black triangle on the webpage in question and therefore a breach of Clause 4.10 was ruled.

18 Claim 'Kyntheum is the first therapy for moderate to severe plaque psoriasis that selectively targets the IL-17RA subunit, thereby blocking the inflammatory signalling of IL-17A, IL-17F, IL-17A/F, IL-17 E and IL17-C'

Under the statement 'The IL-17 pathway', it stated 'Kyntheum is the first therapy for moderate to severe plaque psoriasis that selectively targets the IL-17RA subunit, thereby blocking the inflammatory signalling of IL-17A, IL-17F, IL-17A/F, IL-17 E and IL17-C'. Two references were used to support this claim, including the Kyntheum SPC. The Kyntheum SPC did not support 'first' and the SPC was limited to use in adults. This limitation had not been mentioned and misrepresented the product as similar products had paediatric indications.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not agree that this claim was in breach of the Code. As stated under 16 above, there were two elements to the claim for Kyntheum: that it selectively targeted the pro inflammatory IL-17 receptor subunit A, and that it was the first biologic to do so. The SPC had been used to support the mode of action. It stated that 'Brodalumab is a recombinant fully human monoclonal immunoglobulin IgG2 antibody that binds with high affinity to human IL-17RA…'. A paper by Baker & Isaacs (2018) provided an overview of biologics targeted against elements of the T-helper 17/interleukin-17 and tumour necrosis factor axes, demonstrating that brodalumab was, at the time of publication, the only therapy targeting the IL17 receptor. The paper, rather than the SPC therefore provided the reference for use of the description 'first'. At the time of responding to this complaint, brodalumab remained the only biologic to selectively target the IL-17 receptor subunit A, so the claim was still valid.

This section of the website was focused on mode of action, as clearly highlighted by the heading and the tab selected to navigate to the section. As such, there was no reason to refer to the therapeutic indications or patient populations and Leo did not agree that there was any suggestion that the product was indicated for paediatric use. There was accordingly no breach of Clause 3.2. Leo stated that there was accordingly no breach of either Clause 3.2 or Clause 7.2.

Following a request for further information, Leo stated that MAT-39266 November 2020 was generated by Leo Pharma Global and certified by the Global team and not the UK/IE team. Leo submitted at the time the complaint was made, the complainant would have seen MAT-39266 on the live DermaWorld site and not MAT-30814, which was the UK approved version. Leo

stated it was currently clarifying the situation and would make a decision regarding whether to make a voluntary admission of a breach of Clause 14.1 in due course.

PANEL RULING

The Panel noted its comments at Point 16 above which it considered were relevant here and considered that the complainant had not established that reference to 'first' within the claim in question was misleading as alleged and no breach of Clause 7.2 was ruled.

The Panel considered that the complainant had not established that the mode of action webpage in question promoted use of Kyntheum in children and no breach of Clause 3.2 was ruled.

Video - 'How Kyntheum works' (UK/IE MAT 30646 V2 July 2020)

The complainant referred to a video entitled 'How Kyntheum Works' which according to the complainant was on the Mode of Action (ref MAT-39266 Nov 2020) and Resources (ref MAT-30822 V3 August 2020) webpages.

19 Image of an apparently naked man

COMPLAINT

The 'Mode of Action' and 'Resources' page had a video called 'How Kyntheum works' - the video included an image of an apparently naked man sitting on an underground train seat between other passengers holding an A3 newspaper which covered his upper thigh to mid chest. The complainant alleged that this image was using nakedness in a social setting to attract attention and was distasteful and did not hold medicines or the health professional audience in special standing.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 9.1 and 9.2.

RESPONSE

Leo did not agree that the image was in breach of the Code. The description provided by the complainant was not an accurate representation of the image on the website. The man was visible only from the waist up so it was not possible to conclude that he was naked, only that his chest was bare. The newspaper was standard broadsheet size, so considerably bigger than A3.

The complainant appeared to have drawn on comments made by the Panel during consideration of Case AUTH/2982/10/17 (Member of the public vs LEO Pharma). During its consideration of that case the Panel noted that one of the items at issue included 'an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest'. The Panel considered that the subject's nakedness in a social setting was designed to draw attention to the material, queried whether this complied with the supplementary information to Clause 9.1 and requested that Leo's attention be drawn to this matter.

Leo submitted that at the time of the previous complaint Kyntheum was not licensed. The imagery was used in internal communication (and clearly marked 'For internal use only'). Leo gave considerable thought to the subsequent use of this imagery in promotion and considered that a cropped version of the image would eliminate the concern about nakedness whilst still expressing the message of the campaign – that skin clear of psoriasis improved confidence, potentially giving the confidence for a man to bare his chest in a social setting. In this context, Leo Pharma believed that the link between clear skin (both for psoriasis and other chronic inflammatory skin conditions) and confidence was well established and widely recognised.

Leo submitted that the Panel had acknowledged in Case AUTH/2982/10/17 that it was acceptable to show bare skin when advertising prescription medicines so long as the image was relevant and complied with the Code (ie recognised the special nature of medicines and the professional audience, and was not for the purpose of attracting attention to the material), and that the quality and appearance of a patient's skin was relevant to the product. The Panel had previously decided that improving the confidence of psoriasis patients could be justification for an advertising campaign showing an individual who was undressed in a social setting (Case AUTH/2304/3/10 Doctor vs Forest Laboratories). Plaque psoriasis could occur anywhere on the body, so an image of a partially undressed individual was directly relevant to the disease and contributed to the overall message of clearance improving confidence.

The image presented a man with the confidence to expose his skin on public transport following clearance of his psoriasis. The image was not sexual and the approach was justified in the context of the condition and treatment under consideration. Leo stated that it considered this recognised the special nature of medicines and the professional standing of the audience, was not likely to cause serious or widespread offence, and did not fail to maintain high standards. Leo denied a breach of Clauses 9.1 and 9.2.

PANEL RULING

Clause 9.1 of the Code stated that high standards must be maintained at all times. Clause 9.2 stated that all material and activities must recognise the special nature of medicines and the professional standing of the audience to which they are directed and must not be likely to cause offence. The supplementary information to Clauses 9.1 and 9.2 (suitability and taste), stated, *inter alia*, that the display of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose was an unacceptable style of promotion.

Similarly to point 3, the Panel noted that the man in the image was bare chested, sitting on an underground train, in between two fully clothed individuals. Whilst the Panel noted that in this instance there appeared to be a small section of skin on the individual's thigh that was visible, in the Panel's view, given the indication of the medicine, it was not necessarily unacceptable to show bare skin in advertising material so long as the image was relevant, complied with the Code, recognised the special nature of medicines and the professional audience, was not for the purpose of attracting attention to the material, and that the quality and appearance of the patient's skin was relevant to the product.

In the Panel's view, whilst it would be unusual for a man to be bare chested on a train, and therefore the image might attract attention in that regard, the image did not portray one of a sexual nature and was relevant to the therapeutic area. The theme of the advertisement was improving the confidence of psoriasis patients. The Panel considered that the image was

unlikely to offend the majority of the intended audience of health professionals, particularly given Kyntheum's indication and that plaque psoriasis could affect the chest.

Whilst noting the complainant's views, the Panel did not consider that the image within the video failed to meet the requirements of Clauses 9.1 or 9.2 as alleged, and no breach of Clauses 9.1 and 9.2 were ruled.

20 Claim 'Kyntheum PASI 100 at 12 weeks:44% in AMAGINE-2 and 37% in AMAGINE-3'

COMPLAINT

On this video was a footnote which stated 'Kyntheum PASI 100 at 12 weeks: 44% in AMAGINE-2 and 37% in AMAGINE-3'.

The complainant alleged that this claim was made without any context like study design, comparators, patient population, exclusions to the study, and the information was so minimal it did not provide sufficient information to the reader as to assess the validity, applicability or importance of the results.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that the footnote was in breach of the Code. The statement summarised the PASI 100 outcomes with Kyntheum in two phase 3 studies – AMAGINE-2 and AMAGINE-3 (Lebwohl M *et al* N 2015) which showed 272 out of 612 patients (44%) in AMAGINE-2 and 229 out of 624 patients (37%) in AMAGINE-3 on brodalumab 210mg reaching PASI 100 at 12 weeks. It therefore accurately reflected the study findings. The statement was readily understood in this context, in the absence of details of study design, patient population and study exclusions. The statement was not comparative and there was accordingly no requirement to provide details of comparators. The additional information listed by the complainant would not have altered the interpretation of the statement, which was sufficiently complete to inform readers. Leo denied a breach of Clause 7.2.

PANEL RULING

Whilst it was not clear from the PDFs provided by Leo how a health professional would likely navigate the website and locate the Mode of Action and Resources webpages, the Panel considered that each webpage of the website must not be misleading when read in isolation.

The Panel noted that the video at issue displayed the claim 'Kyntheum PASI 100 at 12 weeks: 44% in AMAGINE-2 and 37% in AMAGINE-3' at the bottom of the screen at times 0:15 – 0:41 and 3:18 – 3:30, referenced to Lebwohl *et al* 2015. Neither the video itself, nor the mode of action webpage contained any further information about the Kyntheum clinical studies. The Resources webpage contained a number of documents and videos which required the user to additionally click to access; the main body of the resources webpage contained no information about the Kyntheum clinical studies.

The Panel noted that Clause 7.2 stated, *inter alia*, that material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

The supplementary information to Clause 7.8 Artwork, Illustrations, Graphs and Tables stated that care should be taken not to mislead when expressing data as percentages; patient numbers should be included wherever possible. The Panel considered that this principle would apply to information presented within a promotional video.

The Panel considered that the claim 'Kyntheum PASI 100 at 12 weeks: 44% in AMAGINE-2 and 37% in AMAGINE-3', without any further information about the studies such as number of patients treated, neither within the video itself nor on the two webpages that hosted the video, meant that the material was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and a breach of Clause 7.2 was ruled.

21 Comparison between IL-17, TNF alpha and IL-12/23 treatments

COMPLAINT

In the video, a comparison was made between IL-17, TNF alpha and IL-12/23 treatments through the visual of each product acting as a fly swat. The complainant alleged that it was not clear what the context of the comparison was. The condition whether it was plaque psoriasis, Crohn's Disease, psoriatic arthritis needed to be stated as other products in these classes had multiple indications. The only comparative data for this product was versus ustekinumab so it was inappropriate to bring all these other classes of medicines into the promotion for comparative purposes.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.3.

RESPONSE

Leo did not agree that this claim was in breach of the Code. The context of the video was clearly moderate-severe plaque psoriasis; this was stated verbally in the voice over and written in the on-screen captions. The video did not refer to any specific treatment apart from Kyntheum. The fly swats represented action against possible inflammatory targets and were labelled accordingly. No comparison was made between any of these modes of actions in terms of efficacy or safety.

Leo submitted that the video was not misleading in any way; there were no comparisons made and the disease area was clearly stated. Leo denied a breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the opening slide of the video stated that Kyntheum was indicated for the treatment of moderate to severe plaque psoriasis in adult patients who were candidates for systemic therapy; this was also stated verbally at the beginning of the video. Following this, the video stated that there were lots of treatments for moderate to severe plaque psoriasis available, at which point fly swatters stating TNF alpha, IL-17 and IL-12/23 appeared on the screen

The Panel noted the complainant's allegation that the context of the treatment comparison was not clear and that the condition, whether it was plaque psoriasis, Crohn's Disease or psoriatic arthritis needed to be stated as other products in these treatment classes had multiple indications. The Panel considered that it was clear that the treatments were mentioned in relation to moderate to severe plaque psoriasis. The Panel did not consider that the complainant had established that the context of the treatment comparison was misleading in terms of the condition being treated and therefore ruled no breach of Clause 7.2 in relation to the narrow allegation.

The Panel noted the complainant's allegation that the only comparative data for Kyntheum was versus ustekinumab so it was inappropriate to bring other classes of medicines into the promotion for comparative purposes.

The video stated that there were lots of treatments for moderate to severe plaque psoriasis available at which point fly swatters stating TNF alpha, IL-17 and IL-12/23 appeared on the screen and asked the question 'how is Kyntheum different and why does it matter'. It went on to state that Kyntheum was the first and only treatment for moderate to severe plaque psoriasis that selectively targeted the interleukin 17 receptor subunit A. The video further stated that because IL-17 was produced by multiple cell types, upstream inhibition of TNF alpha, IL-12 or IL-23 only partly attenuated IL-17 production but that Kyntheum blocked all relevant IL-17 cytokines regardless of which cells produced them by binding the IL-17 receptor subunit A with high affinity.

The Panel noted Leo's submission that the fly swats represented action against possible inflammatory targets and were labelled accordingly. The Panel disagreed with Leo's submission that no comparison was made between any of these modes of action in terms of efficacy or safety; the opening question 'how is Kyntheum different and why does it matter' implied that differences between treatments with regard to mode of action had clinical relevance.

This was emphasised by the clinical trial claim 'Kyntheum PASI 100 at 12 weeks: 44% in AMAGINE-2 and 37% in AMAGINE-3' which appeared at the bottom of the screen throughout parts of the video. Additionally, towards the end of the video was the claim 'Kyntheum fights psoriasis differently and raises the bar for the treatment of moderate to severe psoriasis'. The Panel considered that the claim 'raises the bar' implied some form of advantage over other medicines.

The Panel considered that whilst it might be acceptable to discuss modes of action, extrapolation of *in vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance as stated in the supplementary information to Clause 7.2.

The Panel noted that the active comparator used in the Phase III studies was ustekinumab which was a human IgG1κ monoclonal antibody against the p40 subunit common to interleukin-12 and interleukin-23.

The video did not name any medicines for the treatment of plaque psoriasis other than Kyntheum, however, it referred to the inflammatory targets of Kyntheum and other medicines.

The Panel considered that claims such as 'Kyntheum PASI 100 at 12 weeks: 44% in AMAGINE-2 and 37% in AMAGINE-3' and 'Kyntheum fights psoriasis differently and raises the bar for the treatment of moderate to severe psoriasis', within this mode of action video, implied that Kyntheum's mode of action in relation to targeting the interleukin 17 receptor subunit A, in comparison with other medicines for plaque psoriasis which targeted IL-17, TNF alpha, IL-12 or IL-23, had direct clinical relevance and significance. This, however, had not been demonstrated in clinical trials for all the available medicines for moderate to severe plaque psoriasis which targeted IL-17, TNF alpha, IL-12 or IL-23. The Panel thus considered that the video was misleading in that regard and a breach of Clause 7.3 was ruled.

22 Claim 'Kyntheum blocks all relevant IL-17 cytokines regardless of which cells produce them by binding the IL-17 receptor subunit A with high affinity. This directly inhibits the action of multiple proinflammatory IL-17 cytokines and prevents positive feedback and feedforward loops, resulting in normalisation of the skin'

COMPLAINT

This complainant alleged that the claim was unreferenced and that he/she was unaware of any plaque psoriasis biologic which resulted in 'normalisation', which implied a cure.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that this claim breached the Code. The claim 'Kyntheum blocks all relevant IL-17 cytokines regardless of which cells produce them by binding the IL-17 receptor subunit A with high affinity. This directly inhibits the action of multiple proinflammatory IL-17 cytokines and prevents positive feedback and feedforward loops, resulting in normalisation of the skin' was clearly referenced in the on-screen caption to the SPC and to Russell *et al* 2014.

The SPC supported binding to the IL-17 receptor subunit A with high affinity. The paper by Russell *et al* (2014) focused on the normalization of gene expression profiles in psoriatic skin by treatment with brodalumab. In the conclusion of the paper, the author noted: 'In summary, blockade of IL-17RA with brodalumab lead to rapid molecular and histologic resolution of the inflammation circuits that characterize psoriasis'.

Leo submitted therefore the statement in the video was substantiated with details of the referenced study clearly provided. Leo denied a breach of Clauses 7.2, 7.4 or 7.6.

PANEL RULING

The Panel noted that the claim at issue (present at 2:56 – 3:22 minutes) was stated within the same video as referred to in Points 19, 20 and 21 above.

The Panel noted Leo's submission that the claim was referenced to the SPC and Russell *et al* 2014. The Panel noted that Russell *et al* examined the molecular and cellular effects of blockade of IL-17 signalling in human psoriatic skin before and following treatment with a single dose of brodalumab in 25 patients. The Panel noted that the discussion section stated 'All biopsies in this study were collected by week 6, limiting the analysis of long-term effects in this

single dose study' and 'Analysis of these data cannot distinguish between whether the small set of incompletely normalized genes have some IL-17-pathway–independent drivers, or whether more extended exposure is necessary for normalization'. In this regard, the Panel queried whether the statement 'blockade of IL-17RA with brodalumab lead to rapid molecular and histologic resolution of the inflammation circuits that characterize psoriasis', highlighted by Leo from Russell *et al*, sufficiently substantiated the claim at issue.

The Panel noted, however, that Section 5.1 of the Kyntheum SPC, under the heading mechanism of action, stated, 'Blocking IL-17RA inhibits IL-17 cytokine-induced responses resulting in normalization of inflammation in the skin'.

Whilst it would have been helpful if the claim referred to normalisation of inflammation in the skin rather than normalisation of the skin, in the Panel's view, on the evidence before it, bearing in mind the intended audience, the complainant had not established that the claim was misleading and incapable of substantiation as alleged and, on balance, no breach of Clauses 7.2 and 7.4 were ruled.

Clause 7.6 stated that when promotional material referred to published studies, clear references must be given. The Panel noted Leo's submission that the claim was referenced to the SPC and to Russell *et al* 2014. Based on the complainant's very narrow allegation that the claim was unreferenced, the Panel ruled no breach of Clause 7.6.

23 Claim 'Kyntheum delivers the chance for completely clear skin'

COMPLAINT

Another claim 'Kyntheum delivers the chance for completely clear skin'
was unreferenced and 'delivers the chance' was unqualified. The complainant stated that chance was synonymous with probability and the probability of completely clear skin out of all possible outcomes was not provided. The skin condition which this claim referred to had been omitted - for example it might refer to another type of psoriasis and was therefore incomplete.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.6.

RESPONSE

Leo did not agree that this claim breached the Code. The claim was clearly made in the context of the licensed indication which was stated at the start of the home page of the Kyntheum website; readers could not access subsequent pages without passing through the home page and seeing the indication. The indication was reiterated in writing on the first screen of the video itself and was stated verbally by the narrator at the start of the video. It was therefore obvious that this claim related to use in moderate-severe plaque psoriasis.

Leo submitted that Section 5.1 of the Kyntheum SPC showed that completely clear skin (PASI 100) was achieved in 41.6% of patients after 12 weeks of treatment, a substantial proportion of patients receiving Kyntheum in the pooled studies. It was therefore true to say that Kyntheum delivered the chance for completely clear skin. The definition of 'chance' according to the Oxford English Dictionary was 'the probability of something desirable happening'. Leo believed that a 41.6% probability of achieving complete skin clearance was justification for stating that Kyntheum 'delivers the chance' – it was not a guarantee of success.

Leo submitted that it was incorrect to state that the statement was unreferenced. The subtitles at the bottom of the page clearly referenced 'Kyntheum delivers the chance for completely clear skin to References 2 and 12 – the references list appeared at the end of the video. Reference 2 was Lebwohl *et al* (2015) which supported the PASI 100 clearance. Reference 12 was a paper by Strober *et al* (2021) which addressed the clinical meaningfulness of completely clear skin.

Leo submitted that the claim was substantiated and the references clearly stated and it denied a breach of Clauses 7.2 or 7.6.

PANEL RULING

The Panel noted its comments above at Point 4 in relation to PASI 100 data from the Phase III clinical trials.

The Panel noted the complainant's allegation that 'delivers the chance' was unqualified and that the probability of completely clear skin out of all possible outcomes was not provided. The Panel noted that the claim 'Kyntheum delivers the chance for completely clear skin' was referenced to Lebwohl *et al* (2015) and Strober *et al* (2016). The footnote on the slide stated 'Kyntheum PASI 100 at 12 weeks: 44% in AMAGINE-2 and 37% in AMAGINE-3'. Whilst the Panel noted that the supplementary information to Clause 7 stated that, in general, claims should not be qualified by footnotes, in these circumstances the footnote appeared directly below the claim when it appeared as a subtitle and would be the only text seen on the screen when there were no subtitles. The Panel considered that within the particular circumstances of this case, the complainant had not established that the claim was misleading as alleged and no breach of Clause 7.2 was ruled.

In relation to the allegation that the skin condition which this claim referred to had been omitted, the Panel noted its comments above at Point 21 in relation to Kyntheum's indication being stated and verbalised in the video in question and no breach of Clause 7.2 was ruled in that regard.

Clause 7.6 stated that when promotional material referred to published studies, clear references must be given. In the Panel's view, the claim in question did not refer to a published study.

Nonetheless, the Panel noted that the claim was referenced in the video and based on the complainant's very narrow allegation that the claim was unreferenced, the Panel ruled no breach of Clause 7.6.

24 Claim 'Kyntheum fights psoriasis differently and raises the bar for the treatment of moderate to severe psoriasis'

COMPLAINT

The complainant alleged that the claim of 'differently' was a hanging comparison - no comparator had been stated. 'Raises the bar' was unqualified. The type of psoriasis had not been classified and the adult population had not been cited, indicating a broader licensed use which was off label. The entire statement was unreferenced.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.6.

RESPONSE

Leo did not agree that this claim breached the Code. The statement that Kyntheum fights psoriasis differently was made at the end of the video as part of the summing up. It was made in the context of the stated licensed indication, which had been clearly stated and referred back to the mode of action which, at the time of responding to this complaint, was different from that of all other available treatments for moderate to severe plaque psoriasis. When considered overall, the statement was not a hanging comparison and it was correct to say that Kyntheum fights psoriasis differently.

Leo stated that the phrase 'Raises the bar' directly referred to the use of PASI 100 as an endpoint in the studies. Studies for biologic therapy of moderate to severe psoriasis had previously used lower PASI endpoints, but AMAGINE 2 and 3 included PASI 100. The statement 'Raises the bar' was correctly referenced to Lebwohl *et al* (2015). The statement was therefore substantiable in terms of the endpoint used in the study and the aim to strive for complete skin clearance.

In summary, Leo stated that the licensed indication was clearly stated in the video and there was no suggestion of a broader use off-label, the reference to 'fights psoriasis differently' referred to the evidence in the video, was linked to the mode of action and did not comprise a hanging comparison and the statement 'raises the bar' was substantiated and correctly referenced. Leo denied a breach of Clauses 3.2, 7.2 and 7.6.

PANEL RULING

The Panel noted its comments above at Point 21 in relation to Kyntheum's indication being stated and verbalised in the video in question. In the Panel's view, the indication was clear and the complainant had not established that the video promoted use in a broader patient population than licensed as alleged and no breach of Clause 3.2 was ruled.

In the Panel's view, the claim 'Kyntheum fights psoriasis differently and raises the bar for the treatment of moderate to severe psoriasis' was a comparison with all other treatments for moderate to severe plaque psoriasis and was not a hanging comparison as alleged and no breach of Clause 7.2 was ruled based on the very narrow allegation.

The Panel considered that reference to 'raises the bar for the treatment of moderate to severe psoriasis' was ambiguous and implied a clinical advantage in relation to all other available treatment options; comparative studies had not been done with Kyntheum and all other available treatment options for moderate to severe plaque psoriasis. The Panel considered that the claim in the context of the video was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and was thus misleading and a breach of Clause 7.2 was ruled.

Clause 7.6 stated that when promotional material referred to published studies, clear references must be given. In the Panel's view, the claim in question did not refer to a published study. Furthermore, the claim was referenced and based on the complainant's very narrow allegation that the claim was unreferenced the Panel ruled no breach of Clause 7.6.

25 Claim 'Kyntheum: Confidence Starts with Clearance'

A slide stated 'Kyntheum: Confidence Starts with Clearance'.

The complainant alleged that this statement was unreferenced and he/she had been unable to locate any studies in which Kyntheum provided 100% clearance as the word 'clearance' would imply, and a change in confidence to emerge in this study population as a result.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that the claim was in breach of the Code. The Code required that when promotional material referred to published studies, clear references must be given (Clause 7.6). This claim did not refer to published studies so no reference was required.

The claim 'Kyntheum confidence starts with clearance' related to the effect of skin clearance on quality of life. Quality of life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which were related to overall confidence. A paper by Warren *et al* (2021) analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement ($P<0.0001$).

Leo submitted that the meaning of 'clearance' in the context of psoriasis was not broadly understood to mean 100% clearance by healthcare practitioners. The dermatology healthcare community and clinical research studies specifically referred to Complete Skin Clearance (CSC) if all lesions were resolved. It was accepted that below CSC, there were varying degrees of clearance, defined as 'partial clearance – this might be a reduction in lesions overall, or on a particular part of the body. Leo stated that the claim was therefore substantiable, not misleading and denied a breach of Clauses 7.2, 7.4 or 7.6.

PANEL RULING

The Panel considered that its comments and rulings at Point 4 were also relevant here and therefore, based on the similar very narrow allegation, ruled no breach of Clauses 7.2, 7.4 and 7.6.

Speed of Onset Tab (August 2020 UK/IE MAT-30815 V2)

26 Black Triangle

COMPLAINT

On the 'Speed of onset' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo stated that it did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left-hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. The black triangle was present on the page adjacent to the first mention of the product, in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top left of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

27 Claim 'Speed of onset: Kyntheum effect observed as early as 2 weeks after treatment'

COMPLAINT

On the speed of onset tab was a claim 'Speed of onset: Kyntheum effect observed as early as 2 weeks after treatment'. The term 'Kyntheum effect' was not quantified and was not a clinical parameter and there were no reported data points at 2 weeks in the Kyntheum SPC. The claim of effect as early as 2 weeks was greatly exaggerated when you read the PASI 75 data at week 12 in the SPC - this certainly represented a small proportion of patients if an 'effect' at two weeks existed.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo stated that it did not agree that this information breached the Code. The statement 'Speed of onset: Kyntheum effect observed as early as 2 weeks after treatment' was clearly referring to the fact that an effect of Kyntheum is apparent after 2 weeks. The subheading stated that this assessment was based on time for 25% of patients to achieve at least PASI 75. The data were derived from an analysis by Yao & Lebwohl (2018) which was set up to review the time required for drugs for moderate-to-severe psoriasis to produce a clinically meaningful improvement (TOA), defined as the time at which 25% of the sample population reached PASI 75. In the analysis, the authors concluded that Kyntheum met the endpoint of 25% of patients reaching PASI 75 in 2.1 weeks.

Leo stated that whilst the SPC included no data points at 2 weeks, the statement identified by the complainant was not inconsistent with the SPC which stated that 83-86% of patients achieved PASI 75 at 12 weeks. The statement about speed of onset was not misleading or exaggerated. Leo denied a breach of Clauses 7.2 or 7.10.

PANEL RULING

The Panel noted that the webpage at issue had the headline claim 'Speed of onset: Kyntheum effect observed as early as 2 weeks after treatment' beneath which was the subheading 'A review of data relating to time to onset of action in moderate to severe plaque psoriasis, assessed the time necessary for 25% of patients to achieve at least a PASI 75 response'. The Panel considered that it was clear from the content and layout of the webpage that the claim 'Speed of onset: Kyntheum effect observed as early as 2 weeks after treatment' was related to the measure of time necessary for 25% of patients to achieve at least PASI 75 which was the primary outcome of a review by Yao and Lebwohl (2019) which looked at published and presented efficacy data from a number of antipsoriatic medicines for moderate to severe plaque psoriasis.

Based on the narrow allegation, the Panel did not consider that the complainant had established that the claim within the context of the webpage was misleading or exaggerated Kyntheum's properties and no breach of Clauses 7.2 and 7.10 were ruled.

28 Bar chart 'Time taken for 25% of patients to achieve PASI 75'

COMPLAINT

A bar chart was shown with various biologics and 'Time taken for 25% of patients to achieve PASI 75'. The complainant alleged that there had been no black triangle included on the Kyntheum brand, yet it had been included on other competitor drugs, and was therefore misleading - it looked like this product did not have additional safety monitoring whilst other products did. The dosing for secukinumab only included a specific sub population; those with a body weight greater than 100kg who warranted a 'higher dose'. The study designs from which these figures had been calculated had not been included nor was there sufficient statistical analysis information, resulting in inadequate level of information available for the reader to understand the relevance of the results.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 4.10 and 7.2.

RESPONSE

Leo did not agree that use of this chart breached the Code. It would be clear to readers that Kyntheum was a black triangle product since the black triangle was included prominently next to the brand name on the home page which all readers must pass through to access this material.

The black triangle for Kyntheum was also visible at the top of the page at issue. Leo stated that this met the Code requirement for digital materials which stated that the black triangle for a promoted product must be located adjacent to the first mention of the product. Although there was no Code requirement to include black triangles on competitor products, this was previously considered standard good practice within Leo Pharma but had recently been discontinued.

Leo submitted that the graph was adapted from a published paper, as referenced (Yao & Lebwohl). It presented the information from the study which was set up to review the time required for drugs for moderate-to-severe psoriasis take to produce a clinically meaningful

improvement (TOA), defined as the time at which 25% of the sample population reached PASI 75 or the time at which the sample population reached a mean PASI 50. The results clearly demonstrated that brodalumab had the fastest TOA for both outcome measures. The authors consolidated clinical data from recent publications and presentations of certolizumab, tildrakizumab, apremilast and low-dose acitretin as well as two previous TOA reviews – Nast *et al* 2011 and Papp *et al* 2017. The studies for secukinumab provided high and low dose data for mean PASI 50, but only high dose data for TOA. Therefore, only the high dose results were shown on the chart.

Leo stated that there was no requirement to include details of study design or analysis on materials, provided its omission did not render them misleading. The chart was not misleading and contained the relevant data to aid interpretation: time taken with range or 95% confidence intervals, numbers of patients and an indication where the results were derived from a single study.

The black triangle for Kyntheum was present on the page and the bar chart was not misleading or exaggerated and Leo therefore denied a breach of Clauses 4.10 or 7.2.

PANEL RULING

The Panel noted Leo's submission that it would be clear to readers that Kyntheum was a black triangle medicine since the black triangle was included next to the brand name on the homepage which all readers must pass through to access this material. Nonetheless, the Panel considered that each webpage must not be misleading when read in isolation.

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. The Panel therefore ruled no breach of Clause 4.10 in that regard.

The Panel considered that the bar chart in question was inviting readers to make a comparison between medicines. The bar chart had been adapted by Leo from the published paper to include the addition of black triangles for certain competitor medicines which, in the Panel's view, gave the immediate impression that Kyntheum was not a medicine that required additional monitoring in relation to adverse reactions like some of its competitors which was not so. Furthermore, the black triangles next to the competitor medicines were larger and more prominent compared with the black triangle adjacent to Kyntheum in the navigation bar at the top of the webpage in question. The Panel noted the layout of the webpage and considered it was misleading to omit the black triangle for Kyntheum within the bar chart at issue and a breach of Clause 7.2 was ruled.

The Panel noted that the bar chart in question gave n-numbers for each bar and stated that estimates were either times based on linear interpolation between time points from a single study or weighted means from multiple studies and that confidence intervals or ranges were provided where available.

The Panel considered that the complainant had not established that there was insufficient information on the webpage to enable the reader to understand the relevance of the results as alleged and no breach of Clause 7.2 was ruled in that regard.

Efficacy Tab (August 2020 UK/IE MAT-30816 V2)

29 Black triangle

COMPLAINT

On the 'Efficacy' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left-hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page.

Leo stated that the black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

30 Claim 'Strive for complete clearance'

COMPLAINT

The complainant alleged that Kyntheum did not have data to show complete clearance and this was not achievable in every patient, therefore this statement was misleading. It might not be appropriate for patients due to reasons of safety or efficacy to continue on this product and 'strive for complete clearance' as Leo asked so this statement did not promote the rational use of a medicine.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.10 and 9.1.

RESPONSE

Leo did not agree that use of this statement breached the Code. 'Strive for complete clearance' referred to using PASI 100 as the indicator of treatment success in plaque psoriasis rather than PASI 75; this was explained in the text immediately under the statement. There was good evidence that complete clearance (PASI 100) was associated with better quality of life for patients than PASI 75. Quality of Life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). A paper by Warren *et al* (2021)

analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (P<0.0001).

Furthermore, there was substantial evidence that patients and clinicians should strive towards complete skin clearance or PASI 100, including Strober (2021). This was in line with the NICE guidelines for the assessment and management of psoriasis (2021) which stated that treatment goals should aim to minimise the impact of the condition, and that relevant assessment tools should be used to ensure these goals were met.

Contrary to the complainant's allegation, Kyntheum did have data to support complete clearance (Lebwohl *et al* 2015). This was presented in the graph of PASI responses at 12 weeks vs ustekinumab which showed that 37-44% of patients on Kyntheum achieved PASI 100.

Leo submitted that the statement was not at odds with the requirement to promote rational use of medicines. The term 'strive' meant 'to try very hard' (Oxford English Dictionary). It was used to acknowledge that prescribers would try very hard to achieve PASI 100 (the best outcome) for their patients, given the quality of life benefits this outcome brought. However, the phrase, including use of the word 'strive', made clear that complete clearance was an aim and did not suggest this was achievable in every patient. The information in the chart entitled 'PASI 75, 90 and 100 responses at week 12' showed very clearly that not every patient would achieve PASI 100. There was nothing at any point on this page which suggested that patients should remain on treatment which was not appropriate for them and monitoring risk vs benefit on an ongoing basis was a fundamental part of the prescriber's role.

Leo submitted that the statement was not misleading or exaggerated and had no impact on patient safety. It sought simply to encourage prescribers to consider the highest possible treatment goals, consistent with the NICE guideline. Leo denied a breach of Clauses 2, 7.2, 7.10 or 9.1.

PANEL RULING

The Panel noted that the webpage headline claim was 'strive for complete clearance with Kyntheum'.

The Panel noted that the SPC gave pooled PASI 100 results from AMAGINE-2 and AMAGINE 3 which showed that 41.6% and 51% of patients administered Kyntheum 210mg every 2 weeks achieved PASI 100 at 12 and 52 weeks, respectively. The Panel considered that the complainant had not established his/her narrow allegation that Leo did not have data to show complete clearance and the Panel ruled no breach of Clause 7.2 in that regard.

The Panel considered that the claim 'strive for complete clearance' implied that complete clearance was a possible treatment outcome to aim for with the use of Kyntheum not that complete clearance would be achieved in every patient as alleged. In this regard, the Panel noted that further down the webpage was a bar graph showing the percentage of patients achieving PASI 75, 90 and 100 responses with Kyntheum (210mg every 2 weeks) at 12 weeks vs. both ustekinumab and placebo in AMAGINE-2 and AMAGINE-3; in this Kyntheum group, PASI 100 was achieved in 37% in AMAGINE-3 and 44% in AMAGINE-2. The Panel, therefore, based on the complainant's narrow allegation, did not consider that the claim 'Strive for complete clearance with Kyntheum' as it appeared on the webpage in question misleadingly

implied that complete clearance was achievable in every patient as alleged and no breach of Clause 7.2 was ruled in that regard.

In the Panel's view, the complainant had not established that the claim 'strive for complete clearance' did not promote the rational use of Kyntheum by encouraging continued use which might not be appropriate for some patients due to reasons of safety or efficacy as alleged. The Panel therefore ruled no breach of Clause 7.10.

The Panel noted its comments and rulings above and consequently ruled no breach of Clauses 9.1 and 2.

31 Claim 'Clearance rates with Kyntheum were sustained through to two years'

COMPLAINT

The complainant alleged that the SPC only recommended treatment beyond 16 weeks in some patients with initial partial response who might subsequently improve. The SPC for Kyntheum only reported data points to 52 weeks. This claim lacked information on when to continue treatment beyond 16 weeks, the promotion of clearance rates beyond 52 weeks was off label and the lack of statistical analysis of the data presented a misleading and inaccurate picture of the product. Also, it was not stated what population these results were in, how large the population size was, what was the level of 'clearance rate', therefore being incomplete and lacking information for the reader to decide the importance of the claim.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not agree that the presentation of clearance rates after 2 years of treatment was in breach of the Code.

Section 4.2 of the Kyntheum SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
> Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'

Leo stated that the complainant had misinterpreted this section of the SPC. There was no limit on the duration of use of Kyntheum. Discontinuation after 12-16 weeks was only recommended for those who had not responded to treatment. The guidance about continuation in patients with initial partial response was included to indicate that some of these patients might achieve better results with longer treatment. It did not mean that this was the only patient group that could continue treatment beyond 16 weeks.

Leo stated that Section 5.1 of the SPC described the use of Kyntheum in the AMAGINE-1, AMAGINE-2 and AMAGINE-3 clinical trials up to 52 weeks as this was the analysis presented in the submission for marketing authorisation and also referenced the long term extension study.

Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for longer periods was not inconsistent with the SPC. Leo stated that it did not therefore accept that there had been any breach of Clause 3.2 of the Code.

Leo stated that the claim was presented with a graph, comprising an accurate representation of the data from a study by Puig *et al* (2020) which was designed to evaluate the efficacy and safety of brodalumab through 120 weeks of treatment in the AMAGINE-2 trial. The study showed that clearance rates were sustained across the long term extension. The text stated clearly that p values were not provided in the original paper. The presentation of data reflecting that published in a peer reviewed journal could not be viewed as 'misleading and inaccurate'.

Leo noted that the complainant mentioned that it was not stated what population these results were in, the population size or level of 'clearance rate'. Leo submitted that this was a promotional website so in the absence of any other information it could be assumed that the population represented the full licensed population (ie adults with moderate to severe plaque psoriasis). Details of patient numbers were provided on the x-axis of the graph and this was colour coded with a key to indicate the different levels of clearance rates. There was therefore sufficient information for a reader to be able to form their own view of the data.

Leo stated that the claim was therefore not inconsistent with the SPC, was not misleading. Leo denied a breach of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that the claim 'Clearance rates with Kyntheum were sustained through to two years' was above a graph headed 'PASI 75, 90 and 100 responses in patients who received Kyntheum 210mg during the long-term extension' which also provided n numbers up to week 120 and stated that a p-value was not available.

The Panel noted its comments and rulings at Point 6 above which it considered were also relevant here.

The Panel noted that the Kyntheum SPC referred to three Phase 3 studies (AMAGINE-1, AMAGINE-2 and AMAGINE 3) and stated that all three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension. The Panel noted that the SPC only reported results up to week 52.

The Panel considered that companies might be able to make claims based on data with a longer time-period of observation than that cited in the SPC so long as the promotion was not inconsistent with the SPC and it complied with the Code.

In the Panel's view, as the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, the complainant had not established that the promotion of clearance rates beyond 52 weeks was inconsistent with the SPC as alleged and the Panel ruled no breach of Clause 3.2.

Puig *et al* (2020) evaluated the efficacy and safety of brodalumab through 120 weeks in the AMAGINE-2 trial. The authors stated that of patients who received brodalumab 210mg every 2 weeks, 84.4%, 75.6%, and 61.1% achieved 75%, 90%, and 100% improvement from baseline in

PASI at 120 weeks, respectively. The Panel noted that Puig *et al* concluded that brodalumab showed sustained skin clearance through 120 weeks.

In the Panel's view, whilst more study detail would have been helpful, such as clarifying that the long-term extension was open-label, the complainant had not established that the claim in the context of the webpage was misleading as alleged and no breach of Clause 7.2 was ruled.

32 Graph labelled 'PASI 75, 90 and 100 responses in patients who received Kyntheum 210 mg during the long term extension'

COMPLAINT

The graph showed the percentage of responders up to 120 weeks. The complainant alleged that the SPC only recommended treatment beyond 16 weeks in some patients with initial partial response who might subsequently improve. The SPC for Kyntheum only reported data points to 52 weeks. This claim lacked information on when to continue treatment beyond 16 weeks, the promotion of clearance rates beyond 52 weeks was off label and the lack of statistical analysis of the data presented a misleading and inaccurate picture of the product. There was no statistical evaluation of the results with the exception 'P values not available in source data'. The lack of study design information and statistical analysis provided an incomplete picture of the data.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not agree that the presentation of data relating to clearance rates up to 120 weeks of treatment was in breach of the Code. Section 4.2 of the Kyntheum SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
> Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'

Leo stated that the complainant had misinterpreted this section of the SPC. There was no limit on the duration of use of Kyntheum. Discontinuation after 12-16 weeks was only recommended for those who had not responded to treatment. The guidance about continuation in patients with initial partial response was included to indicate that some of these patients might achieve better results with longer treatment. It did not mean that this was the only patient group that could continue treatment beyond 16 weeks.

Leo stated that Section 5.1 of the SPC described the use of Kyntheum in the AMAGINE-1, AMAGINE-2 and AMAGINE-3 clinical trials up to 52 weeks as this was the analysis presented in the submission for marketing authorisation and also referenced the long term extension study. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for longer periods was not inconsistent with the SPC. Leo denied a breach of Clause 3.2 of the Code.

Leo submitted that the graph (presented with the claim referenced under 31 above) comprised an accurate representation of the data from a study by Puig *et al* (2020) which was designed to evaluate the efficacy and safety of brodalumab through 120 weeks of treatment in the AMAGINE-2 trial. The study showed that clearance rates were sustained across the long term extension. 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100. As noted by the complainant, the web page clearly stated that statistical significance (p values) were not provided in the original (peer reviewed) paper. There was no requirement to include further details of the study design in the context of this claim and the associated graph. The presentation of data reflecting that published in a peer reviewed journal could not be viewed as 'misleading and inaccurate' and there was sufficient information for a reader to be able to form their own view of the data.

Leo submitted that the statement was not inconsistent with the SPC, was not misleading and it denied a breach of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted its comments and rulings above at Point 31 which it considered were also relevant here and therefore ruled no breach of Clauses 3.2 and 7.2.

33 Claim 'Kyntheum efficacy was unaffected by previous biologic use'

COMPLAINT

The complainant alleged that for a product with a black triangle with an SPC stating '0.3% of patients had anti-brodalumab antibodies at development', it was not possible to make such a strong claim in such a new product.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.4.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The statement described the findings of Papp *et al* (2018) who analysed the results of two large phase III studies in order to investigate the impact of previous biologic exposure on the efficacy and safety of brodalumab and ustekinumab. 1,236 patients were on brodalumab 210mg every two weeks; 902 were biologic naïve and 334 had previous exposure to biologics. Efficacy in the two groups was statistically equivalent: 40.9% and 39.5% of biologic-naive and biologic-experienced patients achieved PASI 100 at week 12. In addition, Section 5.1 of the SPC stated that examination of various patient subgroups across the three phase trials, including use of prior biologics and biologic failures, failed to identify differences in response in all key endpoints.

Leo submitted that the statement was an accurate representation of the study findings and was in line with similar information in the SPC and was therefore consistent with the requirements of Clause 7.4 of the Code.

PANEL RULING

The Panel noted its comments and rulings above at Point 7 which it considered were also relevant here and ruled no breach of Clause 7.4.

QOL (August 2020 UK/IE MAT-30817 V2)

34 Claim 'Quality of life: the effect of Kyntheum on a range of measures'

COMPLAINT

The complainant alleged that this claim was on the QOL tab and was unreferenced and unqualified; what effect and which measures the statement was referring to had not been provided to the reader.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.6.

RESPONSE

Leo did not agree that this statement was in breach of the Code. It was quite clearly a heading describing the content of the page, and not a claim; subsequent statements which described the effects of Kyntheum were. It was not misleading and did not need to be referenced. Leo denied a breach of Clauses 7.2 and 7.6

PANEL RULING

The Panel noted that the webpage in question was headed 'Quality of life: the effect of Kyntheum on a range of measures', beneath which was a number of statements on the effect of psoriasis on quality of life and psychological comorbidities in the UK followed by data on the effects of Kyntheum on HADS depression and anxiety scores in patients who had moderate or severe depression/anxiety before Kyntheum treatment started. Towards the bottom of the webpage was a video of a Kyntheum patient's story titled 'Living with psoriasis: a personal story'. The Kyntheum data which showed change from baseline in HADS anxiety and depression scores was referenced to Papp *et al* (2016).

The Panel considered that the complainant had not established that the webpage heading 'Quality of life: the effect of Kyntheum on a range of measures' was misleading or needed to be referenced and no breach of Clauses 7.2 and 7.6 were ruled.

35 Claim 'Kyntheum improved depression and anxiety by week 12'

COMPLAINT

The complainant alleged that Kyntheum was not indicated in the treatment of depression and anxiety and no study was powered to show improvement in these areas at week 12. In fact, the SPC Section 4.4 provided extensive guidance on managing patients with depression, suicidal ideation, mood changes and recommended 'the risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and or suicidal ideation or behaviour or for patients who develop such symptoms'. This claim was inaccurate, promoted the product for depression, was misleading, did not promote the rational use of a medicine and was likely to prejudice patient safety.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.10 and 9.1.

RESPONSE

Leo submitted that this section of the website, presented under the heading 'Quality of life: The effect of Kyntheum on a range of measures', was clearly intended to demonstrate the improvements in quality of life (QoL) for patients with moderate to severe psoriasis following treatment. This context was clear from the multiple references to the burden of psoriasis and the psychological symptoms associated with psoriasis, both before and after the statements identified by the complainant.

The improvements in QoL were assessed using a range of related measures, including depression and anxiety. These symptoms were clearly identified on the page as common psychological symptoms associated with psoriasis (Kurd SK *et al* 2010). The webpage then went on to show the depression and anxiety outcomes based on the 661 patients randomised within the AMAGINE 1 study (Papp *et al* 2016). A small number of patients were found to have 'moderate' or 'severe' anxiety (69 patients) or depression (55 patients) at baseline (as measured by HADS) and these patients showed an improvement in their HADS scores at week 12. Overall, looking at the change in mean HADS scores for anxiety and depression across all randomised patients, there was a statistically significant improvement with Kyntheum treatment, however there was no statistical significance for the small number of patients with moderate-severe anxiety or depression.

Leo stated that the references to improvements in depression and anxiety must not properly be reviewed in isolation but were clearly intended to be considered in the context in which they were presented, namely as symptoms related to moderate-severe psoriasis. No health professional reviewing this section of the website could construe this as a claim that Kyntheum has efficacy as a specific treatment for depression or anxiety, rather than recognising that these were two aspects of overall quality of life that might be impacted positively through Kyntheum treatment of moderate-severe psoriasis. No superlatives had been used and Leo did not believe the properties of Kyntheum had been exaggerated. Leo denied any breach of Clauses 3.2 or 7.10 of the Code.

Leo noted that the complainant had stated that Section 4.4 of the SPC (special warnings and precautions for use) provided 'extensive guidance on managing patients with depression, suicidal ideation and mood changes…'. In fact, the relevant part of Section 4.4 of the SPC focussed on suicidal ideation and behaviour and noted that the majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour and that a causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established.

Leo submitted that suicidal ideation/behaviour was not listed as an adverse event in Section 4.8 of the SPC and in the Kyntheum development programme as a whole across five different therapeutic indications, six cases of completed suicide were identified during 10,438 patient years of follow-up exposure in 6,243 patients. In a review (Farahik *et al* 2016), the authors concluded that two completed suicides in one clinical trial, AMAGINE-2, did not necessarily constitute a causal relationship, especially given that patients with psoriasis were already at higher risk for depression, suicidal ideation, attempt and completed suicide.

Leo stated that whilst a causal association between Kyntheum had not been established and suicidal ideation/ behaviour was not listed as an adverse event in Section 4.8 of the SPC, in view of the information provided in Section 4.4, Leo agreed that the provision of balanced information would require some reference to such concerns in this section of the website, which addressed symptoms of depression in patients with psoriasis. Leo therefore accepted that, in this respect, this section of the website did not meet the standards required by Clause 7.2 of the Code. As a consequence, Leo also agreed that this section of the website did not maintain high standards and was therefore in breach of Clause 9.1.

Leo submitted, however, in the overall context of this webpage which focussed on quality of life in patients with psoriasis and in view of the fact that no causal relationship between Kyntheum and suicidal ideation and behaviour had been established, Leo did not agree that the way in which this data was presented here had brought the industry into disrepute and did not accept that there had been a breach of Clause 2.

PANEL RULING

The Panel noted its comments above at Point 34 in relation to the content and layout of the webpage at issue. Below the claim 'Kyntheum improved depression and anxiety by week 12' were two graphs showing change from baseline for Kyntheum and placebo treated patients in HADS depression and HADS anxiety scores. Each graph depicted the percentage of patients who had experienced improvement and the percentage whose score had returned to normal. Above the graphs were the claims 'The HADS depression score improved in 73% of patients treated with Kyntheum who had moderate or severe depression before treatment started' and 'The HADS anxiety score improved in 67% of patients treated with Kyntheum who had moderate or severe anxiety before treatment started'. The graphs gave the n numbers in each group: HADS depression (Kyntheum n=30 and placebo n=22) and HADS anxiety (Kyntheum n=42 and Placebo n=27). There was no reference to any statistical analyses.

The claims and graphs were referenced to Papp *et al* 2016, which was a Phase III, double-blind, placebo controlled study (AMAGINE-1). The Panel noted that the effect of Kyntheum compared with placebo on HADS anxiety and depression scores at week 12 was neither a primary nor key secondary objective of the study. The Panel further noted Leo's submission that the change in mean HADS scores for anxiety and depression across all randomised patients in the study, showed a statistically significant improvement with Kyntheum treatment, however, there was no statistical significance for the small number of patients with moderate-severe anxiety or depression at baseline.

In the Panel's view, the claim 'Kyntheum improved depression and anxiety by week 12' implied that there was a statistically significant improvement in depression and anxiety from baseline in patients with diagnosed depression and/or anxiety. However, there was no statistically significant difference versus placebo for the small number of patients with moderate or severe anxiety or depression at baseline. The sub-claims 'The HADS depression score improved in 73% of patients treated with Kyntheum who had moderate or severe depression before treatment started' and 'The HADS anxiety score improved in 67% of patients treated with Kyntheum who had moderate or severe anxiety before treatment started' added to the misleading impression that the data was statistically significant which was not so. In the Panel's view, the claim 'Kyntheum improved depression and anxiety by week 12' was misleading and exaggerated the medicine's properties and a breach of Clauses 7.2 and 7.10 were ruled.

In the Panel's view, the claim 'Kyntheum improved depression and anxiety by week 12' on the webpage and website in question was set clearly within the context of psoriasis treatment and, on the balance of probabilities, the intended audience would not be misled that Kyntheum was licensed for the treatment of anxiety or depression; the Panel considered that the complainant had not established that the claim promoted Kyntheum for the treatment of depression or anxiety as alleged and no breach of Clause 3.2 was ruled.

The Panel noted that Section 4.4 (special warnings and precautions for use) of the Kyntheum SPC stated:

> 'Suicidal ideation and behaviour
> Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established.
>
> The risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum.'

The Panel noted Leo's submission that in view of the information provided in Section 4.4, the provision of balanced information would require some reference to such concerns in this section of the website, which addressed symptoms of depression in patients with psoriasis. The Panel considered that the webpage's focus on improvement in HADS anxiety and depression scores after Kyntheum treatment in patients who had moderate/severe depression or anxiety, without any reference to the warning in the Kyntheum SPC about patients with a history of depression and/or suicidal ideation or behaviour was misleading and did not encourage the rational use of the medicine and breaches of Clauses 7.2 and 7.10 were ruled in that regard. High standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Leo.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted that the webpage in question referred to there being 350 cases of suicide in the UK annually attributable to psoriasis prior to claiming that Kyntheum improved depression and anxiety by week 12. There was no reference to the suicidal ideation and behaviour warning in the Kyntheum SPC. In the Panel's view, the unbalanced presentation of information on the webpage at issue, in relation to depression and suicidal ideation and behaviour, meant that the material had the potential to prejudice patient safety and brought discredit upon and reduced confidence in the industry; a breach of Clause 2 was ruled.

36 Black triangle

COMPLAINT

On the 'QOL' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. The black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

37 Graphs on HADS depression score and HADS anxiety score

COMPLAINT

The complainant stated that two graphs were presented on HADS depression score and HADS anxiety score and showed % change from baseline for Kyntheum and placebo arms. Both graphs showed a very small population, not statistically powered to show an effect to support the claims of supporting depression and anxiety. The claims 'The HADS depression score improved in 73% of patients treated with Kyntheum who had moderate or severe depression before treatment started' and 'The HADS anxiety score improved in 67% of patients treated with Kyntheum who had moderate or severe anxiety before treatment started' were without any qualification of the study design, the population size and lacked any statistical analyses, presenting an incomplete and misleading picture of the data.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that the graphs were in breach of Clause 7.2. The allegations raised in this complaint were part of the same point raised under point 35 above (this complaint related to the graphs under the headings criticised in point 35) and could not be considered separately. Leo stated that its response to point 35 took into account the graphs as well as the headings and its response to those allegations was relevant here also.

The graphs referenced by the complainant show the depression and anxiety outcomes based on the small number of patients within the overall 661 patient cohort of the AMAGINE-1 trial (Papp *et al* 2016*)*, who were found to have 'moderate' or 'severe' anxiety (69 patients) or depression (55 patients) at baseline (as measured by HADS). These patients showed an improvement in their HADS scores at week 12 as shown in the graphs. Overall, considering the

change in mean HADS scores for anxiety and depression across all randomised patients, there was a statistically significant improvement with Kyntheum treatment, however no statistical significance was shown for the small number of patients with moderate-severe anxiety or depression in the referenced paper published in a peer reviewed journal.

Leo stated that additional details of trial design were not required to allow readers to form their own view of the data presented in the graphs and these could not be misleading in the absence of statistical analyses if such statistical data were not presented in the original paper by Papp *et al* published in a peer reviewed journal. In terms of other allegations by the complainant, the number of patients included in the Papp *et al* paper were clearly stated on the graphs.

In terms of the data presented Leo did not believe the graphs were incomplete or misleading and it denied that there had been any breach of Clause 7.2.

PANEL RULING

The Panel considered that the allegations in relation to the graphs in question were covered under Point 35 above and made no further ruling in this regard.

Dosing (August 2020 UK/IE MAT-30818 V2)

38 Black triangle

COMPLAINT

On the 'Dosing' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page.

The black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

39 Claim 'Kyntheum has a simple induction and dosing schedule'

COMPLAINT

The reference for this promotional claim was listed as Reference 1, Kyntheum SPC. The SPC did not support this claim of a simple induction and dosing schedule ('simple' was a word which was not in the SPC), the reference was incorrect and therefore misleading. In fact this claim was contrary to the SPC which required 'after proper training in subcutaneous injection technique, patients may self inject Kyntheum when deemed appropriate by a physician'.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.4.

RESPONSE

Leo submitted that as stated in its response to Point 5 above, it did not agree that the statement 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0,1 and 2 followed by 210mg every 2 weeks)' was in breach of the Code.

Leo submitted that the statement was an accurate representation of the dosing regimen in the SPC. The dose strength and frequency of Kyntheum were the same for all patients. There was no requirement to adjust the dose on the basis of weight or age. The regimen (weekly for 2 weeks, then fortnightly) was simple. The statement was specifically about the dosing schedule, not about the route of delivery. The need for injection training was not relevant; it did not mean that the dosing schedule was not simple.

Leo submitted that the statement was not inconsistent with the SPC, was not misleading and was capable of substantiation and it denied a breach of Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel noted its comments and rulings above at Point 5 which it considered were also relevant here.

The Panel noted Leo's submission that the claim 'Simple induction and dosing schedule (210 mg administered by subcutaneous injection at weeks 0, 1 and 2 followed by 210 mg every 2 weeks)' was specifically about the dosing schedule and not about the route of delivery. In this regard, the Panel noted that the claim at issue on the dosing page was different to that at point 5 in that the information in brackets (210mg administered by subcutaneous injection at weeks 0, 1 and 2 followed by 210mg every 2 weeks) was not included.

The Panel noted, however, that the claim on the webpage at issue was immediately above a diagram showing the timing of injections during the induction phase (first injection, wait one week, second injection, wait one week then third injection), and ongoing treatment (wait two weeks after the induction phase and continue injections at 2 weekly intervals).

In the Panel's view, the claim at issue referred to the dosing of Kyntheum and not the method of administration. In that regard, the Panel considered that the complainant had not established that the claim 'Kyntheum has a simple induction and dosing schedule' was inconsistent with the SPC, misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of Clauses 3.2, 7.2 and 7.4.

40 Ongoing treatment graphic

COMPLAINT

A graphic showing the dosing regimen in the induction phase and ongoing treatment was depicted. For the 'Ongoing treatment' graphic, it stated 'Continue at 2-weekly intervals'. There was no information on when dosing should be reviewed. The complainant alleged that the SPC only recommended treatment beyond 16 weeks in some patients with initial partial response who might subsequently improve. The SPC for Kyntheum only reported data points to 52 weeks. This representation of dosing was inaccurate and did not promote the rational use of the medicine.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo did not agree that use of this graphic was in breach of the Code. The text under the graphic clearly stated 'Consult the SPC for full details'. However, the complainant had misinterpreted guidance in the Kyntheum SPC; there was no limit on the duration of use of Kyntheum. The guidance about continuation after 16 weeks in patients with initial partial response was included to indicate that some of these patients might achieve better results with longer treatment. It did not mean that this was the only patient group where treatment beyond 16 weeks was recommended.

Leo stated that Section 5.1 of the SPC described the use of Kyntheum in the AMAGINE-1, AMAGINE-2 and AMAGINE-3 clinical trials up to 52 weeks, as this was the analysis presented in the submission for marketing authorisation, and also referenced the long term extension study. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum ongoing treatment was not inconsistent with the SPC.

Leo submitted that the graphic was not inconsistent with the SPC, was accurate and not misleading, promoted rational use of Kyntheum as a 2-weekly ongoing treatment and it denied a breach of Clauses 7.2 and 7.10.

PANEL RULING

The Panel noted its comments at Point 6 in relation to the Kyntheum SPC and its description of the graphic at Point 39.

The Panel further noted that the SPC stated that Kyntheum was intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

In the Panel's view, as the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, it did not consider that the complainant had established that reference to 'Ongoing treatment' in the graphic at issue, which stated 'Continue at 2-weekly intervals' was inaccurate or did not promote the rational use of the medicine as alleged and therefore no breach of Clauses 7.2 and 7.10 was ruled.

Safety (August 2020 UK/IE MAT-30819 V2)

41 Black triangle

COMPLAINT

On the 'Safety' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. Leo submitted that the black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

42 Adverse events on safety page

COMPLAINT

Two tables of adverse events were included on this page. However, the adverse events were limited to the AMAGINE-2 and 3 studies. The SPC listed more adverse events, many of which were common and serious, and this had been omitted from this page. For example, influenza, tinea infections, anaphylactic reaction, diarrhoea, nausea, myalgia, fatigue and conjunctivitis had not been included on this safety page. This was inaccurate, misleading and misrepresented safety. There was also no information on the page to reflect the extensive warnings on suicidal ideation and behaviour from Section 4.4 of the SPC. This was likely to prejudice patient safety.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.9 and 9.1.

RESPONSE

Leo did not agree that the publication of these tables was in breach of the Code. The Safety section of the website presented the safety profile for Kyntheum across the Phase III studies – AMAGINE-2 and AMAGINE-3 (Lebwohl M *et al* 2015). The page in question had a clear heading stating 'Safety profile for Kyntheum across Phase III trials' and the tables accurately reflected the findings of the two studies. The Phase III clinical trial data provided robust safety information useful for health professionals, distinct from that set out in the SPC. Leo believed it

was of significant value to health professionals to present the numbers and percentages of adverse events of interest rather than broader definitions of 'common, uncommon and rare' adverse events as presented in the SPC and accordingly such information had been provided on the website in relation to the clinical trial data, reflecting Lebwohl M *et al* (2015), as referenced, including data on suicide attempts. However, the text on the website made clear that the safety information presented was not complete; beneath both tables referenced by the complainant, a statement advised health professionals to 'consult the SPC for full details'.

Leo submitted that the complainant's allegation that there was no information on the page to reflect the warnings on suicidal ideation and behaviour from Section 4.4 of the SPC was incorrect. The text below the tables included information regarding suicidality:

> 'In the brodalumab clinical trials programme, there were 6 completed suicides of which 4 were in the psoriasis programme (N= 4,664). The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour and available evidence does not support a causal association between brodalumab and SIB'.

Leo submitted that this statement reflected the first paragraph from Section 4.4 of the SPC, referenced Lebwohl *et al* (2018) and advised the reader to consult the SPC for full details. In these circumstances, the material presented on these webpages, which reflected Lebwohl M *et al* (2015) and Lebwohl *et al* (2018) and directed the reader to the SPC for more complete information, was accurate and not misleading consistent with Clause 7.2 of the Code. It reflected available evidence regarding safety as required by Clause 7.9. In these circumstances Leo did not accept that there had been any breach of Clause 9.1 or Clause 2 of the Code.

PANEL RULING

The Panel noted that the webpage in question was headed 'Safety profile for Kyntheum across phase III trials' and referred to adverse event data from AMAGINE-2 and AMAGINE-3.

The first table was headed 'Adverse events during the induction phase (12 weeks) of the AMAGINE-2 and AMAGINE-3 trials' and gave the incidence of any adverse event, serious adverse event, adverse event leading to study discontinuation and adverse event reported in ≥5%, in the Kyntheum 210mg, ustekinumab and placebo groups, for each individual trial. It also stated beneath the table that one fatal event was reported, cerebral infarction 20 days after last dose.

The second table was headed 'Summary of exposure-adjusted event rate of treatment-emergent adverse events through week 52 of the AMAGINE-2 and AMAGINE-3 trials' and gave the number and exposure-adjusted event rate per 100 patient-years of any adverse event, serious adverse event, fatal event, adverse event leading to study discontinuation, adverse event leading to discontinuation of study drug, Grade 3,4 or 5 adverse event and adverse event of interest in the Kyntheum 210mg and ustekinumab groups, for each individual trial. It also gave further information beneath the table regarding the 6 completed suicides in the Kyntheum clinical trial programme and details of other fatal events.

The Panel noted that Section 4.8 of the Kyntheum SPC (undesirable effects) gave a tabulated list of adverse reactions from clinical trials and post marketing experience.

In the Panel's view, it was not necessarily unacceptable to present safety data from a particular clinical trial or trials, however, the Code required that the promotion of a medicine must not be inconsistent with the particulars listed in its SPC, and therefore, in the Panel's view, the data presented from such trials must not mislead the reader as to the safety profile of the medicine as stated in the SPC.

The Panel noted that the Code required the prescribing information to contain, *inter alia*, a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the SPC, together with a statement that prescribers should consult the SPC in relation to other adverse reactions.

The Panel noted that there was a prominent link to the Kyntheum prescribing information in an orange banner near the top of the webpage in question; the Panel did not have a copy of this prescribing information and Leo made no submission in that regard. Nonetheless, the complainant's allegation was in relation to the information presented in the body of the webpage in question and was not regarding the content of the prescribing information. The Panel noted that the requirements of the Code regarding the content of prescribing information did not necessarily have to be repeated in other sections of the promotional material; much would depend on content, layout, audience and intended use of the material.

The Panel noted Leo's submission that it was of value to health professionals to present the numbers and percentages of adverse events of interest rather than broader definitions of 'common, uncommon and rare' as presented in the SPC and that the information reflected Lebwohl M *et al* (2015), as referenced, including data on suicide attempts. The Panel noted that beneath each table the reader was directed to consult the SPC for full details.

The Panel noted the complainant's allegation that the SPC listed influenza, tinea infections, anaphylactic reaction, diarrhoea, nausea, myalgia, fatigue and conjunctivitis which the complainant alleged had not been included on this safety page and was misleading and misrepresented safety.

The Panel noted that the SPC stated that the most commonly reported adverse reactions in all Kyntheum-treated patients were arthralgia (4.6%), headache (4.3%), fatigue (2.6%), diarrhoea (2.2%), and oropharyngeal pain (2.1%). The first table in the webpage in question listed nasopharyngitis, upper respiratory tract infection, headache and arthralgia as adverse events reported in ≥5% of Kyntheum treated patients in one or both of AMAGINE-2 and AMAGINE-3.

The Panel considered that it was clear from the webpage heading that the safety information presented was from Phase III trials and the subheadings were clear which Phase III clinical studies the adverse event data had been taken from. Beneath both tables it was stated 'please consult the SPC for full details'; whilst it would have been preferable for this statement to have been more explicit that there were other adverse reactions listed in the SPC, the Panel considered, based on the content and layout of the webpage, that a health professional would unlikely be misled that this webpage was a complete list of all Kyntheum adverse reactions.

The Panel considered that whilst it would have been preferable to have also provided the information in Section 4.8 of the SPC on the webpage in question, which included both clinical trials and post marketing experience, the webpage was clear which phase III clinical studies the

adverse event data was from and there was a clear link to prescribing information on that webpage. In the particular circumstances of this case, on balance, the Panel did not consider that the complainant had established that the webpage at issue was inaccurate, misleading or misrepresented the safety of Kyntheum as alleged and no breach of Clauses 7.2 and 7.9 were ruled.

The Panel noted that there were details about completed suicides and suicidal behaviour on the webpage and therefore, on the very narrow allegation that there was no information on the page to reflect the warning on suicidal ideation and behaviour from Section 4.4 of the SPC, the Panel ruled no breach of Clause 7.2.

The Panel consequently ruled no breach of Clauses 9.1 and 2.

Patient Support (August 2020 UK/IE MAT-30820 V2)

43 Black triangle

COMPLAINT

On the 'Patient Safety' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. In addition the black triangle could be seen on the patient support materials.

Leo submitted that the black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

44 Link on page entitled 'visit takectrl.net'

COMPLAINT

A message was displayed 'You are being redirected to takectrl.net Our free web based support programme designed for people living with psoriasis'. The patient support tab stated that the takectrl website was designed only for patients who had been prescribed Kyntheum. This was inconsistent information and was directing people living with psoriasis (these might be a patient

or might be a member of the public) to a post prescription of Kyntheum support website, therefore proactively advertising a prescription only medicine to the public.

When writing to Leo, the Authority asked it to consider the requirements of Clause 26.1.

RESPONSE

Leo did not agree that this link was in breach of the Code. The website was intended only for health professionals, so there would be no patients visiting takectrl.net from the patient support page; the information had been included solely to inform health professionals of the patient support service that was available to patients prescribed Kyntheum. Above the link it stated clearly that 'Only patients who have been prescribed Kyntheum have access to the CTRL website which was password protected. The password can be found on the CTRL leaflet within the patient pack'.

Leo stated that as the pop-up would only be seen by health professionals on the website the text: 'You are being redirected to takectrl.net. Our free web based support programme designed for people living with psoriasis' was appropriate – these readers were health professionals who already knew it was only for Kyntheum patients. The link accessed a password protected page which did not mention Kyntheum. No-one could get access to the site without a patient pack password.

Leo submitted that this webpage did not therefore promote Kyntheum to the public and it denied a breach of Clause 26.1.

PANEL RULING

The Panel noted Leo's submission that the information about the patient support programme was on a website intended only for health professionals and the information was to inform those health professionals of the support that was available to patients prescribed Kyntheum. The Panel noted that above a picture of a hard copy patient support pack it stated, 'The Kyntheum patient pack has been designed to help patients on their treatment journey and includes an information booklet, diary, alert card, calendar and CTRL leaflet. Whether they're looking for more information about their treatment and what to expect, or a way to track progress and document their experience, this pack has something for them'. Beneath the image was the statement 'The pack is given to patients prescribed Kyntheum at their initial dosing appointment' followed by a heading which stated that CTRL was a tailored online support programme designed to help patients feel in control of their treatment; beneath a snapshot of the CTRL website it stated 'Only patients who have been prescribed Kyntheum have access to the CTRL website which is password protected. The password can be found on the CTRL leaflet within the patient pack' followed by a prominent link entitled 'Visit takectrl.net'. The Panel noted Leo's submission that the pop up which appeared when the link was accessed stated: 'You are being redirected to takectrl.net. Our free web based support programme designed for people living with psoriasis'.

The Panel noted from the patient support webpage that the CTRL website was password protected. The Panel considered that whilst it would have been helpful for the pop-up, which re-directed users to the takectrl.net website, to have stated that the CTRL website was only for patients who had been prescribed Kyntheum, the webpage which hosted the link was to inform health professionals only and the link to the CTRL website was password protected; the

password was within the pack given to patients at their initial Kyntheum dosing appointment. Therefore, the Panel considered that the complainant had not established that the takectrl.net website was accessible to the public, nor that a prescription only medicine had been advertised to the public and no breach of Clause 26.1 was ruled.

Resources tab (August 2020 UK/IE MAT-30822 V3)

45 Black triangle

COMPLAINT

On the 'Resources' tab, the black triangle for Kyntheum had not been included next to the brand name anywhere on the page.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page.

Leo submitted that the black triangle was present on the page adjacent to the first mention of the product in line with the requirements of clause 4.10.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the black triangle was adjacent to the first mention of Kyntheum which was within the navigation bar near the top of the webpage at issue. Based on the narrow allegation that the black triangle had not been included next to the brand name anywhere on the page the Panel ruled no breach of Clause 4.10.

46 Link to document entitled 'Summary of NICE guidance' (ref UK/IE MAT-31038 V2)

COMPLAINT

On clicking on this document, an item UK/IE MAT-31038 V2 opens. The document featured a picture of an apparently naked man sitting on an underground train seat between other passengers holding an A3 newspaper which covered his upper thigh to mid chest. The complainant alleged that this image was using nakedness in a social setting to attract attention and was distasteful and did not hold medicines or the health professional audience in special standing.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 9.1 and 9.2.

RESPONSE

Leo did not agree that the image was in breach of the Code. The description provided by the complainant was not an accurate representation of the image on the website. The man was

visible only from the waist up so it was not possible to conclude that he was naked, only that his chest was bare. The newspaper was standard broadsheet size, so considerably bigger than A3.

The complainant appeared to have drawn on comments made by the Panel during consideration of Case AUTH/2982/10/17 (Member of the public vs Leo Pharma). During its consideration of that case the Panel noted that one of the items at issue included 'an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest'. The Panel considered that the subject's nakedness in a social setting was designed to draw attention to the material, queried whether this complied with the supplementary information to Clause 9.1 and requested that Leo's attention be drawn to this matter.

Leo stated that at the time of the previous complaint Kyntheum was not licensed. The imagery was used in internal communication (and clearly marked 'For internal use only'). Leo gave considerable thought to the subsequent use of this imagery in promotion and considered that a cropped version of the image would eliminate the concern about nakedness whilst still expressing the message of the campaign – that skin clear of psoriasis improved confidence, potentially giving the confidence for a man to bare his chest in a social setting. In this context, Leo Pharma believed that the link between clear skin (both for psoriasis and other chronic inflammatory skin conditions) and confidence was well established and widely recognised.

Leo submitted that the Panel had acknowledged in Case AUTH/2982/10/17 that it was acceptable to show bare skin when advertising prescription medicines so long as the image was relevant and complied with the Code (ie recognised the special nature of medicines and the professional audience, and was not for the purpose of attracting attention to the material), and that the quality and appearance of a patient's skin was relevant to Kyntheum. The Panel had previously decided that improving the confidence of psoriasis patients could be justification for an advertising campaign showing an individual who was undressed in a social setting (Case AUTH/2304/3/10 Doctor vs Forest Laboratories). Plaque psoriasis could occur anywhere on the body, so an image of a partially undressed individual was directly relevant to the disease and contributed to the overall message of clearance improving confidence.

Leo submitted that the image presented a man with the confidence to expose his skin in public following clearance of his psoriasis. The image was not sexual and the approach was justified in the context of the condition and treatment under consideration. Leo stated that it considered this recognised the special nature of medicines and the professional standing of the audience, was not likely to cause serious or widespread offence, and did not fail to maintain high standards and it denied a breach of Clauses 9.1 and 9.2.

PANEL RULING

The Panel noted that the image within the document in question was a vertically cropped version of the image at Point 3 above. The Panel noted its comments and rulings at Point 3 above and considered that they were relevant here; in line with these rulings, the Panel therefore ruled no breach of Clauses 9.1 and 9.2.

47 Claim 'Confidence Starts With Clearance' within the Summary of NICE Guidance document (ref UK/IE MAT-31038 V2)

COMPLAINT

Beside the image of the naked man in Point 46, there was a claim 'Confidence Starts With Clearance'. This claim was unreferenced. The statement was incomplete so it was impossible to know if it could be verified or not. The complainant stated that he/she had been unable to locate any studies in which Kyntheum provided 100% clearance as the word 'clearance' would imply, and a change in confidence to emerge in this study population as a result.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that the claim was in breach of the Code. The Code required that when promotional material referred to published studies, clear references must be given (Clause 7.6). This claim did not refer to published studies so no reference was required.

Leo submitted that the claim '(Kyntheum) confidence starts with clearance' related to the effect of skin clearance on quality of life. Quality of life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence. A paper by Warren *et al* (2021) analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI (Psoriasis Area Severity Index) response level and DLQI 0/1 achievement ($P<0.0001$).

Leo submitted that the meaning of 'clearance' in the context of psoriasis was not widely understood to mean 100% clearance. The dermatology healthcare community and clinical research studies specifically referred to Complete Skin Clearance (CSC) if all lesions were resolved. It was accepted that below CSC, there were varying degrees of clearance, defined as 'partial clearance' – this might be a reduction in lesions overall, or on a particular part of the body. (In any event and for completeness, there were data to support complete clearance of psoriasis following treatment with Kyntheum. This was presented in the graph of PASI responses at 12 weeks vs ustekinumab (Lebwohl M *et al* 2015) in the AMAGINE 2 and AMAGINE 3 analysis which showed that 37-44% of patients on Kyntheum achieved PASI 100.)

Leo submitted that the claim was therefore substantiable, not misleading and references were not required and it denied a breach of Clauses 7.2, 7.4 or 7.6.

PANEL RULING

The Panel considered that its comments and rulings at Points 4 and 25 above, for which the Panel ruled upon the claim 'Confidence Starts With Clearance', based on the similar very narrow allegation, were also relevant here and the Panel therefore ruled no breach of Clauses 7.2, 7.4 and 7.6.

48 Black triangle on 'Summary of NICE guidance' document (ref UK/IE MAT-31038 V2)

COMPLAINT

The complainant alleged that the black triangle had not been listed next to the first mention of the brand name on this digital item, as required by the Code.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page.

Leo submitted that the black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted its comments at Point 45 in relation to the resources webpage which hosted the link to the summary of NICE guidance document. The Panel noted, as stated on the webpage, that the summary of NICE guidance document could be downloaded and therefore it was considered as a separate digital item.

The Panel noted that the material at issue was entitled 'Summary of NICE guidance for treating severe plaque psoriasis with Kyntheum' beneath which was an image overlaid with, *inter alia*, the Kyntheum logo which had the black triangle. The mention of Kyntheum within the logo was the most prominent mention but not the first mention of the product name within the material.

The Panel noted that the supplementary information to Clause 4.10 stated that in digital communications the black triangle symbol should be located adjacent to the first mention of the product as this was ***likely to be considered*** the most prominent display of the name of the product (emphasis added).

The Panel noted that in the summary of NICE guidance document, whilst the black triangle did not appear adjacent to the first mention of Kyntheum in the heading, it had appeared next to the most prominent display of the product name which was in the logo, which was directly beneath the product name within the heading, and, in the Panel's view, the name of the product in this logo was more prominent than in the document heading and therefore, on balance, the Panel considered that the requirements of Clause 4.10 had been met and ruled no breach.

49 Reproduction of NICE guidance

COMPLAINT

The complainant alleged that reproductions of official documents must not be used for promotional purposes unless permission had been given by the body. This promotional item reproduced NICE guidance however NICE prohibit the reproduction of their guidance for promotional use.

When writing to Leo, the Authority asked it to consider the requirements of Clause 9.6.

RESPONSE

Leo did not agree that this item was in breach of the Code. It was not a reproduction of the NICE guidance on Kyntheum, it was a summary of the content of the guidance. The guidance was in the public domain and, provided the summary met the Code quality standards, it was acceptable for Leo Pharma to produce it and share it with health professionals. Leo denied a breach of Clause 9.6 of the Code.

PANEL RULING

The Panel noted that Clause 9.6 stated that reproductions of official documents must not be used for promotional purposes unless permission had been given in writing by the appropriate body.

The Panel considered that it was clear that the summary document had been created by Leo and that this was Leo promotional material; the Leo corporate logo was featured on the material which also contained prescribing information. The Panel did not consider that summarising NICE recommendations in promotional material meant that an official document had been reproduced as prohibited by Clause 9.6. The Panel ruled no breach of Clause 9.6 in that regard.

50 Claim 'When compared indirectly it appears to be as effective as other anti-leukin-17 agents'

COMPLAINT

The complainant alleged that claims and statements had been made under the heading 'NICE has issued the following recommendation' which could not be used or substantiated in a promotional sense in accordance with the Code. For example, an indirect comparison was made with other products but no explanation was made as to how this comparison was made nor was it appropriate to make such comparisons in promotion 'When compared indirectly it appears to be as effective as other anti-leukin-17 agents'. This was NICE's opinion and there was no data available against other IL-17 agents for the company to promote this. It was one thing for NICE to mention this, it was an entirely different matter when a pharmaceutical company with an IL-17 repeated it on a promotional website.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.4.

RESPONSE

Leo did not agree that this item was in breach of the Code. The content of this webpage was an accurate summary of the NICE guidance on brodalumab (Kyntheum) issued to the NHS and published on NICE's website.

Leo submitted that the reference to an 'indirect comparison' referred to a network meta-analysis, comparing brodalumab with adalimumab, apremilast, dimethyl fumarate, etanercept, infliximab, secukinumab and ustekinumab using data from 59 trials (28,346 patients) and considered by NICE's Appraisal Committee for the purposes of guidance. This 'base case' analysis showed

that brodalumab had the second highest probability after ixekizumab of achieving a PASI 75 response. In addition, 5 sensitivity analyses incorporating different modelling assumptions were provided to NICE. NICE's Evidence Review Group (ERG) preferred a 'placebo-adjusted' version of the network meta-analysis, which took into account the wide variation in response rates in the placebo groups of 49 trials included in the meta-analysis. This analysis resulted in the same treatment rankings as the unadjusted base-case analysis. NICE's Appraisal Committee concluded that, with the ERG's adjustment, brodalumab remained ranked among the top few treatments in terms of PASI response rate.

Leo submitted that the information presented in this section of the website accurately reflected the fact and substance of NICE conclusions and recommendations for brodalumab. The text was not misleading and could be substantiated by NICE's guidance. Leo denied a breach of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that the brodalumab Nice Guidance TA511 (2018) stated 'When compared indirectly, it appears to be as effective as other anti-interleukin-17 agents' which was beneath the heading 'Why the committee made these recommendations'.

The Panel noted Leo's submission that the reference to an 'indirect comparison' referred to a network meta-analysis, comparing brodalumab with adalimumab, apremilast, dimethyl fumarate, etanercept, infliximab, secukinumab and ustekinumab using data from 59 trials (28,346 patients) and considered by NICE's Appraisal Committee for the purposes of guidance.

The Panel noted that Leo's NICE summary document quoted the NICE guidance which referred to brodalumab appearing to be as effective as other anti-interleukin-17 agents when compared indirectly. In the Panel's view, there was no misleading implication that a direct comparison had been made and the Panel considered that the complainant had not established that the claim within the material at issue was misleading or incapable of substantiation in that regard and no breach of Clauses 7.2 and 7.4 were ruled.

51 Link to document entitled 'Summary of SMC guidance' (UK/IE MAT-31039 V2)
COMPLAINT

On clicking on this document, an item UK/IE MAT-31039 V2 opened. The complainant alleged that the document featured a picture of an apparently naked man sitting on an underground train seat between other passengers holding an A3 newspaper which covered his upper thigh to mid chest. This image was using nakedness in a social setting to attract attention and was distasteful and did not hold medicines or the health professional audience in special standing.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 9.1 and 9.2.

RESPONSE

Leo did not agree that the image was in breach of the Code. The description provided by the complainant was not an accurate representation of the image on the website. The man was visible only from the waist up so it was not possible to conclude that he was naked, only that his chest was bare. The newspaper was standard broadsheet size, so considerably bigger than A3.

Leo submitted that the complainant appeared to have drawn on comments made by the PMCPA during consideration of Case AUTH/2982/10/17 (Member of the public vs Leo Pharma). During its consideration of that case the Panel noted that one of the items at issue included 'an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest'. The Panel considered that the subject's nakedness in a social setting was designed to draw attention to the material, queried whether this complied with the supplementary information to Clause 9.1 and requested that Leo's attention be drawn to this matter.

Leo submitted that at the time of the previous complaint Kyntheum was not licensed. The imagery was used in internal communication (and clearly marked 'For internal use only'). Leo gave considerable thought to the subsequent use of this imagery in promotion and considered that a cropped version of the image would eliminate the concern about nakedness whilst still expressing the message of the campaign – that skin clear of psoriasis improved confidence, potentially giving the confidence for a man to bare his chest in a social setting. In this context, Leo Pharma believed that the link between clear skin (both for psoriasis and other chronic inflammatory skin conditions) and confidence was well established and widely recognised.

The Panel had acknowledged in AUTH/2982/10/17 that it was acceptable to show bare skin when advertising prescription medicines so long as the image was relevant and complied with the Code (ie recognised the special nature of medicines and the professional audience, and was not for the purpose of attracting attention to the material), and that the quality and appearance of a patient's skin was relevant to Kyntheum. The Panel had previously decided that improving the confidence of psoriasis patients could be justification for an advertising campaign showing an individual who was undressed in a social setting (Case AUTH/2304/3/10 Doctor vs Forest Laboratories). Plaque psoriasis could occur anywhere on the body, so an image of a partially undressed individual was directly relevant to the disease and contributed to the overall message of clearance improving confidence.

Leo submitted that the image presented a man with the confidence to expose his skin in public following clearance of his psoriasis. The image was not sexual and the approach was justified in the context of the condition and treatment under consideration. Leo considered this recognised the special nature of medicines and the professional standing of the audience, was not likely to cause serious or widespread offence, and did not fail to maintain high standards and denied a breach of Clauses 9.1 and 9.2.

PANEL RULING

The Panel noted that this was the same image as in Point 46.

The Panel noted its comments and rulings at Point 46 and ruled no breach of Clauses 9.1 and 9.2.

52 Claim 'Confidence Starts With Clearance'

COMPLAINT

Beside the image of the naked man in Point 51, there was a claim 'Confidence Starts With Clearance'. This claim was unreferenced. The statement was incomplete so it was impossible

to know if it could be verified or not. The complainant stated that he/she had been unable to locate any studies in which Kyntheum provided 100% clearance as the word 'clearance' would imply, with a change in confidence to emerge in this study population as a result.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo stated that it did not agree that the claim was in breach of the Code. The Code required that when promotional material referred to published studies, clear references must be given (Clause 7.6). This claim did not refer to published studies so no reference was required.

Leo submitted that the claim '(Kyntheum) confidence starts with clearance' related to the effect of skin clearance on quality of life. Quality of life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence. A paper by Warren *et al* (2021) analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement ($P<0.0001$).

Leo submitted that the meaning of 'clearance' in the context of psoriasis was not broadly understood to mean 100% clearance by healthcare practitioners. The dermatology healthcare community and clinical research studies specifically referred to Complete Skin Clearance (CSC) if all lesions were resolved. It was accepted that below CSC, there were varying degrees of clearance, defined as 'partial clearance – this might be a reduction in lesions overall, or on a particular part of the body. In any event and for completeness, there were data to support complete clearance of psoriasis following treatment with Kyntheum. This was presented in the graph of PASI responses at 12 weeks vs ustekinumab (Lebwohl M *et al* 2015) in the AMAGINE 2 and AMAGINE 3 analysis which showed that 37-44% of patients on Kyntheum achieved PASI 100.

Leo submitted that the claim was therefore substantiable, not misleading, references were not required and denied a breach of Clauses 7.2, 7.4 or 7.6.

PANEL RULING

The Panel considered that its comments and rulings at Points 4, 25 and 47 above, for which the Panel ruled upon the claim 'Confidence Starts With Clearance', based on the similar very narrow allegation, were also relevant here and the Panel therefore ruled no breach of Clauses 7.2, 7.4 and 7.6.

53 Black triangle on document in Point 51 'Summary of SMC guidance' (UK/IE MAT-31039 V2)

COMPLAINT

The black triangle had not been listed next to the first mention of the brand name on this digital item, as required by the Code.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.10.

RESPONSE

Leo did not agree that this page was in breach of the Code. The black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. The black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted its comments at Point 45 in relation to the resources webpage which hosted the link to the summary of SMC guidance document. The Panel noted, as stated on the webpage, that the summary of SMC guidance document could be downloaded and therefore it was considered as a separate digital item.

The Panel noted that the material at issue was entitled 'Summary of SMC guidance for treating moderate to severe plaque psoriasis with Kyntheum' beneath which was an image overlaid with, *inter alia*, the Kyntheum logo which had the black triangle. The mention of Kyntheum within the logo was the most prominent mention but not the first mention of the product name within the material.

The Panel noted that the supplementary information to Clause 4.10 stated that in digital communications the black triangle symbol should be located adjacent to the first mention of the product as this was ***likely to be considered*** the most prominent display of the name of the product (emphasis added).

The Panel noted that in the summary of SMC guidance document, whilst the black triangle did not appear adjacent to the first mention of Kyntheum in the heading, it had appeared next to the most prominent display of the product name which was in the logo, which was directly beneath the product name within the heading, and, in the Panel's view, the name of the product in this logo was more prominent than in the document heading and therefore, on balance, the Panel considered that the requirements of Clause 4.10 had been met and ruled no breach.

54 Reproduction of SMC guidance

COMPLAINT

The complainant alleged that reproductions of official documents must not be used for promotional purposes unless permission had been given by the body. This promotional item reproduced SMC guidance however SMC prohibit the reproduction of their guidance for promotional use.

When writing to Leo, the Authority asked it to consider the requirements of Clause 9.6.

RESPONSE

Leo did not agree that this item was in breach of the Code. It was not a reproduction of the SMC guidance on Kyntheum, it was a summary of the content of the guidance. The guidance was in the public domain and, in Leo's view, provided the summary met the Code quality standards, it was acceptable for the company to produce it and share it with health professionals. Leo denied a breach of Clause 9.6 of the Code.

PANEL RULING

The Panel noted that Clause 9.6 stated that reproductions of official documents must not be used for promotional purposes unless permission had been given in writing by the appropriate body.

The Panel considered that it was clear that the summary document had been created by Leo and that this was Leo promotional material; the Leo corporate logo was featured on the material which also contained prescribing information. The Panel did not consider that summarising SMC guidance in promotional material meant that an official document had been reproduced as prohibited by Clause 9.6. The Panel ruled no breach of Clause 9.6 in that regard.

55 Claim 'Brodalumab was superior to placebo and to an alternative interleukin inhibitor at improving symptoms in adults with moderate to severe plaque psoriasis'

COMPLAINT

The complainant alleged that this promotional claim did not provide any information on the study design, which symptoms and what level of improvement was being claimed and it lacked statistical analysis or information on the comparator drug to support this claim. The SMC could make these statements but Leo could not make such claims in a promotional context for the reasons outlined.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.4.

RESPONSE

Leo did not agree that this item was in breach of the Code. Leo submitted that the content of this webpage was an accurate summary of SMC guidance on brodalumab (Kyntheum) which was in the public domain. Referencing SMC guidance was allowed provided the summary met Code standards. In order to ensure that SMC's conclusions were accurately reported, Leo used the same wording in the summary. This stated 'Brodalumab was superior to placebo and to an alternative interleukin inhibitor…' This statement was correctly referenced on the website to SMC's guidance, where the detailed advice might be accessed, including information regarding the clinical evidence from AMAGINE-2 and AMAGINE-3. A link was provided at the bottom of the webpage to facilitate access to SMC's guidance.

Leo stated that it had provided an accurate summary of SMC's guidance on brodalumab as it was presented on the SMC website. The claim that SMC confirmed superiority of brodalumab vs placebo and an alternative interleukin inhibitor was factually correct and could be substantiated (Kyntheum SPC; Lebwohl M *et al* 2015). Leo denied a breach of Clauses 7.2 or 7.4 of the Code.

PANEL RULING

The Panel noted that the material at issue was a summary of the SMC guidance on Kyntheum together with Kyntheum claims and prescribing information. The SMC summary was brief and stated:

> 'The Scottish Medicines Consortium (SMC) has issued the following advice: Brodalumab (Kyntheum) is accepted for restricted use within NHS Scotland.
>
> - Indication under review: For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.
> - SMC restriction: For patients who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contra-indication to these treatments.
>
> Brodalumab was superior to placebo and to an alternative interleukin inhibitor at improving symptoms in adults with moderate to severe plaque psoriasis.
>
> This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of brodalumab. It is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.'

The Panel noted that this summary was similar to the summary on the first page of the SMC guidance document, however, the SMC guidance document provided a detailed summary of the AMAGINE-2 and AMAGINE-3 trials on subsequent pages. The Panel noted that the claim at issue was on the second page of the summary document produced by Leo. Whilst Leo's summary document cited the SMC guidance with a URL link, in small typeface, within the references section at the bottom of the first and second pages, the Panel noted that Leo's summary document did not direct the reader to view the SMC guidance nor did it provide any information, such as identifying the active comparator, to provide any meaningful context to the claim 'Brodalumab was superior to placebo and to an alternative interleukin inhibitor at improving symptoms in adults with moderate to severe plaque psoriasis'. The Panel considered that the claim within the context of the material at issue was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and a breach of Clause 7.2 was ruled.

The Panel considered that the complainant had not established that the claim in question was incapable of substantiation and no breach of Clause 7.4 was ruled.

APPEAL BY LEO

Leo submitted that the information reflecting the SMC's summary of its advice relating to brodalumab did not constitute a breach of Clause 7.2. A copy of the pages from the website referencing the SMC's advice was provided. The statement identified by the complainant was taken from a webpage that paraphrased the complete summary of the SMC's advice. This was headed 'Summary of SMC Guidance for treating moderate to severe plaque psoriasis with Kyntheum'. The restrictions on use as advised by the SMC were set out in full and the statement accurately reflected the SMC summary. The webpage and the statement at issue

were not presented as a single standalone claim, but as evidence of the fact that SMC had reached the conclusions presented in the summary regarding the product. The statement was explicitly attributed to SMC, the content of the summary was appropriately presented in its entirety and any attempt to expand upon this, or otherwise to revise the summary prepared by SMC, would have been misleading and inappropriate.

Leo submitted that the statement of the SMC's summary advice was referenced and, while the Panel stated that this was in small typeface, there was no suggestion that the reference was not clearly legible. In these circumstances, Leo submitted it was not correct to say that there was no direction to readers to view the complete SMC advice, particularly given the fact that access to the complete advice was facilitated by provision of the URL on the website.

In summary, Leo submitted that the statement was plainly represented as conclusions of the SMC, with a clear invitation to any reader to access the full SMC advice on brodalumab should they wish to do so. Leo did not agree that, taken in its entirety, the information was not sufficiently complete to allow a reader to form a view on the therapeutic value of the medicine.

APPEAL BOARD RULING

The Appeal Board noted that Leo's summary of SMC guidance for treating moderate to severe plaque psoriasis with Kyntheum was brief and stated:

> **'The Scottish Medicines Consortium (SMC) has issued the following advice:** Brodalumab (Kyntheum) is accepted for restricted use within NHS Scotland.
>
> - **Indication under review**: For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.
> - **SMC restriction**: For patients who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contra-indication to these treatments.
>
> **Brodalumab** was superior to placebo and to an alternative interleukin inhibitor at improving symptoms in adults with moderate to severe plaque psoriasis.
>
> This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of brodalumab. It is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.'

The Appeal Board noted that this summary was similar to the summary on the first page of the SMC guidance document which also did not name the comparator. However, the SMC guidance document provided a detailed summary of the AMAGINE-2 and AMAGINE-3 trials on subsequent pages.

The Appeal Board considered that, on the balance of probabilities, readers would know to visit the SMC website to get the full SMC guidance and readers could follow the link within the references section at the bottom of the first and second pages of the Leo material at issue to reach the full SMC guidance document which named the comparator in the registration trials.

The Appeal Board considered, on balance, that the claim 'Brodalumab was superior to placebo and to an alternative interleukin inhibitor at improving symptoms in adults with moderate to severe plaque psoriasis' within the context of the particular material at issue was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and no breach of Clause 7.2 was ruled. The appeal on this point was successful.

Kyntheum at a glance tab (MAT-21384 May 2019)

56 Picture of an apparently naked man

COMPLAINT

The complainant alleged that in the 'Kyntheum at a glance' tab, there was a picture of an apparently naked man sitting on an underground train seat between other passengers holding an A3 newspaper which covered his upper thigh to mid chest. This image was using nakedness in a social setting to attract attention and was distasteful and did not hold medicines or the health professional audience in special standing.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 9.1 and 9.2.

RESPONSE

Leo did not agree that the image was in breach of the Code. The description provided by the complainant was not an accurate representation of the image on the website. The man was visible only from the waist up so it was not possible to conclude that he was naked, only that his chest was bare. The newspaper was standard broadsheet size, so considerably bigger than A3.

Leo submitted that the complainant appeared to have drawn on comments made by the Panel during consideration of Case AUTH/2982/10/17 (Member of the public vs Leo Pharma). During its consideration of that case the Panel noted that one of the items at issue included 'an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest'. The Panel considered that the subject's nakedness in a social setting was designed to draw attention to the material, queried whether this complied with the supplementary information to Clause 9.1 and requested that Leo's attention be drawn to this matter.

Leo submitted that at the time of the previous complaint Kyntheum was not licensed. The imagery was used in internal communication (and clearly marked 'For internal use only'). Leo gave considerable thought to the subsequent use of this imagery in promotion and considered that a cropped version of the image would eliminate the concern about nakedness whilst still expressing the message of the campaign – that skin clear of psoriasis improved confidence, potentially giving the confidence for a man to bare his chest in a social setting. In this context, Leo believed that the link between clear skin (both for psoriasis and other chronic inflammatory skin conditions) and confidence was well established and widely recognized.

Leo submitted that the Panel had acknowledged in Case AUTH/2982/10/17 that it was acceptable to show bare skin when advertising prescription medicines so long as the image was relevant and complied with the Code (ie recognised the special nature of medicines and the professional audience, and was not for the purpose of attracting attention to the material), and

that the quality and appearance of a patient's skin was relevant to Kyntheum. The Panel had previously decided that improving the confidence of psoriasis patients could be justification for an advertising campaign showing an individual who was undressed in a social setting (Case AUTH/2304/3/10 Doctor vs Forest Laboratories). Plaque psoriasis could occur anywhere on the body, so an image of a partially undressed individual was directly relevant to the disease and contributes to the overall message of clearance improving confidence.

Leo submitted that the image presented a man with the confidence to expose his skin in public following clearance of his psoriasis. The image was not sexual and the approach was justified in the context of the condition and treatment under consideration. Leo stated that it considered this recognised the special nature of medicines and the professional standing of the audience, was not likely to cause serious or widespread offence, and did not fail to maintain high standards and it denied a breach of Clauses 9.1 and 9.2.

PANEL RULING

The Panel noted that the image in question was similar to that as described in Point 3 above, however the image in question appeared to have been cropped horizontally and overlaid with a pack shot of Kyntheum and therefore even less bare skin was visible in comparison to the image at Point 3.

The Panel noted its comments and rulings at Point 3 which it considered were relevant here and therefore ruled no breach of Clauses 9.1 and 9.2.

57 Claim 'Confidence Starts With Clearance'

COMPLAINT

Beside this image of the naked man, there was a claim 'Confidence Starts With Clearance'. This claim was unreferenced. The statement was incomplete so it was impossible to know if it could be verified or not. The complainant stated that he/she had been unable to locate any studies in which Kyntheum provided 100% clearance as the word 'clearance' would imply, and a change in confidence to emerge in this study population as a result.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that the claim was in breach of the Code. The Code required that when promotional material referred to published studies, clear references must be given (Clause 7.6). This claim did not refer to published studies so no reference was required.

Leo submitted that the claim '(Kyntheum) confidence starts with clearance' related to the effect of skin clearance on quality of life. Quality of life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence. A paper by

Warren *et al* (2021) analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (P<0.0001).

Leo submitted that the meaning of 'clearance' in the context of psoriasis was not broadly understood to mean 100% clearance by healthcare practitioners. The dermatology healthcare community and clinical research studies specifically referred to Complete Skin Clearance (CSC) if all lesions were resolved. It was accepted that below CSC, there were varying degrees of clearance, defined as 'partial clearance' – this might be a reduction in lesions overall, or on a particular part of the body. (In any event and for completeness, there were data to support complete clearance of psoriasis following treatment with Kyntheum. This was presented in the graph of PASI responses at 12 weeks vs ustekinumab (Lebwohl M *et al* 2015) in the AMAGINE 2 and AMAGINE 3 analysis which showed that 37-44% of patients on Kyntheum achieved PASI 100.)

Leo submitted that the claim was therefore substantiable, not misleading, references were not required and it denied a breach of Clauses 7.2, 7.4 or 7.6.

PANEL RULING

The Panel considered that its comments and rulings at Points 4, 25, 47 and 52 above, for which the Panel ruled upon the claim 'Confidence Starts With Clearance', based on the similar very narrow allegation, were also relevant here and the Panel therefore ruled no breach of Clauses 7.2, 7.4 and 7.6.

58 Claim 'Complete clearance with Kyntheum induction was sustained through to one year'

COMPLAINT

An SPC from September 2017 was cited to support this. This was not the latest version of the SPC and therefore an out-of-date reference had been used. The SPC did not make this statement anyway and the information was therefore misleading.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.4.

RESPONSE

Leo submitted that, unfortunately, in this instance, an error had occurred with the process of uploading the correct document to the live website. Both the reviewed and approved document on PromoMats and the 'Pre-Live' document on the website staging platform (which was used by Leo for final form certification) showed the correct SPC (last accessed March 2020). However, the live version of the webpage included in error a reference to the SPC of September 2017 as noted by the complainant. Leo stated that it was continuing to work with its global Leo IT colleagues and its external partner agencies to ensure this did not occur in future. Leo therefore agreed that a breach of Clause 14.1 had occurred, as material had been presented on the website which did not reflect that certified.

Leo stated that all versions of the SPC had contained data relating to PASI 100 results, which equated to complete skin clearance. In Figure 1 of both the 2017 SPC and the current SPC

(2020) within Section 5.1, a graph illustrated the percentage of patients reaching PASI 100 at 12 weeks (41.6%) and at 52 weeks (51.0%), demonstrating that complete skin clearance (PASI 100) was sustained through to one year. Leo submitted that the reference therefore supported the claim and was not in breach of Clauses 7.2 or 7.4.

Following a request for further information, Leo submitted that the March 2020 version of this webpage was not published online and that since this was one of a number of discrepancies noted with this case in relation to Clause 14.1, Leo wanted to gain more clarity before making a decision about a voluntary admission.

PANEL RULING

The Panel noted Leo's submission that the 2017 SPC was referenced instead of the 2020 SPC in error.

The Panel further noted Leo's submission that in Figure 1 of both the 2017 and 2020 Kyntheum SPCs, within Section 5.1, a graph illustrated the percentage of patients reaching PASI 100 at 12 weeks (41.6%) and at 52 weeks (51.0%) which according to Leo demonstrated that complete skin clearance (PASI 100) was sustained through to one year.

Whilst concerned that the incorrect SPC had been referenced, the Panel considered, based on the narrow allegation, that the complainant had not established that the claim in question was misleading or incapable of substantiation as alleged and no breach of Clauses 7.2 and 7.4 were ruled.

59 Series of clinical images

COMPLAINT

A series of clinical images at baseline, 4 weeks, 12 weeks, 24 weeks and 52 weeks had been included. The complainant alleged that there was no clinical measurement or context as to how these results changed over time and therefore the information supporting the images was incomplete for the reader to decide how important they were. The SPC only recommended treatment beyond 16 weeks in some patients with initial partial response who might subsequently improve and this had not been clarified.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 9.1.

RESPONSE

Leo did not agree that this item was in breach of the Code. Below the images was a clear statement which explained that these are: 'For illustrative purposes only. These images provide a look at Kyntheum impact on one particular patient in the AMAGINE-1 study and do not necessarily represent the results experienced by all patients'.

Leo submitted that the complainant had misinterpreted the SPC for Kyntheurm. Section 4.2 of the SPC stated:

'Posology

> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
> Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'

Leo submitted that there was accordingly no limit on the duration of use of Kyntheum. Discontinuation after 12-16 weeks was only recommended for those who had not responded to treatment. The guidance about continuation in patients with initial partial response was included to indicate that some of these patients might achieve better results with longer treatment. It did not mean that this was the only patient group that could continue treatment beyond 16 weeks.

Leo stated that Section 5.1 of the SPC described the use of Kyntheum in the clinical trial programme up to 52 weeks as this was the analysis presented in the submission for marketing authorisation. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for longer periods was not inconsistent with the SPC.

Leo submitted that these images together with the accompanying text, were not therefore inconsistent with the SPC, they were accurate and not misleading. Their use did not represent a failure to maintain high standards and Leo denied a breach of Clauses 3.2, 7.2, 7.4 or 9.1 the Code.

PANEL RULING

The Panel noted that below the claim at Point 58 ('Complete clearance with Kyntheum induction was sustained through to one year') was a series of 5 images showing a patient's legs at baseline, 4 weeks, 12 weeks, 24 weeks and 52 weeks accompanied by the statement 'For illustrative purposes only. These images provide a look at Kyntheum impact on one particular patient in the AMAGINE-1 study and do not necessarily represent the results experienced by all patients', in small font below the images.

The Panel considered that the claim 'complete clearance with Kyntheum induction was sustained through to one year', which was directly above the series of images in question, added to the ambiguity regarding clinical context as it had not been made clear that Kyntheum was administered once every two weeks throughout the 52 weeks and not just during induction. However, the Panel noted that Kyntheum was intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

The Panel noted that the Kyntheum SPC referred to three Phase 3 studies (AMAGINE-1, AMAGINE-2 and AMAGINE 3) and stated that all three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension. The Panel noted that the SPC reported PASI 100 results during induction and maintenance up to week 52 from a pooled analysis of AMAGINE-2 and AMAGINE-3.

In the Panel's view, as the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, the complainant had not established that the promotion of clearance up to 52 weeks was inconsistent with the SPC as alleged and the Panel ruled no breach of Clause 3.2 in that regard.

The Panel noted that whilst some study details from AMAGINE-2 and AMAGINE-3 were given further down the webpage in the form of a graph, accompanied by a claim that 51% of patients achieved PASI 100 at 1 year with Kyntheum, there appeared to be no details regarding AMAGINE-1, which this series of patient images was stated to have been taken from.

However, whilst the Panel considered that additional information regarding the details of AMAGINE-1 on the webpage in question would have been helpful, based on the very narrow allegation that there was no clinical measurement or context as to how these results changed over time, the Panel considered that the complainant had not established that the series of images, which were labelled as being at baseline, 4 weeks, 12 weeks, 24 weeks and 52 weeks, beneath the claim 'complete clearance with Kyntheum induction was sustained through to one year', on the webpage in question, was misleading as alleged and based on the complainant's very narrow allegation no breach of Clause 7.2 was ruled. The Panel consequently ruled no breach of Clause 9.1.

60 Safety and tolerability information

COMPLAINT

The complainant alleged that the 'Safety & Tolerability' information on this page presented a number of issues. The title of the piece had an asterisk to state that this section had been restricted to 'Pooled data from AMAGINE-1, AMAGINE-2 and AMAGINE-3'. This restricted presentation of data did [not] reflect the currently available safety information as per the SPC for Kyntheum and misrepresented the safety aspects of this product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.9 and 9.1.

RESPONSE

Leo did not agree that this webpage was in breach of the Code. The Safety section of this part of the website presented the safety profile for Kyntheum across the Phase III studies – AMAGINE-2 and AMAGINE-3 (Lebwohl M *et al* 2015). The page in question was made clear that the information represented pooled data from the two trials and the tables accurately reflected the findings of those two studies.

Leo submitted that the Phase III trial data provided robust safety information in the context of the focus of this section of the website - Kyntheum at a glance, which aimed to summarise the most common or important adverse events. The fact that the data were limited to the clinical trials was clearly stated and the SPC was referenced.

Leo submitted that in circumstances where this section of the website was explicitly characterised as a summary, and where the SPC was referenced, Leo did not believe that the webpage was misleading contrary to Clause 7.2 or failed to meet the requirements of Clause 7.9. In these circumstances Leo did not accept that there had been any breach of Clause 9.1 or Clause 2 of the Code.

PANEL RULING

In the Panel's view, it was not necessarily unacceptable to present safety data from a particular clinical trial or trials, however, the Code required that the promotion of a medicine must not be inconsistent with the particulars listed in its SPC, and therefore the data presented from such trials must not mislead the reader as to the safety profile of the medicine as stated in the SPC.

The Panel noted that the section titled 'Safety and Tolerability' on the 'at a glance' webpage in question included an asterisk which took the reader to a footnote which stated 'Pooled data from AMAGINE-1, AMAGINE-2 and AMAGINE-3 (210mg Q2W [every two weeks]) N=1,496, placebo, N=879 in very small font below the list of bullet points; however, the Panel noted that, not all of the bullet points were in relation to these three clinical trials. For example, the first bullet point was a statement about adverse reactions from Section 4.8 of the SPC which included data from clinical trials and post marketing experience.

Whilst the Panel disagreed with Leo's submission that the fact that the data were limited to the clinical trials was clearly stated, the Panel nonetheless did not consider that the complainant had made out his/her complaint as to why he/she considered that the information in the safety and tolerability section of this at a glance webpage did not reflect the safety information in the SPC for Kyntheum or misrepresented the safety of the medicine. It was not for the Panel to infer reasons to support a complainant's complaint and therefore the Panel ruled no breach of Clauses 2, 7.9 and 9.1.

61 Claim 'The most commonly reported adverse reactions reporter [sic] in all Kyntheum treated arthralgia (4.6%), headache (3.1%), fatigue (2.6%), diarrhoea (2.2%) and oropharyngeal pain (2.1%)'

COMPLAINT

In the SPC, influenza, tinea infections, nausea, myalgia, fatigue and injection site reactions were all listed as having a 'Common' frequency but had been omitted from the information provided. The complainant alleged that this was misleading and did not present a balanced view of safety.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.9 and 9.1.

RESPONSE

Subject to allegation 63 below, Leo did not agree that this webpage was in breach of the Code.

Leo submitted that the safety section of this part of the website presented the safety profile for Kyntheum across the Phase III studies – AMAGINE-2 and AMAGINE-3 (Lebwohl M *et al* 2015). The page in question made clear that the information represented pooled data from the two trials and the statements accurately reflected the findings of the two studies. The Phase III data provided the most robust safety data in the context of the focus of this section of the website - Kyntheum at a glance, intended to summarise the most common or important adverse events from the clinical trials. The fact that the data were limited to the clinical trials was clearly stated and the SPC was referenced.

Leo stated that in circumstances where this section of the website was explicitly characterised as a summary, and where the SPC was referenced, Leo did not believe the webpage was misleading contrary to Clause 7.2 or failed to meet the requirements of Clause 7.9. In these

circumstances Leo did not accept that there had been any breach of Clause 9.1 or Clause 2 of the Code.

PANEL RULING

The Panel noted, contrary to the complainant's allegation, that the claim in question on the webpage stated: 'The most commonly reported adverse reactions in all Kyntheum-treated arthralgia (4.6%), headache (4.3%), fatigue (2.6%), diarrhoea (2.2%) and oropharyngeal pain (2.1%)'which was consistent with the Kyntheum SPC which stated:

> 'Summary of the safety profile
> The most commonly reported adverse reactions in all Kyntheum-treated patients were arthralgia (4.6%), headache (4.3%), fatigue (2.6%), diarrhoea (2.2%), and oropharyngeal pain (2.1%).'

The Panel noted the complainant's concern that the SPC listed other side effects as common in frequency and that it was misleading to omit these from this section.

The Panel noted that the Code required the prescribing information to contain, *inter alia*, a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other adverse reactions.

The Panel further noted that there was a link to the Kyntheum prescribing information in an orange banner near the top of the webpage; the Panel did not have a copy of this prescribing information and Leo made no submission in that regard. Nevertheless, the complainant's allegation was in relation to the safety and tolerability section in the body of the webpage at issue and not regarding the content of the prescribing information. The Panel noted that the requirements in the Code regarding the content of prescribing information did not necessarily have to be repeated in other sections of the promotional material; much would depend on content, layout, audience and intended use of the material.

The Panel noted that the claim in question referred to '*the most* commonly reported adverse reactions'; it did not refer to all commonly reported adverse reactions. In the Panel's view, the complainant had not established that the claim at issue on the webpage in question was misleading or did not present a balanced view of safety as alleged and based on the complainant's narrow allegation the Panel ruled no breach of Clauses 7.9, 9.1 and 2.

62 Claim 'Patients with psoriasis have an increased risk of anxiety, depression and suicidal ideation compared with the general population'

COMPLAINT

The complainant alleged that this claim did not refer to the safety and tolerability of Kyntheum *per se* - this information was misleading and amounted to padding when placed under the heading 'Safety and Tolerability* *Pooled data from AMAGINE-1, AMAGINE-2 and AMAGINE-3 (210 mg Q2W (every two weeks), N=1496, placebo N = 879)'. This was particularly the case

when the product carried serious precautions and warnings around this area in Section 4.4 of the SPC.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that this statement was in breach of the Code. Leo's intention for this section of the website was to provide a broad overview of the key safety and tolerability information in brief, through the use of a bullet-pointed list. As such Leo covered the important common adverse events and additional warnings and precautions. The statement regarding the increased risk of anxiety, depression and suicidal ideation compared with the general population was factually correct and capable of substantiation. (The complainant did not suggest otherwise.) Such information provided relevant context to any health professional assessing a patient with psoriasis, consistent with Section 4.4 of the SPC and reminded them to ask questions and look out for these important conditions, given the reports of suicidal ideation and behaviour reported in patients prescribed Kyntheum.

Leo stated that it strongly disagreed that flagging the increased incidence of anxiety, depression and suicidal ideation in psoriasis patients in a section on safety and tolerability amounted to 'padding'; the information was accurate and not misleading, consistent with the requirements of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the safety and tolerability section of this webpage had two bullet points in relation to depression and suicide.

The first was the statement in question: 'Patients with psoriasis have an increased risk of anxiety, depression and suicidal ideation compared with the general population' and the second stated: 'Suicidal ideation and behavior (SIB), including completed suicide, have been reported in patients treated with Kyntheum. The majority of such patients had a history of depression and/or significant life stressors. A causal association between treatment with Kyntheum and increased risk of SIB has not been established'.

Whilst the two statements were not immediately adjacent to one another, they were both within the same section of the webpage under the safety and tolerability heading, and it appeared to the Panel that the first statement was to provide some context for the second statement. The Panel noted that the second statement was similar to wording in Section 4.4 of the Kyntheum SPC beneath the heading suicidal ideation and behaviour. However, the Panel was concerned to note that further relevant information from that section of the SPC was not included on the webpage, including that the risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms and the advice in relation to the need to be alert for the emergence or worsening of certain symptoms and when it was recommended to discontinue treatment with Kyntheum.

The Panel, however, considered that the complainant had not established that the statement 'Patients with psoriasis have an increased risk of anxiety, depression and suicidal ideation compared with the general population' within the safety and tolerability section of the webpage

in question was misleading as alleged and based on the complainant's very narrow allegation no breach of Clause 7.2 was ruled.

63 Statement 'Exercise caution when prescribing Kyntheum to patients with a history of Crohn's Disease'

COMPLAINT

Section 4.4 of the SPC states 'Kyntheum is not recommended in patients with inflammatory bowel disease', the SPC included 'Crohn's Disease' in its definition of inflammatory bowel disease. The complainant alleged that this promotional claim and the SPC information were in conflict with each other on a serious safety issue.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 3.2 and 9.1.

RESPONSE

Leo responded to allegations 63 and 64 together as it considered that they were both part of the same bullet point on the webpage and involved identical issues.

See Point 64 for further details.

PANEL RULING

Refer to point 64.

64 Statement 'Patients with a history of Crohn's Disease should be followed for signs and symptoms of active Crohn's Disease. If patients develop active Crohn's disease, treatment should be discontinued permanently'

COMPLAINT

The complainant alleged that the SPC was referenced again, however, the SPC did not support this claim. Section 4.4 of the SPC recommended that if a patient developed signs and symptoms of inflammatory bowel disease, Kyntheum should be discontinued and appropriate medical management should be initiated and as mentioned above the product was not recommended in patients with inflammatory bowel disease. The 'wait and see' approach in the promotional claim on the progression of Crohn's Disease puts patient safety at risk and was extremely aggressive and irresponsible marketing from Leo.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 3.2 and 9.1.

RESPONSE

Leo submitted that an update to the Kyntheum SPC took place in July 2020. The update included a small number of changes, one of which related to wording around inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis. This resulted from a comprehensive EMA PRAC review of all IL-17 inhibitor medicinal products, commencing in April

2020 and prompted by a risk of inflammatory bowel disease (IBD) raised during a routine assessment of secukinumab. Following the review, the CHMP recommended that Leo implement updates to the SPC and PIL. This update was also recommended to the manufacturers of other biologics in the IL-17 class.

Leo stated that the original wording of the warning in relation to Crohn's disease in Section 4.4 of the SPC read as follows:

> 'Crohn's disease
>
> There is limited data in patients with a history of Crohn's disease. Exercise caution when prescribing Kyntheum to patients with a history of Crohn's disease. Patients with a history of Crohn's disease should be followed for signs and symptoms of active Crohn's disease. If patients develop active Crohn's disease, treatment should be discontinued permanently.'

Leo stated that the current wording in Section 4.4 (from July 2020) reads:

> 'Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)
>
> Cases of new or exacerbations of inflammatory bowel disease have been reported with IL-17 inhibitors. Therefore Kyntheum is not recommended in patients with inflammatory bowel disease (see section 4.8). If a patient develops signs and symptoms of inflammatory bowel disease, or experiences an exacerbation of pre-existing inflammatory bowel disease, Kyntheum should be discontinued and appropriate medical management should be initiated.'

Leo stated that it regretted that this section of the website was not updated following revision to the Kyntheum SPC in July 2020, when advice in relation to Crohn's disease changed. Before July 2020, the SPC stated that caution should be exercised in 'patients with a history of Crohn's disease' and that, should symptoms of active Crohn's disease develop, treatment with Kyntheum should be discontinued permanently'. From July 2020, the SPC no longer referred to patients with a history of Crohn's disease but stated that Kyntheum was not recommended in patients 'with' inflammatory bowel disease (IBD) and that if a patient developed signs and symptoms of IBD or an exacerbation of pre-existing IBD, Kyntheum should be discontinued.

Leo submitted that a key feature of the revision to the SPC was the extension of warnings to cover types of IBD other than Crohn's disease. Neither before nor after the revision has Kyntheum been contraindicated in patients with a history of Crohn's disease. Before the revision, the SPC referred to the need to exercise caution in patients with a 'history' of Crohn's disease and to discontinue treatment should symptoms of active disease develop. Following the revision, the focus was solely on patients 'with' IBD (where treatment was not recommended) and the need to discontinue if new or increased symptoms develop.

Leo stated that it accepted that the wording of this webpage should have been reviewed and updated following revision to the SPC and that the fact that this did not occur constituted a breach of the high standards Leo expected of itself, in accordance with the Code. Leo therefore agreed with a breach of Clause 9.1 in this instance. Leo was investigating how this error occurred and committed to putting in place procedures to ensure it could not happen in the future.

PANEL RULING

The Panel noted that the bullet point on the webpage in question, in line with the previous SPC, stated:

> 'There is limited data in patients with a history of Crohn's disease. Exercise caution when prescribing Kyntheum to patients with a history of Crohn's Disease. Patients with a history of Crohn's Disease should be followed for signs and symptoms of active Crohn's Disease. If patients develop active Crohn's disease, treatment should be discontinued permanently.'

However, Section 4.4 (Special warnings and precautions for use) of the SPC that was current contemporaneous to the complaint stated:

> 'Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)
> Cases of new or exacerbations of inflammatory bowel disease have been reported with IL-17 inhibitors. Therefore Kyntheum is not recommended in patients with inflammatory bowel disease (see section 4.8). If a patient develops signs and symptoms of inflammatory bowel disease, or experiences an exacerbation of pre-existing inflammatory bowel disease, Kyntheum should be discontinued and appropriate medical management should be initiated.'

And Section 4.8 (undesirable effects) stated:

> '*Inflammatory bowel disease*
> Cases of new or exacerbations of inflammatory bowel disease (including Crohn's disease and ulcerative colitis) have been reported with IL-17 inhibitors (see section 4.4).'

The Panel noted Leo's submission that the bullet point on the webpage in question was a statement from Section 4.4 of a previous version of the SPC and that a key feature of the revision to the SPC was the extension of warnings to cover types of inflammatory bowel disease other than Crohn's disease. The Panel further noted Leo's submission that neither before nor after the SPC revision was Kyntheum contraindicated in patients with a history of Crohn's disease; before the revision, the SPC referred to the need to exercise caution in patients with a 'history' of Crohn's disease and to discontinue treatment should symptoms of active disease develop whereas following the revision, the focus was on patients 'with' inflammatory bowel disease (where treatment was not recommended) and the need to discontinue if new or increased symptoms developed.

Whilst the Panel noted that the contraindication in active Crohn's disease was the same in the two versions of the SPC in question, it considered that the updated SPC contained a warning and precaution in relation to inflammatory bowel disease that was broader than that stated within the previous SPC. The Panel considered that the information on the webpage in question was thus inconsistent with the particulars listed in the SPC and a breach of Clause 3.2 was ruled.

The Panel noted Leo's submission that this section of the website had not been updated following the SPC change and therefore the Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1 as acknowledged by Leo.

Clause 2 was a sign of particular censure and reserved for such use. The Panel considered that it was paramount that health professionals could rely on companies to provide up-to-date safety information in relation to medicines which they marketed. The Panel considered that Leo's failure to update the safety information in relation to inflammatory bowel disease on the webpage in question reduced confidence in and brought discredit upon the industry and a breach of Clause 2 was ruled.

65 Statement 'Suicidal ideation and behaviour (SIB) including completed suicide have been reported in patients treated with Kyntheum. The majority of such patients had a history of depression and/or significant life stressors. A causal association between treatment with Kyntheum and increased risk of SIB has not been established'

COMPLAINT

The complainant alleged that this information was not balanced; it did not reflect the warnings in Section 4.4 of the SPC regarding this topic and was downplaying a potentially very serious issue with the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2 and 9.1.

RESPONSE

Leo stated that it did not agree that this statement was in breach of the Code. This section of the website explicitly provided a summary of information regarding Kyntheum - Kyntheum at a glance. The SPC was referenced.

Leo submitted that the safety section of this part of the website presented the safety profile for Kyntheum across the Phase III studies – AMAGINE-2 and AMAGINE-3 (Lebwohl M *et al* 2015). The page in question made clear that the information represented pooled data from the two trials and the statements accurately reflected the findings of the two studies.

Leo stated that the complainant criticised this part of the website on the basis he/she alleged the information did not reflect the warnings in Section 4.4 of the SPC and was not balanced. In a similar allegation raised in AUTH/2982/10/17 it was noted that the majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour and that a causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established. The information currently criticised by the complainant reflected the Panel's decision in the earlier case consistent with the SPC. Leo concluded that it was also important to put the warning around suicidal ideation in the wider context of the rates of depression in patients with psoriasis to assist health professionals.

Leo submitted that the wording used on the webpage criticised by the complainant reproduced almost exactly the first paragraph of the relevant part of Section 4.4 of the SPC. Leo therefore construed the complainant's allegations related to the fact that the webpage did not include the second paragraph, which described in more detail the assessment and monitoring of patients with a history of depression or suicidal ideation. Leo strongly disagreed. In circumstances where this section of the website was explicitly characterised as a summary, and where the SPC was referenced, Leo did not believe the fact that the complete information from Section 4.4

of the SPC was not reproduced meant that the webpage was misleading contrary to Clause 7.2 or failed to meet the requirements of Clause 7.9. In these circumstances, Leo did not accept that there had been any breach of Clause 9.1 or Clause 2 of the Code.

PANEL RULING

The Panel noted that Section 4.4 (special warnings and precautions for use) of the Kyntheum SPC stated:

> 'Suicidal ideation and behaviour
> Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established.
>
> The risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum.'

The Panel noted that the bullet point in question made reference to reports of suicidal ideation and behaviour, including completed suicide, in patients treated with Kyntheum and that the majority of these patients had a history of depression and that a causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established. The Panel considered that it was misleading to highlight this aspect from Section 4.4 without providing the related clinical recommendations to health professionals which included that if a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum. The Panel therefore ruled a breach of Clause 7.2. High standards had not been maintained in this regard and a breach of Clause 9.1 was ruled.

Whilst the statement did not include the complete wording from Section 4.4 of the SPC, the Panel considered that the complainant had not established that the statement was inconsistent with the wording in the SPC and no breach of Clause 3.2 was ruled in that regard.

Clause 2 was a sign of particular censure and was reserved for such use. Prejudicing patient safety was an activity likely to lead to a breach of Clause 2. The Panel considered that highlighting that a causal association had not been established between Kyntheum and increased risk of suicidal ideation and behaviour without providing the related clinical recommendations to health professionals, particularly in relation to when to discontinue treatment, meant that Leo had reduced confidence in and brought discredit upon the industry and a breach of Clause 2 was ruled.

66 Claims within the video 'Kyntheum Patient Story' (UK/IE MAT-25631 V2)

This video was included in the ‘QoL’ and ‘Resources’ sections. A patient talked about his/her experience with psoriasis and Kyntheum. The Kyntheum SPC was the sole reference for this video.

COMPLAINT

The complainant alleged that the patient referred to psoriasis several times but did not make the licensed indication clear; ie mention plaque psoriasis of moderate to severe disease as per the SPC.

He also stated:

> ‘I would say by the time I injected my second injection the following week, I was feeling better in myself. I could see that the psoriasis was thinning out.’
>
> ‘It’s quality of life, it’s like having a second chance.’
>
> ‘I’m more relieved that I’ve got clear skin for them than myself.’
>
> ‘Now that I’m clear of psoriasis my advice would be to keep going don’t give up hope and if you need it get support.’

The complainant stated that these claims were not representative of a typical patient; plaque psoriasis of this severity would not typically be seen to be ‘thinning out’ after two injections of this medicine. The video was giving false hope.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 26.2.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The video in question was, as stated by the complainant, located on two pages on the website – the QoL and Resources sections. The first screen of the video explained where to find prescribing information (via a link on the webpage) and the adverse event reporting statement, as well as a clear, bold statement stating ‘Kynthuem (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy’. This page stayed onscreen for 6 seconds and therefore provided sufficient time for viewers of the video to read and understand the licensed indication prior to the video being shown.

Immediately after the first ‘holding page’ was a second page, in bold white text on a black background, stating ‘The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient’. This second ‘holding page’ stayed onscreen for an additional 5 seconds.

Leo submitted that the website was directed only to health professionals and was not intended to be accessed by patients or members of the public. The video was devised to address the significant impact psoriasis could have on a patient’s quality of life, as well as the potential improvements that might be seen with Kyntheum. The video did not attempt to quantify improvement or to show images of improvement, but simply documented the impression of an

individual patient, making clear that the patient in question might not be representative and that responses varied between individuals.

Leo submitted that, accordingly, the licensed indication was clearly stated and the video was entirely consistent with Clause 3.2. The information provided was modest and this was accurate, balanced and not misleading, consistent with Clause 7.2. The website was not directed to members of the public, there was no attempt to encourage members of the public to request Kyntheum or to raise unfounded hopes of successful treatment; Leo denied a breach of Clause 26.2.

PANEL RULING

The Panel noted Leo's submission that the video in question was, as stated by the complainant, located on two pages on the website – the QoL and Resources sections; the first frame of the video, which was displayed for 6 seconds, stated 'This is a promotional video intended for UK/IE healthcare professionals only' and further stated 'Kyntheum (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy'; the frame also explained where to find prescribing information and the adverse event reporting statement.

The Panel considered that the complainant had not established that the licensed indication was not made clear as alleged and no breach of Clause 3.2 was ruled.

The Panel considered that the complainant had not established that the video within the website would be viewed by members of the public or patients and therefore Clause 26.2 was not relevant; no breach of Clause 26.2 was ruled.

The Panel noted Leo's submission that the second page of the video stated, 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. However, the Panel noted that it was an established principle that individual patient cases highlighted in promotional material must not be misleading as to the efficacy of the medicine being promoted.

The Panel noted that Section 4.2 of the Kyntheum SPC stated that the recommended dose was 210mg at weeks 0, 1, and 2 followed by 210mg every 2 weeks.

The Panel considered that the reference to psoriasis 'thinning out' was ambiguous in relation to the clinical outcome achieved, however, the Panel noted its comments at Point 11 that the median time to response (PASI 75 response), based on Kaplan-Meier analysis in both AMAGINE-2 and AMAGINE-3 (for the Kyntheum 210mg dose) was 4.1 weeks. The Panel further noted its comments at Point 8 including that Section 5.1 of the SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

The Panel considered that the statement in the video '…by the time I injected my second injection the following week, I was feeling better in myself. I could see that the psoriasis was thinning out', although ambiguous with regard to the clinical outcomes being described, did not appear to be aligned with the trial results for the majority of patients. The Panel considered that the statement was misleading with regard to the clinical result likely to be seen in a patient with

moderate to severe plaque psoriasis after two injections of Kyntheum and a breach of Clause 7.2 was ruled.

The Panel noted that the Kyntheum SPC gave pooled PASI 100 results from AMAGINE-2 and AMAGINE 3 which showed that 41.6% and 51% of patients administered Kyntheum 210mg every 2 weeks achieved PASI 100 at 12 and 52 weeks, respectively.

The Panel further noted that Kyntheum was intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis and that this audience, on the balance of probabilities, would likely understand that clinical results would be dependent on a number of factors. Therefore, the Panel considered that the complainant had not established that the statements 'I'm more relieved that I've got clear skin for them than myself', 'It's quality of life, it's like having a second chance', and 'now that I'm clear of psoriasis my advice would be to keep going don't give up hope and if you need it get support' were giving false hope to the intended health professional audience and no breach of Clause 7.2 was ruled in that regard.

APPEAL BY LEO

This video was intended to show a patient's impression of the impact of treatment of his psoriasis including in terms of quality of life. The video stated expressly that 'the views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient'.

Leo submitted that in reaching its conclusions in relation to the patient's statement 'by the time I injected my second injection the following week, I was feeling better in myself. I could see that the psoriasis was thinning out', the Panel had elided 'thinning out' with one of the outcomes in the AMAGINE-2 or AMAGINE-3 clinical trials. There was no basis for this assumption; 'thinning out' quite clearly did not reflect a scientific assessment such as PASI 75, but was an informal description used by patients to indicate that they had experienced some improvement in the appearance of their psoriasis. It was readily identified as such.

Leo submitted that the statement by the patient in the video that his psoriasis had started to 'thin out' by the time of the second injection (ie to show some improvement) did not suggest a PASI 75 response at that stage, but was entirely consistent with a more substantial, PASI 75, response at 4.1 weeks. While, therefore, the video included a statement indicating that the views and opinions were not claimed to reflect a typical patient response, the experience of the particular patient shown was not inconsistent with that of the majority of patients in the AMAGINE-2 and AMAGINE-3 trials who achieved a PASI 75 response at 4.1 weeks and the patient statement in issue was not misleading.

APPEAL BOARD RULING

The Appeal Board noted that the second frame of the video stated, 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. However, the Appeal Board noted that it was an established principle that individual patient cases highlighted in promotional material must not be misleading as to the efficacy of the medicine being promoted.

The Appeal Board noted that section 4.2 of the Kyntheum SPC stated that the recommended dose was 210mg at weeks 0, 1, and 2 followed by 210mg every 2 weeks.

The Appeal Board noted that the patients second injection would be just one week after his first injection. The Appeal Board did not have before it clinical data at week 1 but noted that section 5.1 of the SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials. Thus, it would follow that response rates at week 1 would be lower than this.

'Thinning out' was casual language to be expected in a patient's description of his/her psoriasis, however, the video was promotional material for health professionals and the company had full editorial control.

The Appeal Board considered that the statement in the video '…by the time I injected my second injection the following week, I was feeling better in myself. I could see that the psoriasis was thinning out', although ambiguous with regard to the clinical outcomes being described, did not appear to be aligned with the trial results for the majority of patients and was not a typical response for week 1. The Appeal Board considered that the statement was misleading with regard to the clinical result likely to be seen in a patient with moderate to severe plaque psoriasis after two injections of Kyntheum and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

Video: 'Experience with Kyntheum' (UK/IE MAT-27679 V3 August 2020)

This video was included in the 'Efficacy' and 'Resources' page.

The complainant alleged that the videos described below raised unfounded hopes of treatment success, and where health professionals had been involved, their views were skewed, unrepresentative of the data and this amounted to selected cherry picking of incredibly positive overly promising results. Statements were sweeping, broad and general akin to consumer advertising. As health professionals, their involvement in these videos and getting so carried away with the company was very concerning.

General response

Leo submitted that the complainant had made the above criticisms in relation to allegations 67-94. Leo provided the following general responses in relation to all such matters as a preliminary submission before addressing the specific allegations in relation to individual videos.

Leo submitted that the videos identified by the complainant were put together from a series of longer video interviews that took place at the British Association of Dermatologists Meeting in 2019 and were subsequently added to the website as a promotional resource. The agency who produced the videos was instructed to ensure that the clips they chose to use were reflective of the opinions and views expressed by the health professionals and not to select only the most positive statements. Leo stated it could provide full interview transcripts to the Authority on request; but could confirm that this brief was followed and the clips shown on the views did reflect the general views and opinions.

Leo submitted that a member of the medical team was present during the interview sessions to ensure Code compliance and to confirm that superlatives and unsubstantiated claims were not made. All videos included a clear 5 second disclaimer in bold white text on a black background

at the start of each video, stating: 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

67 Statement by Dr A 'My promise to my patients is that I will get you clear or nearly clear and brodalumab does what it says on the tin'

COMPLAINT

This claim was a guarantee which was incapable of substantiation and not in line with the Code or SPC for the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.4.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'

Leo submitted that 'Does what it says on the tin' was a colloquial term which meant that a product performed as it claimed to do. In this instance, it meant that the effects of Kyntheum were consistent with the information provided in the SPC, both in terms of efficacy and safety. The claim of 'clear or nearly clear' related to PASI 100 and PASI 75 results obtained in the clinical trial programme. Papp *et al* (2018) reported that 40.9% of biologic-naïve and 39.5% of biologic-experienced patients achieved PASI 100 at week 12. This statement was consistent with the SPC which stated that 83-86% of patients achieved PASI 75 at 12 weeks. Dr A's statement reflected his/her personal commitment 'My promise to my patients…' as to what he/she would achieve from her overall treatment approach. It provided no confirmation of the effect of brodalumab beyond the fact that the product achieved the results stated in the approved SPC reflecting the trial data ('on the tin'). In particular, Dr A's statement provided no broad guarantee of the success of Kyntheum treatment.

In these circumstances, Leo stated that it did not agree that the statement by Dr A was in any way inconsistent with the SPC for Kyntheum or otherwise inaccurate, unbalanced or incapable of substantiation; Leo denied breaches of Clauses 3.2, 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that the Kyntheum SPC gave the proportion of patients treated with Kyntheum 210mg every 2 weeks who had a static physician's global assessment (sPGA) score of 0 or 1 (which Lebwohl *et al* stated was 'clear or almost clear skin') at week 12 and week 52 in AMAGINE-1 and pooled data from AMAGINE-2 and AMAGINE-3. The Panel noted that in AMAGINE-1, the proportion of Kyntheum treated patients who achieved an sPGA score of 0 or 1 was 76% and 83% at weeks 12 and 52, respectively. The Panel noted that in AMAGINE-2 and AMAGINE 3 pooled data, the proportion of Kyntheum treated patients who achieved sPGA score of 0 or 1 was 79% and 65% at weeks 12 and 52, respectively.

The Panel considered that the claim 'My promise to my patients is that I will get you clear or nearly clear…', from a health professional, misleadingly implied that clear or nearly clear skin would be achieved in every Kyntheum treated patient which was not so and a breach of Clause 7.2 was ruled. The misleading impression given in this regard was not capable of substantiation and a breach of Clause 7.4 was ruled.

In the Panel's view, the reference to 'does what it says on the tin' implied that the SPC supported the misleading impression that all Kyntheum treated patients would achieve clear or nearly clear skin which was not so. The Panel therefore considered that the claim 'My promise to my patients is that I will get you clear or nearly clear and brodalumab does what it says on the tin' was inconsistent with the particulars listed in the Kyntheum SPC and a breach of Clause 3.2 was ruled.

APPEAL BY LEO

Leo submitted that the Panel had misconstrued the statement by Dr A. Dr A was stating that he/she gave his/her patients confidence that he/she would help them achieve clear, or nearly clear, skin and that Kyntheum might be part of this. Dr A's promise to his/her patients therefore related to her treatment approach and not to Kyntheum or any other specific medicinal product. In particular:

- He/she did NOT say 'My promise to my patients is that Kyntheum will get you clear or nearly clear', which would be a claim relating to Kyntheum - or even that he/she prescribed Kyntheum to every patient with moderate or severe psoriasis - but rather that he/she would assist her patients to achieve clear skin, or nearly clear skin, through her clinical skill.
- He/she did NOT claim that Kyntheum would necessarily achieve clear, or nearly clear skin, for every patient, but simply that its performance reflected its label ('does what it says on the tin').
- As stated in Leo Pharma's initial response to this complaint, the claim 'does what it says on the tin' could only relate to the benefits as set out in the SPC, which set out the results in terms of PASI 100 and PASI 75 from the AMAGINE-2 and AMAGINE-3 trials.
- Dr A's statement suggested that Kyntheum was an effective treatment (as indicated in its approved label) and that this would be part of her treatment strategy - but did no more than that.

Leo submitted that the statement was not therefore misleading and did not exaggerate the effects of Kyntheum. Leo did not accept that Dr A's statement resulted in breaches of Clauses 3.2, 7.2 and 7.4 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that section 5.1 of the Kyntheum SPC stated that in the pooled analysis of AMAGINE-1 and AMAGINE-2, 41.6% of Kyntheum 210mg treated patients achieved PASI 100 at 12 weeks and 51.0% achieved PASI 100 at 52 weeks. The proportion of patients who achieved PASI 75 with Kyntheum 210mg at week 12 and week 52 in AMAGINE-1 was 83% and 87%, respectively, and in a pooled analysis of AMAGINE-2 and AMAGINE 3 it was 86% and 65%, respectively.

The Appeal Board noted that Kynethum was indicated for the treatment of moderate to severe plaque psoriasis and it considered that it was unrealistic to expect that every Kyntheum treated patient would achieve clear or nearly clear skin.

The Appeal Board considered that the claim in question 'My promise to my patients is that I will get you clear or nearly clear and brodalumab does what it says on the tin' was stated at the beginning of a promotional Kyntheum video. The Appeal Board considered that the first part of the claim 'my promise to my patients is that I will get you clear or nearly clear' was inextricably linked to the second part of the claim 'and brodalumab does what it says on the tin'. The Appeal Board considered that the two parts of the claim could not be separated as asserted by Leo. The Appeal Board was in no doubt that the health professional was talking about Kyntheum as there was a large prominent Kyntheum logo and the text 'Clinical experience with Kyntheum' included on the screen as the health professional stated the claim in question.

The Appeal Board considered that the claim 'My promise to my patients is that I will get you clear or nearly clear and brodalumab does what it says on the tin', from a health professional, misleadingly implied that clear or nearly clear skin would be achieved in every Kyntheum-treated patient which was not so, and this misleading impression was not capable of substantiation. The Appeal Board upheld the Panel's rulings of a breach of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

In the Appeal Board's view, the reference to 'does what it says on the tin' implied that the product label i.e the SPC, supported the misleading impression that all Kyntheum-treated patients would achieve clear or nearly clear skin which was not so. This type of language was more akin to consumer advertising and not the language expected when advertising a prescription only medicine to health professionals. The Appeal Board considered that the claim 'My promise to my patients is that I will get you clear or nearly clear and brodalumab does what it says on the tin' was inconsistent with the particulars listed in the Kyntheum SPC and the Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

68 Statement by Dr B 'Particularly in patients with moderate to severe psoriasis, particularly patients where I'm looking for a really brisk response to the disease, Kyntheum would be a first choice drug. It's a good deal more effective than some of the older drugs such as IL-12, 23s and anti TNFs'

COMPLAINT

The complainant stated that Kyntheum was not a first choice drug according to NICE guidelines. The complainant alleged that 'It's a good deal more effective' lacked quantification and he/she had been unable to source comparative data with any other treatment with the exception of ustekinumab, therefore comparative promotional claims like this sentence should not be used. A company could not extrapolate claims of superiority versus other drugs when they had no clinical data to support such claims.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The statement by Dr B referring to 'a first choice drug' was immediately preceded by 'particularly patients where I'm looking for a really brisk response …'. This reinforced the fact that the statement was based on his own experience and practice. It was not necessarily a breach of the Code to provide a clinician's personal view, even if this did not follow NICE guidelines, provided it complied with the licensed indication and the SPC, which in this case it did. In addition, the comments were reflective of substantiable clinical evidence.

Leo submitted that the overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. In referring to Kyntheum being 'a good deal more effective than some of the older drugs', the views of Dr B could be substantiated by the placebo-adjusted network meta-analysis relied upon by NICE for the purposes of its guidance on brodalumab for the treatment of moderate and severe plaque psoriasis (TA511).

Leo submitted that this placebo adjusted network meta-analysis relied upon by NICE compared brodalumab with adalimumab (anti-TNF), apremilast (PDE inhibitor), dimethyl fumarate (NRF activator), etanercept (anti-TNF), infliximab (anti-TNF), secukinumab (IL-17 inhibitor), ixekizumab (IL-17 inhibitor) and ustekinumab (IL12/23 inhibitor) using data from 59 trials (28,346 patients) and in the 49 cases involving a placebo comparator adjusted these to account for placebo response. The placebo-adjusted network meta-analysis showed that brodalumab had the second highest probability after ixekizumab of achieving a PASI 75 response. NICE's Appraisal Committee concluded, based on this analysis, that brodalumab remained ranked among the top few treatments in terms of PASI response rate. As such, the claim 'it is a good deal more effective…' was consistent with and substantiated by NICE's conclusions.

Therefore, Leo did not agree that Dr B's statement was inaccurate or unbalanced contrary to Clause 7.2; the comparison with other products was based on relevant features (briskness of response) and was not misleading consistent with Clause 7.3 and the claims were capable of substantiation as required by Clause 7.4.

PANEL RULING

In relation to the allegation that Kyntheum was not a first choice drug according to NICE guidelines, the Panel noted that the Code required promotion to be in accordance with the terms of a medicine's marketing authorisation; the Code did not require a medicine to be promoted in accordance with NICE guidelines and therefore the Panel ruled no breach of Clause 7.2 based on the very narrow allegation.

The Panel noted the complainant's allegation that the statement 'It's a good deal more effective than some of the older drugs such as IL-12, 23s and anti TNFs' lacked quantification and that, with the exception of ustekinumab, there was no comparative data versus other drugs to support such a claim; the Panel noted Leo's submission that the views of this health professional could be substantiated by the placebo-adjusted network meta-analysis relied upon by NICE for the purposes of its guidance on brodalumab for the treatment of moderate and severe plaque psoriasis. The Panel further noted Leo's submission that this placebo adjusted network meta-analysis compared brodalumab with adalimumab (anti-TNF), apremilast (PDE inhibitor), dimethyl fumarate (NRF activator), etanercept (anti-TNF), infliximab (anti-TNF),

secukinumab (IL-17 inhibitor), ixekizumab (IL-17 inhibitor) and ustekinumab (IL12/23 inhibitor) using data from 59 trials (28,346 patients) and in the 49 cases involving a placebo comparator adjusted these to account for placebo response; the placebo-adjusted network meta-analysis showed that brodalumab had the second highest probability after ixekizumab of achieving a PASI 75 response and based on that analysis NICE's appraisal committee concluded that brodalumab remained ranked among the top few treatments in terms of PASI response rate.

The Panel noted that Lebwohl *et al* (2015) investigated brodalumab vs ustekinumab in two Phase III, randomized, double-blind, placebo controlled and active comparator-controlled studies (AMAGINE-2 and AMAGINE-3). One of the primary aims of this study was to evaluate the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100). The week 12 PASI 100 response rates were significantly higher with brodalumab 210mg than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001).

The Panel considered that the claim 'It's a good deal more effective than some of the older drugs such as IL-12, 23s and anti TNFs' was ambiguous with regard to what other medicines Kyntheum was being compared with and the context of that comparison. The Panel noted that whilst there was data from the AMAGINE trials which showed that week 12 PASI 100 response rates were significantly higher with brodalumab 210 mg than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001), there wasn't any head to head trial data with any other medicine. In the Panel's view, the claim misleadingly implied that there was comparative head to head data with more than one medicine which was not so and a breach of Clauses 7.2 and 7.3 was ruled. The misleading impression given by the claim was not capable of substantiation and a breach of clause 7.4 was ruled.

69 Statement by Dr C 'Typically I get a response within 4 weeks after the first injection, in fact after the trial injection by the nurse in the community, they'll often report back to the nurse on telephone consultation that they've already got near clearance or clearance although we do set clinical assessment at 3 month basis so it's not until the 3 months by that time usually we get PASI 100 response upon the first time we meet them'

COMPLAINT

The complainant alleged that this claim was unsubstantiated. The results cited by the doctor were not representative of the clinical trials or the SPC and built a false, exaggerated and overly positive impression of the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2, 7.4 and 7.10.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. The statement by Dr C clearly indicated that this reflected his/her own professional experience in the real world rather than trial data. This was clearly demonstrated by the wording he/she used, which started with 'Typically I get a response…' which made no general claim in relation to the

overall responses which might be obtained by other dermatologists treating other patients, consistent with the 'holding page' at the start of the video.

Leo stated that, for completeness, the statement 'Typically, I get a response within 4 weeks after the first injection' was in any event consistent with the Yao and Lebwohl data (2019), demonstrating that 50% of patients achieved a mean PASI 50 within 1.8 weeks and substantiable by those data. The statement '…it's not until the 3 months by that time usually we get PASI 100 response upon the first time we meet them' was consistent with data reported by Papp *et al* (2018), who found that 40.9% of biologic-naïve and 39.5% of biologic-experienced patients achieved PASI 100 at week 12.

Leo submitted that the statement by Dr C clearly indicated that this reflected his/her own personal experience and made no general claim about effects in other patients. It was not inconsistent with the SPC contrary to Clause 3.2 or inaccurate or misleading contrary to Clause 7.2; the statements were substantiable by referenced to published studies and the interview with Dr C did not exaggerate the effects of Kyntheum contrary to Clause 7.10.

PANEL RULING

The Panel noted that it was an established principle that promotional material, even if citing a health professional's own clinical experience, needed to comply with the requirements of the Code.

The Panel noted that Section 4.2 of the Kyntheum SPC stated that the recommended dose was 210mg at weeks 0, 1, and 2 followed by 210mg every 2 weeks.

The Panel noted its comments at Point 11 above that the median time to response (PASI 75 response), based on Kaplan-Meier analysis in both AMAGINE-2 and AMAGINE-3 (for the Kyntheum 210mg dose) was 4.1 weeks. The Panel considered, therefore, that the complainant had not established that the first part of the claim which stated '…Typically I get a response within 4 weeks after the first injection' was misleading, incapable of substantiation, exaggerated the properties of Kyntheum or was inconsistent with the SPC and no breach of Clauses 3.2, 7.2, 7.4 and 7.10 were ruled in that regard.

The Panel noted from the supplement to Lebowhl *et al* (2015), that PASI 90 response rates in AMAGINE-2 and AMAGINE-3, for patients on brodalumab 210mg, at week 2, were under 10%.

The Panel considered that the second part of the claim '…in fact after the trial injection by the nurse in the community, they'll often report back to the nurse on telephone consultation that they've already got near clearance or clearance…' implied that clearance or near clearance was likely to be seen after one injection of Kyntheum; the Panel considered that the implication that a patient with moderate to severe plaque psoriasis was likely to have this clinical result after one injection was inconsistent with the SPC, misleading and exaggerated Kyntheum's properties. A breach of Clauses 3,2, 7.2 and 7.10 were ruled. The misleading impression given by the statement was incapable of substantiation and a breach of Clause 7.4 was ruled.

The Panel noted that the claim in question ended with '… although we do set clinical assessment at 3 month basis so it's not until the 3 months by that time usually we get PASI 100 response upon the first time we meet them'. In the Panel's view, reference to 'usually' implied most often. The Panel noted that Section 5.1 of the SPC presented the pooled results from

AMAGINE-2 and AMAGINE-3 in relation to PASI 100 in graphical form with results which showed that 41.6% of patients administered Kyntheum 210mg every 2 weeks (N=339) achieved PASI 100 at 12 weeks. The Panel considered that usually (most often) a patient would not achieve PASI 100 by 12 weeks and therefore the claim was inconsistent with the particulars in the SPC, misleading and exaggerated Kyntheum's properties and a breach of Clauses 3.2, 7.2 and 7.10 were ruled. The misleading impression given by the statement was incapable of substantiation and a breach of Clause 7.4 was ruled.

70 Statement by Dr D 'Brodalumab acts very fast. It is literally weeks, but I always prepare patients that the best results are going to evolve in 8 to 12 weeks from when they start administration. I see lots of happy patients at week 12 and beyond'

COMPLAINT

The complainant alleged that the claim 'very fast' had not be qualified in terms of clinical parameter or patient population and was unreferenced. The word 'best' in results was a superlative and should not be used. There was no data in the SPC to support the claim of 'happy patients'.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4, 7.6 and 7.10.

RESPONSE

Leo did not agree that these statements constituted a breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. The claim that 'Brodalumab acts very fast' was qualified in the very next sentence, in which Dr D states 'It is literally weeks'. Evidence from Yao and Lebwohl demonstrated that the time for 25% of patients to achieve PASI 75 was 2.1 weeks, based on 1,236 patients. This measure equated to TOA or the time until the onset of action – a statistically reliable and clinically relevant measure of speed of efficacy.

Leo submitted that the use of the word 'best' in this instance was not a superlative used in comparison to other treatments. Instead, Dr D is stating that there would be a delay of 8-12 weeks before the patients start to see their own optimal results. This did reflect clinical data that showed results for PASI 75 and PASI 100 were both improved at 12 weeks vs earlier time points (Lebwohl *et al* (2015). As such, the use of 'best' meaning 'optimum' in this interview was not a breach of the Code.

Leo stated that the statement 'I see lots of happy patients at week 12 and beyond' was clearly based on personal experience and reflected positive outcomes at week 12, consistent with Lebwohl *et al* (2015).

Leo submitted that the statements by Dr D were clearly stated to be based on his/her own experience, they were not misleading and, where appropriate they were capable of substantiation consistent with Clauses 7.2 and 7.4 of the Code. There were no references to published studies and therefore Clause 7.6 was not relevant. The properties of Kyntheum were not exaggerated and Leo denied a breach of Clause 7.10.

PANEL RULING

The Panel considered that Clause 7.6 was not relevant as the claim was not related to a published study; it was an account of a health professional's own clinical experience and no breach of Clause 7.6 was ruled.

The Panel considered that the reference to 'very fast' was quantified by reference to 'literally weeks' in the claim. The Panel noted its comments at Point 11 above that the median time to response (PASI 75 response), based on Kaplan-Meier analysis in both AMAGINE-2 and AMAGINE-3 (for the Kyntheum 210mg dose) was 4.1 weeks. The Panel further noted its comments at Point 8 including that Section 5.1 of the SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

The Panel noted that Section 5.1 of the SPC presented the pooled results from AMAGINE-2 and AMAGINE-3 in relation to PASI 100 in graphical form with results which showed that 41.6% of patients administered Kyntheum 210mg every 2 weeks (N=339) achieved PASI 100 at 12 weeks.

The Panel considered that reference to '…the best results are going to evolve in 8 to 12 weeks from when they start administration…' was not a superlative; it was a reference as to when optimum results might be expected; this did not appear to be inconsistent with the trial results. The Panel ruled no breach of Clause 7.10 in that regard.

The Panel considered that the complainant had not established that the claim 'Brodalumab acts very fast. It is literally weeks, but I always prepare patients that the best results are going to evolve in 8 to 12 weeks from when they start administration. I see lots of happy patients at week 12 and beyond' in the context of a video giving a verbal account of a health professional's clinical experience with Kyntheum was misleading, incapable of substantiation or exaggerated Kyntheum's properties as alleged and no breach of Clauses 7.2, 7.4 and 7.10 were ruled.

71 Statement by Dr E 'What patients say is that when they've started brodalumab they get really quite swift clearance of their skin or at least swift massive improvement in their psoriasis'

COMPLAINT

The complainant stated that this claim was unqualified, unreferenced and 'swift massive improvement' was exaggerated. The type of population or psoriasis had not been mentioned either.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.6 and 7.10.

RESPONSE

Leo did not agree that these statements constituted a breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient

response to Kyntheum – individual response and experience may vary from patient to patient'. The claim around 'really quite swift clearance' was preceded by 'What patients say', highlighting the personal experience basis for this statement. However, in any event data were available to substantiate the rapid onset of action of Kyntheum and the magnitude of improvement:

- Yao and Lebwohl (2019) stated that 'Brodalumab may continue to have the most rapid onset of action of available anti-psoriatic therapies'.
- Dr E stated that patients report either swift clearance or massive improvement. This was consistent with data reported by Papp *et al* (2018), who found that 40.9% of biologic-naïve and 39.5% of biologic-experienced patients achieved PASI 100 at week 12.and with the SPC which stated that 83-86% of patients achieved PASI 75 at 12 weeks. Both PASI 75 and PASI 100 might be described as representing clearance of psoriasis or 'massive improvement'.

Leo submitted, therefore, the statement was not misleading and was capable of substantiation, consistent with Clauses 7.2 and 7.4 of the Code. The statement 'massive improvement' was not exaggerated when considered in the context of improvement from moderate- severe plaque psoriasis to PASI 75 and certainly to PASI 100; Leo denied a breach Clause 7.10.

PANEL RULING

The Panel noted that the first frame of the video stated, 'Kyntheum (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy'**.** Based on the narrow allegation that the type of population or psoriasis had not been mentioned, the Panel ruled no breach of Clause 7.2.

The Panel considered that Clause 7.6 was not relevant as the claim was not related to a published study; it was a verbal account of a health professional's own clinical experience and no breach of Clause 7.6 was ruled.

The Panel noted the complainant's allegation that the claim was unqualified but gave no further detail in that regard. It was not for the Panel to infer reasons to support a complaint; it was for the complainant to make his/her case on the balance of probabilities; in that regard the Panel ruled no breach of Clause 7.2.

In relation to the allegation that 'swift massive improvement' was exaggerated, the Panel considered that whilst the term was ambiguous, it did not necessarily imply complete clearance. The Panel noted its comments at Point 4 above in relation to the study design of AMAGINE-2 and AMAGINE-3. Lebowohl *et al* stated that at week 12, the PASI 75 response rates were significantly higher with brodalumab (210mg every 2 weeks) than with placebo (86% vs. 8% [AMAGINE-2] and 85% vs. 6% [AMAGINE-3]; both P<0.001). The Panel noted that Section 5.1 of the SPC presented the pooled results from AMAGINE-2 and AMAGINE-3 in relation to PASI 100 in graphical form with results which showed that 41.6% of patients administered Kyntheum 210mg every 2 weeks (N=339) achieved PASI 100 at 12 weeks.

The Panel noted its comments at Point 11 above that the median time to response (PASI 75 response), based on Kaplan-Meier analysis in both AMAGINE-2 and AMAGINE-3 (for the Kyntheum 210mg dose) was 4.1 weeks. The Panel further noted its comments at Point 8 including that Section 5.1 of the SPC stated that PASI 75 response at 2 weeks ranged between

20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

The Panel considered that the complainant had not established that reference to 'swift massive improvement' was exaggerated and ruled no breach of Clause 7.10.

72 Statement by Dr D 'I've not had a single patient with Kyntheum therapy who has not responded. I have had results that evolve at different speeds'

COMPLAINT

The complainant stated that this doctor had not qualified how many patients she had treated to make this claim but for every patient to respond was not realistic and incompatible with the SPC. The statement was misleading with regard to efficacy.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not believe these statements constituted a breach of the Code. Dr D's statements in relation to patient response are clearly based on her own personal experience (she states I've not had…'). The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. There was in any event good evidence that well over the majority of patients would achieve a substantial response to Kyntheum. In Puig *et al* (2020), 84.4% of patients achieved PASI 75 improvement from baseline at 12 weeks, so an expectation of some response was realistic and representative in the majority of patients. This was not inconsistent with the SPC, which simply described the proportion of patients who achieved PASI 75 at weeks 12 and 52 but did not address the proportion of patients who exhibit some response or what might be observed in real world clinical practice.

Leo submitted, therefore, that the statement by Dr D was not inconsistent with the SPC contrary to Clause 3.2 and was not misleading contrary to Clause 7.2.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Panel noted its comments at Point 4 above in relation to the study design of AMAGINE-2 (n= 1831) and AMAGINE-3 (n=1881). Lebowohl *et al* stated that at week 12, the PASI 75 response rates were significantly higher with brodalumab (210mg every 2 weeks) than with placebo (86% vs. 8% [AMAGINE-2] and 85% vs. 6% [AMAGINE-3]; both P<0.001). The Panel considered that, based on clinical trial data, a PASI 75 response was a realistic treatment goal with Kyntheum by week 12.

The Panel considered that the claim 'I've not had a single patient with Kyntheum therapy who has not responded. I have had results that evolve at different speeds' was vague as it was not clear how many patients this health professional had treated and what he/she meant by 'response'. The Panel considered that the claim implied that all patients would have a response to Kyntheum. In the Panel's view, such a strong claim required some context in order to enable the recipient to form their own opinion of the therapeutic value of the medicine and therefore a breach of Clause 7.2 was ruled.

Section 4.2 of the Kyntheum SPC stated 'Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks'. In the Panel's view, the SPC referred to not every patient responding to Kyntheum and therefore the Panel considered that the claim 'I've not had a single patient with Kyntheum therapy who has not responded. I have had results that evolve at different speeds' was inconsistent with the particulars in the SPC, and a breach of Clause 3.2 was ruled.

73 Statement by Dr B 'In terms of PASI 75, pretty much everybody that you treat with Kyntheum is going to meet that. The thing that surprises you is the number of patients who get PASI 90'

COMPLAINT

The complainant stated 'Pretty much everybody' implied near or approaching 100%, he did not state when patients will reach PASI 75, but the SPC was in conflict with this so the claim was misleading.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not believe these statements constituted a breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient' 'Pretty much everybody' was not a precise figure. It was obviously more than a majority of patients (ie over half) and suggested a figure closer to 100% although clearly less than all patients. The SPC records the percentage of patients who achieved PASI 75 at 12 weeks and 52 weeks but did not consider what percentage might achieve PASI 75 after 52 weeks. The statement by Dr B was not therefore inconsistent with the SPC. The fact that a high percentage of patients achieve PASI 75 following Kyntheum treatment was confirmed by data (including Puig *et al*, 2020) and the SPC and figure of around 85% could be construed as 'pretty much everybody').

Leo submitted that, in these circumstances it did not accept that the statements by Dr B breached Clause 3.2 of the Code or that these were misleading contrary to Clause 7.2 of the Code.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Panel considered that the term 'pretty much everybody' was vague and implied that almost 100% of patients treated with Kyntheum would achieve PASI 75. The Panel noted that, according to the SPC, the proportion of patients who achieved PASI 75 with Kyntheum 210mg at week 12 and week 52 in AMAGINE-1 was 83% and 87%, respectively, and in a pooled analysis of AMAGINE-2 and AMAGINE 3 it was 86% and 65%, respectively.

Puig *et al* (2020) evaluated the efficacy and safety of brodalumab through 120 weeks in the AMAGINE-2 trial. The authors stated that of patients who received brodalumab 210mg every 2 weeks, 84.4% achieved PASI 75 at 120 weeks.

The Panel considered that the claim 'In terms of PASI 75, pretty much everybody that you treat with Kyntheum is going to meet that' was misleading as to the clinical results likely to be seen with treatment based on clinical trial data and a breach of Clause 7.2 was ruled. The Panel considered that the statement was inconsistent with the results provided in the SPC and thus ruled a breach of Clause 3.2.

APPEAL BY LEO

Leo submitted that the statement by Dr B had not breached the Code. In particular, while the wording Dr B used was not reflected in the SPC for Kyntheum, Leo believed there was no inconsistency and Dr B's statement was supported by the clinical trial data.

Leo submitted that the difference between Leo and the Panel in relation to allegation 73 arose from the interpretation of 'pretty much everybody'. This was clearly not a precise quantification of the proportion of patients who would achieve PASI 75 following Kyntheum treatment, but a colloquial phrase indicating a very high proportion. It was Leo Pharma's position that, in circumstances where 'most' or 'the majority' meant 51% or more of patients, 'pretty much everybody' meant substantially more than 51% but less than 100%. This would include 87% of patients (as shown at week 52 in AMAGINE-1). A further analysis of long term data from AMAGINE-2 and AMAGINE -3 by Menter *et al* (2020), found that PASI 75 was achieved by 91.3% of biological-naïve patients at 120 weeks, which was also consistent with an outcome achieved by 'pretty much everybody'.

Leo therefore submitted that Dr B's statement properly reflected the PASI 75 results at 52 weeks described in the SPC for Kyntheum. However, for the avoidance of doubt, Dr B did not specify the period over which PASI 75 outcomes were obtained in his experience and a different percentage of PASI 75 outcomes obtained over a different period to that described in the SPC (eg the 120 week data described in Green *et al*) was not inconsistent with those data.

For these reasons, Leo submitted that Dr B's statement had not breached Clauses 3.2 and 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that Leo had full editorial control over this video and considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Appeal Board considered that the term 'pretty much everybody' implied that nearly 100% of patients treated with Kyntheum would achieve PASI 75. However, according to the SPC, the proportion of patients who achieved PASI 75 with Kyntheum 210mg at week 12 and week 52 in AMAGINE-1 was 83% and 87%, respectively, and in a pooled analysis of AMAGINE-2 and AMAGINE 3 it was 86% and 65%, respectively.

The Appeal Board accepted that verbal language used by a health professional describing his/her clinical experience might not be specific in terms of quantification of results, however, the take home message from the claim at issue was that every patient you treat with Kyntheum (bar the exceptional few) would reach PASI 75 which was not so.

The Appeal Board considered that the claim 'In terms of PASI 75, pretty much everybody that you treat with Kyntheum is going to meet that' was misleading as to the clinical results likely to be seen with treatment based on clinical trial data and it upheld the Panel's ruling of a breach of Clause 7.2. The Appeal Board considered that the statement was inconsistent with the results provided in the SPC and thus it upheld the Panel's ruling of a breach of Clause 3.2. The appeal on both points was not successful.

74 PASI 90

COMPLAINT

In relation to Point 73, for PASI 90, there was no mention of this in the SPC and again he had not quantified how many patients and at what time point they would reach PASI 90.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not believe this statement constituted a breach of the Code. The Puig *et al* paper (2020), reported that 75.6% of patients achieved PASI 90 at 120 weeks. In addition, in the supplementary appendix for Lebwohl *et al* (2015), 70% of patients in AMAGINE-2 and 69% of patients in AMAGINE-3 on brodalumab 210mg achieved PASI 90 at 12 weeks. These data were relevant and substantiate Dr B's comments on the video.

Leo stated that it did not therefore believe that Dr B's observations in relation to PASI 90 were misleading in breach of Clause 7.2.

PANEL RULING

The Panel considered that the part of the claim which stated 'The thing that surprises you is the number of patients who get PASI 90' was vague but, in the Panel's view, likely implied that it was a higher number than might be expected in the patient population being treated.

The Panel noted its comments at Point 12 including that 70% of patients in AMAGINE-2 and 69% of patients in AMAGINE-3 on Kyntheum 210mg achieved PASI 90 at 12 weeks.

The Panel noted its comments at Point 6 including that Puig *et al* (2020) evaluated the efficacy and safety of Kyntheum through 120 weeks in the AMAGINE-2 trial and of the patients who received 210mg every 2 weeks, 75.6% achieved PASI 90.

The Panel did not consider it necessary for all data presented by the speaker to have been mentioned in the SPC, as implied by the complainant; however, it should not be inconsistent with the SPC. The Panel considered that the complainant had not established that the part of the claim which stated 'The thing that surprises you is the number of patients who get PASI 90', in the context of the verbal account given, was misleading as alleged and no breach of Clause 7.2 was ruled.

75 Statement by Dr C 'With brodalumab we usually see PASI 100 in all of our patients within a 6 month period that we have started biologically naive patients on so PASI 100 is usually what we see'

COMPLAINT

The complainant stated that the doctor had failed to mention how many patients he had treated to make this claim. The claim of usually seeing PASI 100 in all patients within 6 months was not supported by the SPC and was atypical. It was misleading and grossly exaggerated the efficacy of the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo submitted that the statement by Dr C represented his/her own opinion and experience (it was prefaced by 'we usually see…'). The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. However, Leo was not aware of evidence indicating the effects of Kyntheum as measured by PASI 100 at 6 months and could not therefore substantiate Dr C's remarks. In these circumstances Leo accepted that Dr C's statement was not compliant with Clause 7.2 of the Code and Leo could not demonstrate that it was compliant with Clause 7.10.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Panel noted that Section 5.1 of the SPC stated that within the Kyntheum Phase III clinical trial programme (AMAGINE-1, AMAGINE-2 and AMAGINE-3) approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC

further stated that in all three clinical trials, examination of use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.

The Panel noted that the SPC gave pooled results from AMAGINE-2 and AMAGINE-3 which showed that 41.6% and 51% of patients administered Kyntheum 210mg every two weeks achieved PASI 100 at 12 and 52 weeks, respectively.

The Panel noted the reference to achievement of PASI 100 in 'all' patients in the claim at issue.

The Panel considered that the claim 'With brodalumab we usually see PASI 100 in all of our patients within a 6 month period that we have started biologically naive patients on so PASI 100 is usually what we see' was misleading and exaggerated the efficacy of Kyntheum as alleged and a breach of Clauses 7.2 and 7.10 was ruled as acknowledged by Leo.

76 Statement by Dr A 'I've had several patients on brodalumab for nearly a year and they haven't shown any deterioration. We haven't had to augment their topical treatment or give them a systemic treatment as well as the brodalumab so in my experience the response is persistent'

COMPLAINT

The complainant stated that this doctor had not qualified how many patients he/she had treated to make this statement. Brodalumab was not indicated for concomitant use with topical or systemic treatments. He/she did not state which type of patients should be left on the product for this length of time as the SPC initially recommends 16 weeks of treatment.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2 and 7.2.

RESPONSE

Leo did not believe this statement constituted a breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo stated that it did not agree that the presentation of data relating to the effects of Kyntheum for nearly a year conflicted with the SPC. Section 4.2 of the Kyntheum SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
> Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'

Leo stated that the complainant had misinterpreted this section of the SPC. There was no limit on the duration of use of Kyntheum. Discontinuation after 12-16 weeks was only recommended for those who had not responded to treatment. The guidance about continuation in patients with initial partial response was included to indicate that some of these patients might achieve better

results with longer treatment. It did not mean that this was the only patient group that could continue treatment beyond 16 weeks.

Section 5.1 of the SPC described the use of Kyntheum as maintenance treatment up to 52 weeks as this was the analysis presented in the submission for marketing authorisation. Figure 1 within Section 5.1, showed a graph which illustrated the percentage of patients reaching PASI 100 at 12 weeks (41.6%) and at 52 weeks (51.0%), demonstrating that complete skin clearance (PASI 100) was sustained through to one year. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for longer periods was not inconsistent with the SPC.

Leo submitted that in addition to data presented in the SPC, the Puig *et al* (2020) paper provided evidence of long term effects of Kyntheum. The paper was designed to evaluate the efficacy and safety of brodalumab through 120 weeks of Kyntheum treatment in the AMAGINE-2 trial. The study showed that clearance rates were sustained across the long term extension. 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100.

Leo submitted that Dr A's statements, based on his/her experience treating 'several' patients for up to one year were therefore consistent with the data presented in the SPC and the Puig et al paper.

Leo stated that brodalumab was not contraindicated for concomitant use with either topical or systemic treatments. Dr A did not refer to any specific topical or systemic therapy used concomitantly with Kyntheum and made no claims in relation to such use. The wording used on the video was not inconsistent with the SPC.

In summary, Leo submitted that the statements by Dr A were not inconsistent with the SPC and there was no breach of Clause 3.2. The references to duration of effects of treatment up to one year reflected the SPC and was readily supported by evidence consistent with Clause 7.2. Leo denied a breach of the Code.

PANEL RULING

The Panel noted that the Kyntheum SPC referred to three Phase 3 studies (AMAGINE-1, AMAGINE-2 and AMAGINE 3) and stated that all three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension. The Panel noted that the SPC reported results up to week 52.

The Panel noted that the SPC gave pooled results from AMAGINE-2 and AMAGINE-3 which showed that 41.6% and 51% of patients administered Kyntheum 210mg every two weeks achieved PASI 100 at 12 and 52 weeks, respectively.

Puig *et al* (2020) evaluated the efficacy and safety of brodalumab through 120 weeks in the AMAGINE-2 trial. The authors stated that of patients who received brodalumab 210mg every 2 weeks, 84.4%, 75.6%, and 61.1% achieved 75%, 90%, and 100% improvement from baseline in PASI at 120 weeks, respectively. The Panel noted that Puig *et al* concluded that brodalumab showed sustained skin clearance through 120 weeks.

In relation to the claim referring to treatment with Kyntheum for nearly a year with a persistent response, the Panel noted that the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, and therefore the complainant had not established that use of Kyntheum for nearly a year was inconsistent with the SPC as alleged and the Panel ruled no breach of Clause 3.2 in that regard.

In relation to the allegation that Kyntheum was not indicated for concomitant use with topical or systemic treatments, the Panel noted that Section 4.4 of the Kyntheum SPC (special warnings and precautions for use) stated:

> 'Concomitant immunosuppressive therapy
> The safety and efficacy of Kyntheum in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.'

The Panel further noted Leo's submission that Kyntheum was not contraindicated for concomitant use with either topical or systemic treatments and the health professional in question did not refer to any specific topical or systemic therapy used concomitantly with Kyntheum. In this regard, the Panel noted that the health professional's only reference to concomitant systemic treatment was that it was not needed. The complainant had not established that the health professional's reference to topical and systemic treatment was inconsistent with the particulars in the Kyntheum SPC and no breach of Clause 3.2 was ruled in that regard.

The Panel noted its comments above and considered that the complainant had not established that the statement given by the health professional in the context of the video at issue was misleading by virtue of not quantifying what he/she meant by 'several patients' in relation to a claim regarding persistent response and, on balance, no breach of Clause 7.2 was ruled.

77 Statement by Dr E 'Since we've commenced some patients on brodalumab, all of them have done very well, all of them have cleared or near cleared and so far that's been maintained to date and that's about 2 years'

COMPLAINT

The complainant stated this product did not have 2 year data in the SPC, the data did not report beyond week 52. This promoted the product in a manner not in accordance with the SPC. This doctor had not qualified how many patients he had treated to make this statement and his claims of clearance for 'all of them' were not a typical experience as per the SPC. The statement was unreferenced.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.6.

RESPONSE

Leo did not agree that the statement relating to clearance rates after 2 years of treatment was in breach of the Code. Section 5.1 of the SPC described the use of Kyntheum as maintenance treatment up to 52 weeks as this was the analysis presented in the submission for marketing authorisation. Since there was no restriction on duration of use in the SPC, presentation of information relating to use of Kyntheum for longer periods was not inconsistent with the SPC.

Leo submitted that the statement could be supported by Puig *et al* (2020). This study was designed to evaluate the efficacy and safety of brodalumab through 120 weeks of treatment in the AMAGINE-2 trial. The study showed that clearance rates were sustained across the long term extension. 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100.

Leo noted that the complainant alleged that Dr E had claimed clearance for all of his/her patients. However, what he/she in fact said was 'all of them have cleared or near-cleared…'. This statement was consistent with the data from Puig *et al* described above. Furthermore, the overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

In summary, Leo submitted that Dr E's statement was consistent with the SPC, which did not limit the duration of treatment with Kyntheum; Leo denied a breach of Clause 3.2 of the Code. The references to 'cleared or nearly cleared' at two years was substantiated by the data reported by Puig *et al* (2020), was accurate and not misleading consistent with the requirements of Clause 7.2.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Panel considered that Clause 7.6 was not relevant as the claim was not related to a published study and therefore no breach of Clause 7.6 was ruled.

The Panel noted its comments at Point 6 above which it considered were also relevant here. The Panel considered that companies might be able to make claims based on data with a longer time-period of observation than that cited in the SPC so long as the promotion was not inconsistent with the SPC and it complied with the Code. In the Panel's view, as the SPC did not give any recommendation on duration of treatment beyond 16 weeks for those patients who had responded to treatment, the complainant had not established that the use of Kyntheum beyond 52 weeks was inconsistent with the SPC as alleged and no breach of Clause 3.2 was ruled in that regard.

In relation to the reference to '…all of them have done very well, all of them have cleared or near cleared and so far that's been maintained to date and that's about 2 years', the Panel noted that Puig *et al* evaluated the efficacy and safety of brodalumab through 120 weeks in the AMAGINE-2 trial. The authors stated that of patients who received brodalumab 210mg every 2 weeks, 84.4%, 75.6%, and 61.1% achieved 75%, 90%, and 100% improvement from baseline in PASI at 120 weeks, respectively. The Panel noted that Puig *et al* concluded that brodalumab showed sustained skin clearance through 120 weeks.

The Panel considered that the claim 'Since we've commenced some patients on brodalumab, ***all of them*** have done very well, ***all of them*** **have cleared or near cleared** and so far that's

been maintained to date and that's about 2 years (emphasis added)' was misleading as to the results likely to be seen with Kyntheum treatment based on clinical trial data of PASI 75%, 90% and 100% and therefore was misleading with regard to the expected efficacy of the product. A breach of Clause 7.2 was ruled.

78 Statement by Dr B 'We started using Kyntheum shortly after NICE Technology approval that came through'

COMPLAINT

The complainant alleged that use of NICE endorsement in promotion was prohibited by the Code, therefore mention of NICE should not be used.

When writing to Leo, the Authority asked it to consider the requirements of Clause 9.6.

RESPONSE

Leo did not agree that the statement 'We started using Kyntheum shortly after NICE Technology approval that came through' constituted reproduction of NICE guidance for promotional purposes. There was no reproduction of NICE's Technology Appraisal Guidance (TA511), Dr B simply referred to the timing of NICE's guidance to indicate when he started prescribing Kyntheum and suggested that such guidance was positive, through the use of the word 'approval'. There was no prohibition on references to NICE in the Code, as suggested by the complainant and the reference by Dr B did not breach Clause 9.6 of the Code.

PANEL RULING

The Panel considered that the statement in question made by the health professional in this promotional video did not constitute the reproduction of NICE guidelines; it was a reference to using the medicine in relation to timelines after it received NICE approval and therefore the complainant had not established that a breach of the Code had occurred in that regard and no breach of Clause 9.6 was ruled.

79 Statement by Dr D 'Their psoriasis starts going away very quickly and they start engaging with other healthy programmes, losing weight getting their confidence back. It really makes me feel great to see that it works so fast and so well'

COMPLAINT

The complainant stated the term 'very quickly' was not qualified and the sentence was all encompassing implying all patients would experience their psoriasis 'going away very quickly'. 'So fast' and 'So well' had also not been qualified and were superlatives.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.10.

RESPONSE

Leo did not believe this statement constituted a breach of the Code. The claim that 'it works so fast and so well' and 'starts going away very quickly' was not qualified, but was based on personal experience, as reinforced by the statements 'It really makes me feel really great'. The

overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. Whilst Dr D did not provide additional clarity around what constituted 'so fast' or 'so well', evidence from Yao and Lebwohl demonstrated that the time for 25% of patients to achieve PASI 75 was 2.1 weeks, based on 1,236 patients. This measure equated to TOA or the time until the onset of action – a statistically reliable and clinically relevant measure of speed of efficacy. Yao and Lebwohl conclude that 'Brodalumab may continue to have the most rapid onset of action of available antipsoriatic therapies'. It was therefore reasonable for a clinician to describe the effect of Kyntheum as 'it works so fast and so well'. These statements were not superlatives (which would instead have involved use of the words 'fastest' and 'best') and reflected the referenced data. Leo denied a breach of Clause 7.10.

PANEL RULING

The supplementary information to Clause 7.10 stated, *inter alia*, that superlatives were grammatical expressions which denoted the highest quality or degree, such as best, strongest, widest etc. The Panel considered, based on the very narrow allegation, that the complainant had not established that 'so fast' and 'so well' within the context of the claim at issue were superlatives and based on the complainant's narrow allegation in this regard no breach of Clause 7.10 was ruled.

The Panel noted that 'so fast' and 'so well' had not been qualified as alleged but that this allegation was not covered by Clause 7.10 which was the only Clause that had been raised in relation to this point.

In relation to the allegation that the term 'very quickly' was not qualified and that the claim was all encompassing, the Panel considered that the statement implied that Kyntheum would produce 'fast' and 'very quick' positive results in all treated patients which exaggerated the medicine's properties and a breach of Clause 7.10 was ruled.

APPEAL BY LEO

Leo submitted that the quotation from the statement by Dr D provided by the complainant was incomplete. If this was provided in its entirety it started:

> 'I have a number of patients who are extremely obese. They are extremely embarrassed about their bodies and plus they have psoriasis. With them the delight is incredible ….'

Dr D then proceeded with the text quoted.

Leo submitted that taken as a whole it was therefore clear that Dr D was referring to the experiences of a small subset of his/her patients. There was no suggestion that Dr D's statement encompassed all treated patients. The fact that a number of Dr D's patients (he/she does not say 'all patients' or 'most patients') experienced very quick results was consistent with the data from the AMAGINE studies as reported in the SPC for Kyntheum, which indicated that around 10% of patients experienced PASI 100 clearance approximately 4 weeks after treatment commenced. Dr D's statement was therefore consistent with the SPC, did not exaggerate the properties of Kyntheum and was not in breach of Clause 7.10.

APPEAL BOARD RULING

The Appeal Board considered that regardless of whether the health professional was talking specifically about obese patients, the claim was all encompassing; it implied that Kyntheum would produce 'fast' and 'very quick' positive results in all such treated patients which exaggerated the medicine's properties. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10. This appeal on this point was not successful.

80 Statement by Dr A 'It's a fabulous feeling when you've promised to get someone's psoriasis away and the drug works and the patients come back every time with a big smile on their face'

COMPLAINT

The complainant stated the 'drug works' was a guarantee and such language should not be used in promotional videos. The only reference for all of the above claims was the Kyntheum SPC – the complainant stated that clearly the Kyntheum SPC did not support the content of these paid for testimonials from the doctors.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Leo did not agree that these statements constituted a breach of the Code. Dr A's statement 'it's a fabulous feeling … when the drug works' plainly did not infer that Kyntheum would work in all cases. In fact, his/her wording suggested the opposite; it was only in the cases when the treatment was effective that she obtained a fabulous feeling. The statement must also be considered in the context of the holding statement at the beginning of the video that 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo submitted that Dr A's statements were based on his/her own personal experience and indicated simply that patients derive some benefit from treatment with Kyntheum. (The reference to 'patients come back every time with a big smile on their face' conveyed nothing more than patients were pleased with the effects of treatment.) There was in any event good evidence that well over the majority of patients would achieve a substantial response to Kyntheum. In Puig *et al* (2020), 84.4% of patients achieved PASI 75 improvement from baseline at 12 weeks, so an expectation of some response was realistic and representative in the majority of patients. This was not inconsistent with the SPC, which simply described the proportion of patients who achieved PASI 75 at weeks 12 and 52 but did not address the proportion of patients who exhibit some response or what might be observed in real world clinical practice.

Leo submitted that Dr A's statement was consistent with and reflected the SPC, which in turn substantiated the content. There was no exaggeration of the properties of Kyntheurm.

In summary, Leo stated that the limited claim of treatment benefit in this video was accurate and balanced and consistent with the SPC, as required by Clauses 7.2 and 7.4 and the overall content complied with Clause 7.10 of the Code.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Panel considered that reference to 'when you've promised to get someone's psoriasis away and the drug [Kyntheum] works and the patients come back every time with a big smile on their face' was not a balanced claim. In the Panel's view, the claim exaggerated Kyntheum's properties by implying that treatment would certainly work in all treated patients and all Kyntheum treated patients would be satisfied with their treatment; a breach of Clauses 7.2 and 7.10 were ruled. The misleading implication could not be substantiated and a breach of Clause 7.4 was ruled.

APPEAL BY LEO

Leo submitted that the issue raised in this point of appeal was similar to that in allegation 67 considered above. Again, Dr A was referring to the promise he/she made to certain patients that he/she would successfully treat their psoriasis ('get someone's psoriasis away'), wording the Panel had construed as involving a promise that Kyntheum would clear the patient's psoriasis. Leo disagreed. Dr A's promise to his/her patients was separate from consideration of any individual treatment. However, once having made that promise he/she described a 'fabulous feeling' when he/she used a treatment which delivered on the promise he/she had made. There was no suggestion that Dr A promised that Kyntheum would be effective in delivering clear skin to all patients and, in fact, the comment that he/she got a 'fabulous feeling' when the 'drug' he/she prescribed did result in clear skin made clear that it did not do so in every patient. In these circumstances, Leo did not accept the findings of breach of Clauses 7.2, 7.4 and 7.10.

APPEAL BOARD RULING

The Appeal Board considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Appeal Board was in no doubt that the health professional was talking about Kyntheum when he/she stated that 'It's a fabulous feeling when you've promised to get someone's psoriasis away and the drug works and the patients come back every time with a big smile on their face'; the claim was stated in a Kyntheum promotional video entitled 'clinical experience with Kyntheum' and the Kyntheum logo was in the bottom right hand corner of the screen as the claim was made.

The Appeal Board considered that the claim 'when you've promised to get someone's psoriasis away and the drug [Kyntheum] works and the patients come back every time with a big smile on their face' was not balanced. The Appeal Board considered that the claim exaggerated Kyntheum's properties by implying that treatment would certainly work in all treated patients and all Kyntheum treated patients would be satisfied with their treatment and this could not be

substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.10. The appeal on all points was unsuccessful.

Video: Patients who have experienced failures on previous biologics (UK/IE MAT-27681 V3 August 2020)

This video was included in the 'Efficacy' and 'Resources' tabs.

81 Statement by Dr A 'After switching from biologics it doesn't seem to matter, I had one patient who had had every single treatment that was available to him and we were unable to get his PASI score below 10 and within 2 injections of brodalumab, he was clear which is remarkable'

COMPLAINT

The complainant stated that this claim was not representative of the data in the SPC and brought false hope. 'He was clear which is remarkable' was an exaggerated claim - the product did not provide such results within 2 injections - if it did, it was an isolated case, and not consistent with the trial data in the SPC.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2, 7.10 and 26.2.

RESPONSE

Leo did not believe this statement was in breach of the Code. The overall content of the video must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo submitted that the statement by Dr A started with 'I had one patient …' – this put the rest of the statement in context by clarifying that it was an isolated case study, and therefore not reflective of the likely results in other patients. Not only that, but Dr A concluded the statement by saying that the response described 'is remarkable', indicating that it was exceptional or unusual. Since Dr A made clear that this was not a typical response, Leo stated that it did not believe it was inconsistent with the content of the SPC.

Leo submitted that the website was directed solely at health professionals and not at members of the public.

In summary Leo submitted that the statement by Dr A referred to a single case study and the video made clear that the views expressed were not claimed to represent a typical patient. The content of the statement was not therefore inconsistent with the SPC, contrary to Clause 3.2, it was not misleading contrary to Clause 7.2 and the effects of Kyntheum were not exaggerated contrary to Clause 7.10. The video was directed solely to health professionals so there could be no breach of Clause 26.2 of the Code.

PANEL RULING

The Panel disagreed with Leo's submission that as it was an isolated case study it was not reflective of results likely to be seen in other patients. The video in question was promotional material and any statement made by a health professional about Kyntheum in promotional material must comply with the requirements of the Code. Further it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties. The disclaimer at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient' did not provide a platform for claims that did not comply with the Code to be made.

The Panel noted that Section 5.1 of the SPC stated that within the Kyntheum Phase III clinical trial programme (AMAGINE-1, AMAGINE-2 and AMAGINE-3), approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC further stated that in all three clinical trials, examination of use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.

The Panel considered that the patient described by the health professional who had had 'every single treatment that was available to him and we were unable to get his PASI score below 10' was not representative of the majority of patients in the clinical trial programme.

The Panel noted that Section 4.2 of the SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.'

The SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

In the Panel's view, 'clear' skin within 2 injections of brodalumab was not a clinical response expected in the majority of Kyntheum treated patients.

The Panel considered that the claim '…within 2 injections of brodalumab, he was clear which is remarkable' was inconsistent with the particulars in the SPC, misleading and exaggerated Kyntheum's properties and a breach of Clauses 3.2, 7.2 and 7.10 were ruled.

The Panel considered that the complainant had not established that the video within the website would be viewed by members of the public or patients; as noted above it was aimed at health professionals and therefore Clause 26.2 was not relevant; no breach of Clause 26.2 was ruled.

82 Statement by Dr F 'from the clinical trials we had quite high hopes for brodalumab in terms of PASI 90 responses but what we were not so sure of is how patients who had failed multiple other biologics in particular multiple other IL-17 drugs would fair and so far our experience has been positive. We have had patients who have failed both one and two anti IL 17s who have gone on to respond very quickly and very well to brodalumab'.

COMPLAINT

The complainant stated that there was no efficacy data in the SPC in patients who had failed 'multiple other biologics' and therefore the comparative claims were not substantiated.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.3 and 7.4.

RESPONSE

Leo did not agree that this statement breached the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo submitted that the statement by Dr F in relation to responses in patients who had 'failed both one and two anti IL 17s' was clearly based on personal experience, as it was prefaced by the wording 'We have had patients …'. In addition, Dr F's personal experience was substantiated by published trial data, most notably from Papp *et al* (2018), showing that, in patients who had been successfully treated with prior biologics, the proportion of patients achieving PASI 75, 90 and 100 at week 12 were 86.3%, 70.4% and 41.7% respectively. The statement did not compare Kyntheum with other therapies and no specific product was referenced. It simply referred to the effects of the product in patients who had previously undergone unsuccessful treatment with biological products and were likely to comprise a group with resistant disease.

In summary, Leo submitted that the statement by Dr F was not misleading and did not involve a comparison in breach of Clause 7.3 and his/her views were capable of substantiation consistent with Clause 7.4 of the Code.

PANEL RULING

The Panel noted that Section 5.1 of the SPC stated that within the Kyntheum Phase III clinical trial programme (AMAGINE-1, AMAGINE-2 and AMAGINE-3) approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC further stated that in all three clinical trials, examination of use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.

The Panel considered that the claim in question was not a comparison of Kyntheum with other treatments; it was a reference to prior biological therapy having been used before commencing treatment with Kyntheum. Based on the narrow allegation, that comparative claims were not substantiated, the Panel ruled no breach of Clauses 7.3 and 7.4.

83 Use of 'very quickly' and 'very well' and reference to PASI 90 in Point 82

COMPLAINT

The complainant alleged that 'Very quickly' and 'Very well' were superlatives and there was no quantification of the results observed.

The complainant stated that PASI 90 was not the primary endpoint in the brodalumab studies - it was PASI 75 so referring to PASI 90 was confusing.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2 and 7.10.

RESPONSE

Leo did not agree that these statements were in breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. This was a personal experience statement, based on the preceding wording 'We have had patients…'. As such, it did not require specific substantiation.

Leo submitted that substantial data were available confirming the benefits of Kyntheum in terms of PASI 90 and the fact that other studies reported in the SPC refer to PASI 75 did not make data based on PASI 90 confusing. The paper by Puig *et al* (2020), reported that 75.6% of patients achieved PASI 90 at 120 weeks. In addition, in the supplementary appendix for Lebwohl (2015), 70% of patients in AMAGINE-2 and 69% of patients in AMAGINE-3 on brodalumab 210mg achieved PASI 90 at 12 weeks.

Leo submitted that in terms of rapidity of effect, Yao and Lebwohl concluded that 'Brodalumab may continue to have the most rapid onset of action of available antipsoriatic therapies'. The fact that Dr F had described the effect of Kyntheum as working 'Very quickly' and 'Very well' was consistent with this conclusion. For the avoidance of doubt, 'very quickly' and 'very well' were not superlatives (the relevant terms would have been 'fastest' or 'quickest' and 'best). While Dr F did not describe how quickly or how well his/her patients responded, such information was available from the Puig *et al* paper.

In summary, Leo submitted that the personal views of Dr F were consistent with published data and not misleading as required by clause 7.2. No superlatives were used by Dr F and the statement did not exaggerate the benefits of Kyntheum consistent with Clause 7.10 of the Code.

PANEL RULING

The Panel considered that 'very quickly' and 'very well' were not superlatives when used in the context of the claim at issue and, based on the very narrow allegation, no breach of Clause 7.10 was ruled.

In relation to the allegation regarding PASI 90 not being the primary endpoint in clinical trials, the Panel considered that the complainant had not established that reference to PASI 90 within the claim at issue would misleadingly imply that PASI 90 was the primary endpoint in the clinical trial programme as alleged and based on the complainant's very narrow allegation no breach of Clause 7.2 was ruled in that regard.

84 Statement by Dr D 'Over the past 5 years in my biologics clinics I've noticed that some patients have failed on other biologics treatments and I needed to switch them to Kyntheum and I was very glad to see that they respond very well'

COMPLAINT

The complainant stated there was no explanation as to why the doctor 'needed' to switch to Kyntheum. A rating scale or measure had not been included to allow the response of 'very well' to be interpreted.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that the statement was in breach of the Code. This was a personal experience statement, based on the starting wording 'Over the past 5 years in my biologics clinics, I've noticed …'. Furthermore, the overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo submitted that, in addition, Dr D's personal experience was reflective of clinical data, most notably from Papp *et al* (2018), showing that in patients who had been successfully treated with prior biologics, the proportion of patients achieving PASI 75, 90 and 100 at week 12 were 86.3%, 70.4% and 41.7% respectively. These significant proportions of patients achieving a 75%, 90% or 100% improvement in psoriasis lesions were entirely consistent with Dr D's opinion that such patients 'respond very well'.

Leo submitted that, accordingly, the statement by Dr D was accurate and balanced consistent with the requirements of Clause 7.2 of the Code.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue.

The Panel noted that Section 5.1 of the SPC stated that within the Kyntheum Phase III clinical trial programme (AMAGINE-1, AMAGINE-2 and AMAGINE-3) approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC further stated that in all three clinical trials, examination of use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.

The Panel noted that Papp *et al* (2018) evaluated the impact of previous biologic use on the efficacy and safety of brodalumab in an integrated analysis of AMAGINE-2 and AMAGINE-3. The authors stated that at week 12 PASI 75 was achieved by 81.7% of biologic-experienced and 87.1% of biologic- naive patients (P = 0.31 between the two brodalumab groups). PASI 90 was achieved by 63.8% of biologic-experienced and 71.6% of biologic-naive patients (P = 0.32 between the two brodalumab groups). PASI 100 was achieved by 39.5% of biologic-experienced and 40.9% of biologic-naive patients (P = 0.64 between the two brodalumab groups). The authors further stated that in the efficacy analysis of patients where prior use of biologics had been successful, the proportions treated with brodalumab achieving PASI 75, 90 and 100 at week 12 were 86.3%, 70.4%, 41.7% compared with 81.3%, 62.7%, 32.0% in patients where previous treatment with a biologic had failed.

The Panel noted that the complainant stated there was no explanation as to why the doctor 'needed' to switch to Kyntheum. In the Panel's view, it was clear that the health professional had switched patients to Kyntheum when they had failed on other biologics treatments and no breach of Clause 7.2 was ruled in that regard.

The Panel considered that whilst it would have been helpful to clarify the response seen, the complainant had not established that the lack of inclusion of a rating scale or measure with regard to the claim 'I was very glad to see that they respond very well' after switching to Kyntheum in the context of the video would be misleading to the intended health professional audience and no breach of Clause 7.2 was ruled.

85 Statement by Dr A 'I used it initially in a patient who had failed on everything else on combination treatments and on every other biologic that we had available to us and was so impressed that even after the first injection before the next injection he was nearly clear and this is a guy we hadn't managed to get his PASI score below 10 on any combination so anecdotally he was my star patient and I've used it in other patients since'

COMPLAINT

The complainant alleged that the anecdotal information was not appropriate for promotional use. The claims of clearance after one injection in this resistant patient did not align with the SPC and exaggerated the efficacy of the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.10.

RESPONSE

Leo did not agree that the statement was in breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo submitted that Dr A commenced this statement with 'I used it initially in a patient…'. This puts the entire statement in context – in other words demonstrating that this was the experience of a single patient and clarifying that it did not imply that this might be used to infer similar responses in other patients. The benefits described in the single patient described by Dr A did not conflict with the SPC, which did not specify the treatment effects visible after one to two injections, but simply referred to the proportion of patients who had achieved PASI75 or PASI 100 by week 12 of the clinical trials. Inevitably patients would respond to treatment at different rates and the experience of Dr A's patient was not therefore inconsistent with the trial data as reported in the SPC.

Leo submitted that a single anecdotal report did not require substantiation. However, the potential benefits of Kyntheum in patients who had previously been treated with other biologic agents was demonstrated by Papp *et al* (2018), in which, the proportion of patients achieving PASI 75, 90 and 100 at week 12 was 86.3%, 70.4% and 41.7% respectively.

Leo stated that Dr A made clear that the patient described was not typical (described as his/her 'star patient) consistent with the holding statement described above which confirmed that the statements in the video were not claimed to reflect the typical patient response; the effects of Kyntheum were not therefore exaggerated.

In summary, Leo submitted that the statement by Dr A was not inconsistent with the SPC contrary to Clause 3.2, it was not misleading contrary to Clause 7.2 and it did not exaggerate the benefits of Kyntheum contrary to Clause 7.10 of the Code.

PANEL RULING

The Panel considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue. Further it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties.

The Panel noted that Section 5.1 of the SPC stated that within the Kyntheum Phase III clinical trial programme (AMAGINE-1, AMAGINE-2 and AMAGINE-3) approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC further stated that in all three clinical trials, examination of use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.

The Panel noted that Section 4.2 of the SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.'

The SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

In the Panel's view, 'nearly clear' skin after the first injection of brodalumab was not a clinical response expected in the majority of Kyntheum treated patients.

The Panel considered that the claim was inconsistent with the particulars in the SPC, misleading and exaggerated Kyntheum's properties and a breach of Clauses 3.2, 7.2 and 7.10 were ruled.

APPEAL BY LEO

Leo submitted that this allegation arose from a video 'Kyntheum - the story so far' (August 2020; UK/IE MAT-27681), a copy of which was provided at Annex 9.

Leo disagreed with the assessment of the Panel in relation to:

> The patient described by Dr A was not presented as representing a typical patient treated with Kyntheum. This was confirmed by:

- The statement at the commencement of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum - individual response and experience may vary from patient to patient'.
- Dr A's description of the patient and his response to treatment:
    - which is inconsistent with any allegation that this was a claim for a standard response; and
    - the wording 'so anecdotally he was my star patient …' which confirmed the unusual and exceptional nature of the outcome.

While the patient described by Dr A did not represent a typical response to Kyntheum treatment, such outcomes in terms of PASI 75 clearance were reported in the clinical trial data (Lebwohl *et al* (2015)). Dr A made clear in his/her description that he/she was referring to an exceptional response seen in a single patient. This did not, therefore, exaggerate the properties of Kyntheum.

The complainant asserted that the statement of Dr A did not align with the SPC. However, the correct test for the purposes of Clause 3.2 of the Code was not whether the statement reflected data included in the SPC, but whether the statement was inconsistent with the SPC. The fact that the SPC was silent in relation to an issue did not mean that a statement referring to that issue was necessarily inconsistent with the SPC. In this case, the SPC for Kyntheum did not exclude the possibility of a response to treatment following the first injection and, while the data reported in the SPC indicated that a PASI 75 response would not be seen in the majority of patients at that stage, the data quoted by the Panel (20-25% at 2 weeks) was entirely consistent with the exceptional case described by Dr A.

In these circumstances, Leo submitted that Dr A's statement did not breach Clauses 3.2, 7.2 and 7.10 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that statements in promotional material in relation to a health professional's clinical experience needed to comply with the requirements of the Code, including that such statements must not be misleading as to the treatment outcomes expected in the patient population at issue. Further it was an established principle that individual patient cases in promotional material must not be misleading or exaggerate a medicine's properties.

The Appeal Board noted that Section 5.1 of the SPC stated that within the Kyntheum Phase III clinical trial programme (AMAGINE-1, AMAGINE-2 and AMAGINE-3) approximately 30% of patients had previously received a biological and 13% of patients were biological failures. The SPC further stated that in all three clinical trials, examination of use of prior biologics, and biologic failures did not identify differences in response in all key endpoints [PASI 75, PASI 100, sPGA success (0 or 1), and sPGA clear (0)] to Kyntheum among these subgroups.

The Appeal Board noted that Section 4.2 of the SPC stated:

> 'Posology
> The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.'

The Kyntheum SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials. The Appeal Board considered that the response rate after one injection was likely to be lower than this.

In the Appeal Board's view, 'nearly clear' skin after the first injection of brodalumab was not a clinical response expected in the majority of Kyntheum treated patients and was thus misleading and exaggerated Kyntheum's properties and the Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal on these rulings was unsuccessful.

The Appeal Board noted that the health professional was referring to one specific patient who had an exceptional outcome. Whilst it was misleading and exaggerated Kynethum's properties to use such an exceptional case in promotional material, the Appeal Board considered that the SPC did not preclude one patient achieving such an outcome and in this regard the Appeal Board considered that the claim at issue was not inconsistent with the SPC and it ruled no breach of Clause 3.2. The appeal on this ruling was successful.

86 Statement by Dr E 'My patients' experience of starting or switching to brodalumab has been really positive and as a consequence my experience understanding what it's like for them to live with psoriasis and then to live without psoriasis and crucially without the knock on effects of psoriasis in terms of quality of life but also in terms of self confidence anxiety depression, it's really made my job much more enjoyable because then I can know that my patients are thriving and engaging in life in a much more positive way'

COMPLAINT

The complainant stated this statement was very broad and all encompassing - all patients had had a 'really positive' experience with Kyntheum. This did not provide a realistic view of the product in terms of efficacy or safety.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.2, 7.9, 7.10 and 9.1.

RESPONSE

Leo did not agree that the statement by Dr E breached the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. The statement by Dr E was based on his/her personal experience, as indicated by the beginning wording 'My patients' experience …'.

Leo submitted that whilst his/her statement inferred that the overall experience of his/her patients had been positive, he/she did not say that 'all' his/her patients had had a 'really positive' experience. In these circumstances, Dr E's references to patients living with and without psoriasis were entirely consistent with the trial data, including that reported in the SPC and the results from the long term extension AMAGINE-2 trial reported by Puig *et al* (2020), which showed that 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks,

75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100. The statement included no superlatives and did not exaggerate the benefits of Kyntheum.

Leo submitted that the statement around anxiety and depression could be substantiated from AMAGINE-1 (Kurd S *et al* 2010). This phase III study specifically looked at anxiety and depression. The baseline HADS scores for anxiety and depression were 6.7 and 5.5 respectively in the brodalumab 210mg cohort (221 patients) and 6.4 and 5.3 respectively in the placebo cohort (220 patients). After 12 weeks of treatment, the HADS scores for anxiety and depression were 4.9 and 3.5 respectively in the brodalumab 210mg cohort and 6.3 and 5.5 respectively in the placebo cohort. These results were statistically significant (both $p<0.001$ vs placebo) demonstrating a significant effect of treatment with brodalumab on anxiety and depression.

Leo submitted that the statement around self confidence could be substantiated from Warren *et al* (2021). Quality of life was commonly assessed in dermatological conditions using the DLQI (Dermatology Life Quality Index) which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the questions within DLQI specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence. Warren *et al* demonstrated through analysing the results of the AMAGINE-2 and AMAGINE-3 studies a significant positive association between PASI response level and DLQI 0/1 achievement ($P<0.0001$).

Leo submitted that the statement by Dr E did not suggest that Kyntheum had no adverse effects and did not say that the product was safe.

In summary, Leo submitted that the statement made by Dr E reflected his/her own personal experience, although his/her references to the effects of Kyntheum could be substantiated by the SPC and published data, so they were not misleading, consistent with Clause 7.2 and the effects of Kyntheum were not exaggerated consistent with clause 7.10. The statement did not suggest that Kyntheum had no adverse effects and reflected the requirements of Clause 7.9. In these circumstances Leo did not believe there was any basis for concluding that the statement failed to maintain high standards as required by Clause 9.1 or brought the industry into disrepute contrary to Clause 2.

PANEL RULING

The Panel considered that the statement in question was a broad sweeping statement regarding a physician's clinical experiences with Kyntheum. However, the information provided in relation to positive effects on quality of life, self-confidence, anxiety and depression and the implication that it applied to all of his patients who were 'thriving and engaging in life' did not provide a balanced view of the efficacy and safety of the medicine and exaggerated the medicine's properties and a breach of Clauses 7.2 and 7.10 were ruled. High standards had not been maintained in this regard and a breach of Clause 9.1 was ruled.

The Panel considered that the complainant had not made out his/her complaint in relation to Clause 7.9 which required, *inter alia*, that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience and no breach of Clause 7.9 was ruled in that regard.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel considered that its rulings of breaches of the Code on this point, including that high standards had not been maintained, adequately covered the matter and no breach of Clause 2 was ruled.

Video: Patient experience of Kyntheum (August 2020 UK/IE MAT-27680 V3)

This video was included in the 'Efficacy' and 'Resources' tabs.

87 Statement by Dr A 'When you clear someone's psoriasis when they've had psoriasis for many years the patients themselves they change, they become much more confident. They wear different clothes, they wear different hairstyles because they can all sorts of things within their workplace. They get promoted much more they have less time off work, they just blossom, you get rid of someone's psoriasis and they simply just blossom'

COMPLAINT

The complainant stated this statement guaranteed that the product would 'clear someone's psoriasis' therefore greatly exaggerated the impact of the product in terms of efficacy and in turn extrapolating this to things like being promoted at work. It was entirely unsuitable content for a promotional video for a prescription only medicine.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.10.

RESPONSE

Leo did not agree that this statement constituted a breach of the Code. The statement 'When you clear someone's psoriasis…' in no way provided a guarantee that the product would 'clear someone's psoriasis'. Dr A was talking about his/her own personal experience, and how it affected patients on the occasions when their psoriasis did clear. In addition, in this statement, the clinician made no mention of the product or products used to produce the clearance. These statements were therefore generic observations about the benefits of successful treatment for psoriasis.

However, Leo accepted that the statement was made in a video entitled 'Patient experience of Kyntheum' so it was reasonable to assume that Dr A intended to convey the message that Kyntheum might achieve the results he/she described. There was however no guarantee that such benefits would be seen in every patient. The overall content of the statement must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'.

Leo submitted that in terms of the particular benefits described by Dr A, these were reflective of clinical data. The effects of Kyntheum in clearing psoriasis were reported in the SPC and also demonstrated by the results from the long term extension AMAGINE-2 trial reported by Puig *et al* (2020), which showed that 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100. The statement included no superlatives and did not exaggerate the benefits of Kyntheum.

Leo submitted that the statement around confidence was consistent with Warren *et al* (2021). Quality of life was commonly assessed in dermatological conditions using the DLQI which provided a score of 0 (no impact on patient's life) to 30 (extremely large effect on patient's life). Although none of the questions within DLQI[2] specifically referred to confidence, they did cover embarrassment, self-consciousness, interference with activities of daily life and creating problems with partners, close friends and relatives, all of which Leo felt were related to overall confidence. A paper by Warren *et al* analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement ($P<0.0001$).

Overall, Leo submitted that the statement included no superlatives and did not exaggerate the benefits of Kyntheum contrary to Clause 7.10 of the Code.

PANEL RULING

The Panel disagreed with Leo's submission that as the clinician had made no mention of the product or products used to produce the clearance the statements were therefore generic observations about the benefits of successful treatment for psoriasis. The Panel noted that the claim was made in the context of a Kyntheum promotional video which also made claims regarding skin clearance with Kyntheum and therefore health professionals viewing the video would likely associate the statements made by this health professional with patients who had been treated with Kyntheum.

Whilst the Panel did not consider that the claim implied that Kyntheum was guaranteed to clear someone's psoriasis as alleged, it considered that associations made between an individual's clearance of psoriasis and him/her being promoted at work in the context of a promotional video entitled 'Patient experience of Kyntheum', exaggerated the properties of Kyntheum as alleged and a breach of Clause 7.10 was ruled.

APPEAL BY LEO

Leo submitted that the complainant had misquoted the statement by Dr A and that the grammatical errors and omissions had altered the meaning and interpretation of the video. In particular, the correct quotation of the relevant section of Dr A's statement should be reproduced as follows:

> 'They wear different clothes. They wear different hairstyles because they can. All sorts of things within their workplace. They get promoted much more.
> They have less time off work.'

Leo submitted that Dr A's statement therefore indicated that effective treatment of psoriasis was not a trivial matter but resulted in improved confidence and changes in behaviour and social interactions which might make a material difference in patient's lives. There was no suggestion that treatment of psoriasis generally (and use of Kyntheum in particular) directly caused a patient to wear different clothes and so on, but that the fact that a psoriasis patient felt better had these effects. It also meant that they required less time off work due to their skin condition, which, in turn, improved their promotion prospects.

Leo submitted that the impact of psoriasis on absence from work was well documented (for example, Finlay and Coles (1995) (Finlay AY and Coles EC. The effect of severe psoriasis on

the quality of life of 369 patients. Br J Dermatol 1995 Feb;132(2):236-44.)). Improved promotion prospects would, of course, be true following treatment of any chronic illness that resulted in periods of absence from work, with reduced opportunity to gain skills and experience.

Leo submitted that the SPC for Kyntheum recorded the impact of treatment on quality of life including the Dermatology Life Quality Index (DLQI) which included questions on the impact of the relevant skin condition on ability to work. Over 50% of patients treated with Kyntheum in AMAGINE-1, AMAGINE-2 and AMAGINE-3 scored 0-1 (the most favourable scores) on the DLQI at 12 weeks compared with 7% or less in patients who received placebo. In these circumstances, when considered in its correct form, the statement by Dr A was not unreasonable and did not exaggerate the effects of Kyntheum.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'When you clear someone's psoriasis when they've had psoriasis for many years the patients themselves they change, they become much more confident. They wear different clothes, they wear different hairstyles because they can all sorts of things within their workplace. They get promoted much more they have less time off work, they just blossom, you get rid of someone's psoriasis and they simply just blossom' in the context of a Kyntheum promotional video entitled 'Patient experience with Kyntheum', meant that health professionals would associate this claim with Kyntheum treatment.

The Appeal Board accepted that psoriasis was a debilitating disease that affected quality of life in many different ways, however, there was no data to show that treatment with Kyntheum increased likelihood of promotion at work. The Appeal Board considered that the claim exaggerated the properties of Kyntheum as alleged and it upheld the Panel's ruling of a breach of Clause 7.10. The appeal on this point was not successful.

88 Statement by Dr B 'I had one patient, a lady who had terrible psoriasis, she worked in healthcare and this was effecting her day to day work. I started treating her with Kyntheum and the next time I saw her she was a changed lady, her skin was totally clear and she couldn't believe how well the drug worked and how much easier it made her day to day life both socially and in terms of conducting her job'

COMPLAINT

The complainant stated this claimed that Kyntheum would make day to day life easier but was not referenced. The doctor failed to mention that the product was only for plaque psoriasis – his/her statement promoted the product in all types of psoriasis. Dr B did not state when he/she reviewed the patient to make the assessment of 'totally clear' and yet again hypes this product in an unrealistic manner.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.6 and 7.10.

RESPONSE

Leo did not believe that this statement was in breach of the Code. The entire website and all of this video related to the use of Kyntheum for the treatment of plaque psoriasis. It would be

unreasonable to conclude in these circumstances that this shorthand reference simply to 'psoriasis' was intended to promote use of Kyntheum for psoriasis indications other than that considered throughout the website or that health professionals accessing the website would construe it in that way. Leo do not therefore accept that the statement by Dr B was inconsistent with the SPC.

Leo submitted that the reference to 'totally clear' was consistent with the trial data, including that reported in the SPC and the results from the long term extension AMAGINE-2 trial reported by Puig *et al* (2020), which showed that 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100. The statement included no superlatives and did not exaggerate the benefits of Kyntheum.

In summary, Leo submitted that the statement by Dr B, considered in context, did not promote Kyntheum beyond the terms of the SPC contrary to Clause 3.2. The statements were capable of substantiation, but did not refer to published studies, therefore there was no requirement to provide clear references in accordance with Clause 7.6 and the properties of Kyntheum were not exaggerated contrary to Clause 7.10.

PANEL RULING

The Panel noted that the first slide of the video, which was displayed for 4 seconds, stated, *inter alia*, 'Kyntheum (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy'. The Panel considered therefore that the complainant had not established that the claim in question promoted the product in all types of psoriasis as alleged and no breach of Clause 3.2 was ruled.

The Panel considered that Clause 7.6 was not relevant as the claim was not in relation to a published study and therefore no breach of Clause 7.6 was ruled.

Based on the narrow allegation that not stating when he reviewed the patient to make the assessment of 'totally clear' 'hypes this product in an unrealistic manner', the Panel noted that the health professional referred to the patient's skin being totally clear the next time he/she saw her after starting treatment. It was not clear what timeframe that was.

The Panel noted that the SPC gave pooled PASI 100 results from AMAGINE-2 and AMAGINE 3 which showed that 41.6% and 51% of patients administered Kyntheum 210mg every 2 weeks achieved PASI 100 at 12 and 52 weeks, respectively. The Panel noted that Kyntheum was intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis. Whilst it would have been helpful for the health professional to have stated how long after initiation he reviewed the patient to make his/her assessment, the Panel considered that the complainant had not established that the health professional referring to the patient having totally clear skin the next time he/she saw the patient hyped the product in an unrealistic manner as alleged and based on the very narrow allegation the Panel ruled no breach of Clause 7.10.

89 Statement by Dr F 'I would say for brodalumab in the relatively small cohort we have the reduction in PASI so far seems to be paralleled by a reduction in the DLQI score also'

COMPLAINT

The complainant stated this was clinical opinion of one individual and had not been referenced by the company in this promotional video so it's impossible for the viewer to know if this was true or not.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that this statement constituted a breach of the Code. The statement was based on personal experience, as highlighted by both the 'holding page' at the start of the video and the opening wording 'I would say for brodalumab in the relatively small cohort we have…'. It was acceptable to use personal experience in promotional material, provided the experience was both compliant with the Code and reflective of the expected response in patients.

Leo submitted that, in this instance, the reduction in PASI being paralleled by a reduction in DLQI was supported by Warren *et al* (2021). This paper analysed the results of the AMAGINE-2 and AMAGINE-3 studies and demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (P<0.0001). While the statement by Dr F was capable of substantiation, the published paper was not mentioned in the video and there was no requirement to include a reference.

Overall, Leo submitted that the statement by Dr F was clearly stated to reflect his/her personal experience and not claimed to be typical of other patients; it was not misleading and capable of substantiation consistent with Clauses 7.2 and 7.4 of the Code. In circumstances where the published paper was not mentioned in the statement, Clause 7.6 did not require that a reference was included.

PANEL RULING

The Panel considered that Clause 7.6 was not relevant as the claim was not in relation to a published study and therefore no breach of Clause 7.6 was ruled.

The Panel noted Leo's submission that reduction in PASI being paralleled by a reduction in DLQI was supported by Warren et al (2021) which analysed the results of the AMAGINE-2 and AMAGINE-3 studies and demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (P<0.0001).

The Panel considered that the complainant had not established that the claim 'I would say for brodalumab in the relatively small cohort we have the reduction in PASI so far seems to be paralleled by a reduction in the DLQI score also', made by the health professional in reference to his/her clinical experience, was misleading or incapable of substantiation and no breach of Clauses 7.2 and 7.4 were ruled.

90 Statement by Dr E 'Patients who have got on brodalumab have had a really positive experience of improvement in their skin but crucially improvement in their holistic well being. For them it can be all the worlds difference. So instead of having to remember day to day activities living with psoriasis like being careful about the choices of clothing you're going to wear, being mindful about how you're going to interact with

the public such as going in to dressing rooms or going in to sports environments, to take away all of that grief is actually for them a massive difference'

COMPLAINT

The complainant stated this was 'padding conflating' the effects of Kyntheum with all sorts of lifestyle improvements but was unreferenced. 'Really positive experience of improvement' had not been quantified or qualified in any manner so it was not clear to the listener as to what this might mean.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.4 and 7.6.

RESPONSE

Leo did not agree that this statement constituted a breach of the Code. The link between improvements in skin (PASI) and wellbeing (DLQI) in patients with psoriasis had been well established and could be substantiated. A paper by Warren *et al (*2021) analysing the results of the AMAGINE-2 and AMAGINE-3 studies demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (P<0.0001). In this section of the video, Dr E was simply translating these 'improved DLQI' benefits into the experiences of his patients. These lifestyle matters were important to patients and Leo disagreed that such information constituted 'padding'. The DLQI specifically covered itchiness, soreness, pain and stinging, embarrassment and self-consciousness, interference with shopping and looking after the home/garden, impact on clothing choice, effect on social/leisure activities, participation in sport, interference in work/study, problems with partners/friends/relatives, sexual difficulties and the direct impact of any treatments. As such, Leo believed that Dr E was summarising the overall impact on quality of life in practical terms. Leo denied a breach of the Code.

Leo submitted that overall the statements were not misleading consistent with the requirements of Clause 7.2, the benefits of Kyntheum in terms of quality of life measures were capable of substantiation, as required by Clause 7.4. However, no published study was mentioned in the video, therefore Clause 7.6 did not require that a reference was included.

PANEL RULING

The Panel considered that Clause 7.6 was not relevant as the claim was not in relation to a published study and therefore no breach of Clause 7.6 was ruled.

The Panel noted Leo's submission that Warren *et al (*2021) analysed the results of the AMAGINE-2 and AMAGINE-3 studies which demonstrated a significant positive association between PASI response level and DLQI 0/1 achievement (P<0.0001) and that in this section of the video, the health professional was translating these improved DLQI benefits into the experiences of his/her patients. The Panel further noted Leo's submission that the DLQI specifically covered itchiness, soreness, pain and stinging, embarrassment and self-consciousness, interference with shopping and looking after the home/garden, impact on clothing choice, effect on social/leisure activities, participation in sport, interference in work/study, problems with partners/friends/relatives, sexual difficulties and the direct impact of any treatments.

Whilst the Panel considered that the claim 'really positive experience of improvement in their skin' was vague, in the context of a video of a health professional describing his/her clinical experience, the Panel did not consider that the complainant had established that it was unclear as alleged and based on the complainant's narrow allegation, the Panel ruled no breach of Clauses 7.2 and 7.4.

91 Statement by Dr F 'The effect appears to be sustained also. A couple of my patients have commented on the speed of onset where they didn't expect much from the biologic given that they had failed one or two anti IL17s previously'

COMPLAINT

The complainant stated that the statement on 'the effect appears to be sustained also' was conjectured and no more detail was provided. It was not clear what the patients' said about 'speed of onset' but a broad comparison against 'two other anti IL17s' could not be substantiated as there was only comparative data against ustekinumab.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Leo did not agree that this statement constituted a breach of the Code. The overall content must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient'. The statement by Dr F that: 'The effect appears to be sustained' was based on his personal experience, but was also aligned with clinical data, most notably by Puig *et al* (2020). This study was designed to evaluate the efficacy and safety of brodalumab through 120 weeks of treatment in the AMAGINE-2 trial. The study showed that clearance rates were sustained across the long term extension. 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100.

Leo stated that in terms of what patients had said about 'speed of onset', a study by Yao and Lebwohl concluded that 'Brodalumab may continue to have the most rapid onset of action of available antipsoriatic therapies'.

Leo submitted that the statement did not involve a comparison with any other product. It simply referred to the potential effects of Kyntheum in patients who had previously been treated with other biological agents.

In summary Leo submitted that the statement was based on individual experience and there was no claim that the effects seen by Dr F represented a typical patient response. However, the statements on duration of effect and speed of onset were not misleading and were capable of substantiation, consistent with Clauses 7.2 and 7.4. The statement included no comparisons and did not breach Clause 7.3.

PANEL RULING

The Panel noted its comments above at Point 81 in relation to Section 5.1 of the SPC and its reference to prior biological use, which it considered were also relevant here.

The Panel considered that the claim in question was not a comparison of Kyntheum with other treatments; it was a reference to prior biological therapy having been used before commencing treatment with Kyntheum. Based on the narrow allegation, the Panel ruled no breach of Clauses 7.3 and 7.4.

Puig *et al* (2020) evaluated the efficacy and safety of brodalumab through 120 weeks in the AMAGINE-2 trial. The authors stated that of patients who received brodalumab 210mg every 2 weeks, 84.4%, 75.6%, and 61.1% achieved 75%, 90%, and 100% improvement from baseline in PASI at 120 weeks, respectively. The Panel noted that Puig *et al* concluded that brodalumab showed sustained skin clearance through 120 weeks.

The Panel noted that Section 5.1 of the SPC stated that PASI 75 response at 2 weeks ranged between 20% and 25% in the Phase 3 trials compared to placebo (0% to 0.6%) and ustekinumab (3% to 3.5%).

The Panel noted Leo's submission that a study by Yao and Lebwohl (2019) concluded that 'Brodalumab may continue to have the most rapid onset of action of available antipsoriatic therapies'.

In the Panel's view, whilst it would have been helpful to have given more detail as to what exactly the health professional was referring to in relation to speed of onset and sustained effect, the complainant had not established that the claim in the context of the video was misleading or incapable of substantiation and based on the complainant's narrow allegation ruled no breach of Clauses 7.2 and 7.4.

92 Statement by Dr A 'So the feedback we've had from patients on brodalumab has been fabulous. They've all got what they've wanted from the treatment. They're all sustaining the treatment response and as far as I'm aware nobody has made any complaint about any side effects or site reactions or anything they can't cope with'

COMPLAINT

The complainant alleged that this was quite an alarming statement and painted a picture of a drug which worked for everyone and for a long time with no safety implications. This promotion did not recognise the special standing of medicines and health professionals and gave a false impression of the product.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.9, 7.10, 9.1 and 9.2.

RESPONSE

Leo submitted that the overall content of this statement must be construed in the context of the holding statement at the beginning of the video 'The views and opinions expressed in this film are not claimed to represent the typical patient response to Kyntheum – individual response and experience may vary from patient to patient' and also on the basis of the totality of information in

the video. The statement by Dr A reflected his/her own personal experience with use of Kyntheum and did not suggest that this would be typical of all patients treated with the product.

In terms of benefits of treatment, the statements by Dr A (that his/her sample of patients 'got what they wanted from the treatment' and 'are sustaining the treatment response') were not inconsistent with the trial data, including that reported in the SPC and the results from the long term extension AMAGINE-2 trial reported by Puig *et al* (2020) which showed that 84.4% of patients achieved PASI 75 improvement from baseline at 120 weeks, 75.6% of patients achieved PASI 90 and 61.1% achieved PASI 100.

Leo submitted that contrary to the complainant's allegation, the statement did not say that there were no safety implications of treatment, but that, as far as Dr A was aware, 'nobody has made any complaint about any side-effects or site-reactions or anything they can't cope with'. While this was Dr A's experience and the video stated explicitly that no claim was made that such experiences are typical, Leo were not able to substantiate her statement in this respect and agree that the information presented should have been more nuanced.

In summary therefore, Leo agreed that the safety information reflected in Dr A's statement was not consistent with Clause 7.9 or Clause 7.10 and to that extent Leo accepted that high standards were not maintained contrary to Clause 9.1. There was however no evidence to support a conclusion that the statement failed to recognise the special nature of medicines or was likely to cause offence, contrary to Clause 9.2 of the Code. Furthermore, in view of the overall impression created by this statement and in the context of the opening statements, Leo suggested that this did not bring the industry into disrepute contrary to Clause 2.

PANEL RULING

The Panel considered that the claim in question exaggerated the properties of Kyntheum and misleadingly implied that the medicine would be effective for all patients with no side effects; breaches of Clauses 7.9 and 7.10 were ruled as acknowledged by Leo. High standards had not been maintained in this regard and a breach of Clause 9.1 was ruled as acknowledged by Leo.

The Panel considered that the misleading impression given by the claim, particularly the implication that the medicine had no side effects, brought discredit upon and reduced confidence in the industry and a breach of Clause 2 was ruled.

The Panel considered that although the claim did not meet the requirements of the Code, the complainant had not established that it did not recognise the special nature of medicines or the professional standing of the audience and no breach of Clause 9.2 was ruled in that regard.

Video: Kyntheum Instructions for Use UK/IE MAT-12742 V7 February 2021

The complainant stated that this video was for health professionals only due to where it had been placed on the website, it discussed a product from Leo and it's use and was therefore promotional.

93 Black triangle and where to find prescribing information

COMPLAINT

The first screen of this video did not contain the black triangle or any information on where to find prescribing information.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 4.4 and 4.10.

RESPONSE

Leo stated that it did not agree that this video was in breach of the Code. On all the Kyntheum pages of the site there was a dark orange band immediately under the navigation section at the top of the page. This dark orange band provided a prominent visual contrast to the beige colour of the navigation section. On the left hand side of this band was the text KYNTHEUM® PRESCRIBING INFORMATION, followed by a small arrow (→), all in white. The text was in capitals and was larger than the navigation headings. Hovering over this text changed the cursor in the conventional manner to indicate that it was an active link. Clicking on this text opened a page with the UK Prescribing Information (PI) on it. It was not possible to navigate to any Kyntheum page without seeing this dark orange band and the text linking to the PI as it was at the top of the initial view of each page.

Clause 4.6 stated that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the prescribing information could be found. The video was embedded within the website and could not be viewed independently of it. The presentation, positioning and wording of the link on the page was clear and prominent and was therefore not in breach of the Code.

Leo submitted that the black triangle was present at the top of the screen next to the first appearance of the product name, at the left hand side of the navigation bar. This came above the mention of the Kyntheum prescribing information - reading from top to bottom it was the first use of the product name on the page. The black triangle was present on the page adjacent to the first mention of the product in line with the requirements of Clause 4.10.

PANEL RULING

The Panel noted Leo's submission that the video was embedded within the website and could not be viewed independently of it. The Panel further noted Leo's submission that on all the Kyntheum pages of the site there was a dark orange band immediately under the navigation section at the top of the page with the white text in capitals stating 'KYNTHEUM PRESCRIBING INFORMATION', followed by a small arrow; the text was in capitals and was larger than the navigation headings and the white text provided a contrast against the orange background. The Panel noted Leo's submission that clicking on this text opened a page with the UK prescribing information and that it was not possible to navigate to any Kyntheum page without seeing this dark orange band and the text linking to the prescribing information as it was at the top of the initial view of each page.

In the Panel's view, Clause 4.6 which required that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the prescribing information can be found, was the relevant clause in relation to the complainant's allegation and to which Leo referred to in its response. The Panel noted, however, that this clause had not been raised by the case preparation manager and therefore it could make no ruling in this regard.

The Panel noted that the case preparation manager had raised Clause 4.4 which referred to the ways in which prescribing information could be provided in digital material. The Panel considered that the complainant had not established that the requirements of Clause 4.4 had not been met and no breach of Clause 4.4 was ruled.

In relation to the allegation that the video did not contain a black triangle, the Panel noted that the copy of the video provided by Leo did contain a black triangle next to the first and most prominent mention of Kyntheum, on the opening slide of the video, and based on the narrow allegation, no breach of Clause 4.10 was ruled.

94 Use of the word 'simple'

COMPLAINT

The complainant stated that whilst the voiceover of the video was directed at patients on how to inject the product, the word 'simple' was used and the patient information leaflet was used as a reference. The use of the word 'simple' was promotional and inconsistent with the SPC and patient information leaflet.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 3.2, 7.2 and 7.4.

RESPONSE

Leo did not agree that this statement was in breach of the Code. The intention of this video and the statement 'In this video, we'll show you how to inject Kyntheum in 4 simple steps' was to provide a clear explanation of injection technique, so that patient concerned about the process of injection might be allayed and patients reassured that this was a relatively straight-forward process.

Leo stated that the fact that there were a series of actions and checks to be undertaken prior to injection of Kyntheum did not mean that each step was anything other than simple and there was no statement in the SPC or PIL which suggested otherwise. The description on the video was not inconsistent with the SPC.

Leo submitted that the fact that each step required for injection was simple, reflected the content of the SPC and the instructions attached to the PIL. For the avoidance of doubt, while the video might only be viewed by health professionals accessing the website, the use of such educational videos with patients was not in breach of the Code. Videos of this kind would be seen only by patients already prescribed the relevant product, to assist them in using the product correctly.

In summary therefore, Leo did not accept that use of the term 'simple steps' was inconsistent with the SPC or otherwise contrary to Clause 3.2. The statement was accurate and not misleading and properly substantiated by the SPC and PIL, consistent with Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that the SPC stated that 'After proper training in subcutaneous injection technique, patients may self-inject Kyntheum when deemed appropriate by a physician. Patients should be instructed to inject the full amount of Kyntheum according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet'.

The Panel noted Leo's submission that the statement 'In this video, we'll show you how to inject Kyntheum in 4 simple steps' was to provide a clear explanation of injection technique, so that patients concerned about the process of injection might be allayed and reassured that this was a relatively straight-forward process.

The Panel considered that the complainant had not made out his/her complaint as to why reference to the term 'simple' was inconsistent with the particulars in the Kyntheum SPC, misleading or incapable of substantiation; it was not for the Panel to infer reasons to support a complaint and based on the very narrow allegation the Panel ruled no breach of Clauses 3.2, 7.2 and 7.4.

Hot Topics Library

95 Prescribing information

COMPLAINT

The complainant stated that in the 'Hot Topics' tab, there was a 'Hot Topics Library' page with a bar at the top of the page which stated 'Kyntheum Prescribing Information'. According to the Code there needed to be a clear and prominent statement as to where to find the prescribing information; this information was omitted from this bar. As the reader scrolls down through the mass of promotional material on this page, the bar at the top was not visible and was lost.

When writing to Leo, the Authority asked it to consider the requirements of Clause 4.6.

RESPONSE

Leo did not agree that this page was in breach of the Code. On all the Kyntheum pages of the site there was a dark orange band immediately under the navigation section at the top of the page. This dark orange band provides a prominent visual contrast to the beige colour of the navigation section. On the left hand side of this band was the text KYNTHEUM® PRESCRIBING INFORMATION, followed by a small arrow (→), all in white. The text was in capitals and was larger than the navigation headings. Hovering over this text changed the cursor in the conventional manner to indicate that it was an active link. Clicking on this text opens a page with the UK Prescribing Information (PI) on it. It was not possible to navigate to any Kyntheum page without seeing this dark orange band and the text linking to the PI as it was at the top of the initial view of each page.

Clause 4.6 stated that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the prescribing information could be found. The presentation, positioning and wording of the link on the page was clear and prominent and was therefore not in breach of the Code.

PANEL RULING

The Panel noted, on the webpage in question, beneath the navigation headings and the headline 'Hot Topics Library', was a dark orange band with the white text 'Kyntheum (brodalumab) prescribing information', all in capitals, followed by an arrow. The Panel further noted Leo's submission that hovering over this text changed the cursor to indicate that it was an active link which when clicked opened a page with the UK prescribing information.

The Panel considered, on the evidence before it, that the complainant had not established that the requirements of Clause 4.6 had not been met as alleged and it therefore ruled no breach of Clause 4.6.

Series of videos

Under the 'Kyntheum Prescribing Information' bar were a series of videos. The complainant stated that as these were present on a promotional page, the content of these videos must be promotional. This was further supported by text under the videos which stated 'Please visit individual treatment pages for product related videos'.

General response

Leo did not agree that these videos were in breach of the Code and provided the following general observations before addressing each of the specific videos identified by the complainant below.

Leo submitted that the complainant was not correct in stating that items present on a promotional page were inherently promotional and required prescribing information and the adverse event reporting statement. The videos from Dr G and Dr H did not refer to any product, while the video from person I talks about behavioural modification to aid adherence in the context of patients with moderate to severe psoriasis who were taking biologics; this video did not refer to and was not promoting a specific product whether supplied by Leo or otherwise.

Leo submitted that nevertheless, there was a clear link to the prescribing information at the top of the page on which all four videos appeared together with a link for reporting adverse events. The videos were embedded within the website and could not be viewed independently of it.

The videos on this page were as follows.

96 'PASI 100 and Absolute PASI with Dr G', UK/IE MAT-25559'

COMPLAINT

The complainant stated that this video did not contain prescribing information or information as to where it might be found. The promotional video did not contain the mandatory prominent statement regarding the reporting of adverse events either.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 4.1, 4.6 and 4.9.

RESPONSE

Leo did not agree that this video was in breach of the Code. This video was non-promotional. It provided educational information regarding the assessment of psoriasis without reference to any products. In these circumstances, Clauses 4.1, 4.6 and 4.9 provided no requirement to include prescribing information or adverse event reporting information in the video. Nevertheless, the Prescribing Information link was available at the top of the webpage, since the Dermaworld pages themselves were promotional.

PANEL RULING

The Panel noted its comments at Point 95 above in relation to the prescribing information link on the Hot Topics Library webpage. The Panel noted Leo's submission that the video was embedded within the website which was promotional and could not be viewed independently of it. The Panel noted that the prescribing information could be accessed via a clear link immediately above the video. In the particular circumstances of this case, the Panel ruled no breach of Clauses 4.1 and 4.6.

Clause 4.9 stated that all promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at [web address which links directly to the MHRA Yellow Card site]. Adverse events should also be reported to [relevant pharmaceutical company]'.

The Panel noted, from the PDF provided by Leo, that the Hot Topics Library webpage included a link at the top of the webpage entitled 'Report adverse event' and a text box at the bottom of the webpage with reporting details. The Panel noted its comments above that the video was embedded within the website and could not be viewed independently of it. The Panel therefore ruled no breach of Clause 4.9.

97 'Patient Behaviour and Adherence with person I', UK/IE MAT-24503

COMPLAINT

The complainant stated that this video did not contain prescribing information or information as to where it might be found. The promotional video did not contain the mandatory prominent statement regarding the reporting of adverse events either.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 4.1, 4.6 and 4.9.

RESPONSE

Leo did not agree that this video was in breach of the Code. This video was non-promotional. It provided educational information regarding the behaviour of patients with psoriasis without reference to any products. In these circumstances, Clauses 4.1, 4.6 and 4.9 provide no requirement to include prescribing information or adverse event reporting information in the video. Nevertheless, the Prescribing Information link was available at the top of the webpage, since the Dermaworld pages themselves were promotional.

PANEL RULING

The Panel noted its comments at Point 95 above in relation to the prescribing information link on the Hot Topics Library webpage. The Panel noted Leo's submission that the video was embedded within the website which was promotional and could not be viewed independently of it. The Panel noted that the prescribing information could be accessed via a clear link within an orange banner immediately above the video. In the particular circumstance of this case, the Panel ruled no breach of Clauses 4.1 and 4.6.

Clause 4.9 stated that all promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at [web address which links directly to the MHRA Yellow Card site]. Adverse events should also be reported to [relevant pharmaceutical company]'.

The Panel noted, from the PDF provided by Leo, that the Hot Topics Library webpage included a link at the top of the webpage entitled 'Report adverse event' and a text box at the bottom of the webpage with reporting details. The Panel noted its comments above that the video was embedded within the website and could not be viewed independently of it. The Panel therefore ruled no breach of Clause 4.9.

98 'Impact of digital technology on healthcare professional interactions with Dr H', UK/IE MAT-25196

COMPLAINT

The complainant stated that this video did not contain prescribing information or information as to where it might be found. The promotional video did not contain the mandatory prominent statement regarding the reporting of adverse events either.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 4.1, 4.6 and 4.9.

RESPONSE

Leo did not agree that this video was in breach of the Code. This video was non-promotional. It provided educational information regarding use of digital technology without reference to any products. In these circumstances, Clauses 4.1, 4.6 and 4.9 provide no requirement to include prescribing information or adverse event reporting information in the video. Nevertheless, the Prescribing Information link was available at the top of the webpage, since the Dermaworld pages themselves were promotional.

PANEL RULING

The Panel noted its comments at Point 95 above in relation to the prescribing information link on the Hot Topics Library webpage. The Panel noted Leo's submission that the video was embedded within the website which was promotional and could not be viewed independently of it. The Panel noted that the prescribing information could be accessed via a clear link within an orange banner above the videos. In the particular circumstances of this case, the Panel ruled no breach of Clauses 4.1 and 4.6.

Clause 4.9 stated that all promotional material must include the prominent statement 'Adverse events should be reported. Reporting forms and information can be found at [web address

which links directly to the MHRA Yellow Card site]. Adverse events should also be reported to [relevant pharmaceutical company]'.

The Panel noted, from the PDF provided by Leo, that the Hot Topics Library webpage included a link at the top of the webpage entitled 'Report adverse event' and a text box at the bottom of the webpage with reporting details. The Panel noted its comments above that the video was embedded within the website and could not be viewed independently of it. The Panel therefore ruled no breach of Clause 4.9.

99 'Immunology - a walk through pathways in plaque psoriasis with Eleanor Needham' UK/IE MAT 24311

COMPLAINT

The complainant alleged that under this video was a link to prescribing information for Kyntheum, however, the video itself did not mention where prescribing information might be found nor did it contain the mandatory prominent statement on adverse events required by the Code.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 4.6 and 4.9

RESPONSE

Leo did not agree that this video was in breach of the Code. On all the Kyntheum pages of the site there was a dark orange band immediately under the navigation section at the top of the page. This dark orange band provided a prominent visual contrast to the beige colour of the navigation section. On the left hand side of this band was the text KYNTHEUM® PRESCRIBING INFORMATION, followed by a small arrow (→), all in white. The text was in capitals and was larger than the navigation headings. Hovering over this text changes the cursor in the conventional manner to indicate that it was an active link. Clicking on this text opened a page with the UK Prescribing Information (PI) on it. It was not possible to navigate to any Kyntheum page without seeing this dark orange band and the text linking to the PI as it was at the top of the initial view of each page.

Clause 4.6 stated that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the prescribing information could be found. The video was embedded within the website and could not be viewed independently of it. The presentation, positioning and wording of the link on the page was clear and prominent and was therefore not in breach of the Code.

Leo submitted that a link directing health professionals to where adverse events might be reported was on the welcome page, from where the video was accessed.

PANEL RULING

The Panel noted Leo's submission that the video was embedded within the website and could not be viewed independently of it.

The Panel noted, from the PDF provided by Leo, that immediately beneath the title of the video was a prominent statement 'Kyntheum (brodalumab) prescribing information'. The Panel

considered that the complainant had not established that the requirements of Clause 4.6 had not been met and no breach of Clause 4.6 was ruled.

The Panel noted its description of the webpage in relation to adverse event reporting as described above at Point 96. The Panel noted its comments above that the video was embedded within the website and could not be viewed independently of it. The Panel therefore ruled no breach of Clause 4.9.

100 Statement by member of the medical team

COMPLAINT

The complainant stated that the employee discussed how various cytokines worked in terms of psoriasis then proceeded to discuss several biological products:

> 'Biologic therapies have been designed to break this chronic inflammatory cycle in the skin in moderate to severe plaque psoriasis patients by targeting key pro inflammatory cytokines. Adalinumab, ethanercept, infliximab and certolizab pegol all target TNF. Ustekinumab targets IL-12 and IL-23 while guselkumab, tildrakizumab and risankizumab only target IL-23. IL-23 maintains Th17 cells which produce three types of IL-17, IL-17A, IL-17 A/F and IL-17F. Secukinumab and ixekizumab target IL-17A and the A portion of the A/F hetereodimer. In addition to Th17 cells other cells also produce IL-17A, AF and F. These three forms of IL-17 all activate keratinocytes by binding to the IL-17 receptor A and C subunits.'

The complainant stated that comparisons should not be made between brodalumab and products for which there was no head to head data in a promotional presentation; Leo only had such data against ustekinumab.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.3.

RESPONSE

Leo did not agree that this video constituted a breach of the Code.

In the video, the presenter outlined the different modes of action for each product. At no point were any claims or comparisons made based on clinical efficacy or safety of the relevant products. Instead, the focus was on the mode of action. The differences between the products in terms of mode of action could clearly be substantiated through the individual product SPCs.

Leo submitted, in summary, the video included no comparisons and there was no breach of Clause 7.3 of the Code.

PANEL RULING

The Panel noted that the video discussed inflammatory pathways and targets and the mode of action of different biologics. In the Panel's view, there did not appear to have been any comparisons made between the medicines in terms of efficacy or safety. The Panel considered that the complainant had not established that comparing the mode of action of different biologics was misleading and no breach of Clause 7.3 was ruled.

Resources section of website

101 Document entitled 'Plaque psoriasis diagnostic and monitoring tool' (UK/IE MAT 26724)

COMPLAINT

The complainant stated that at the bottom of the document was a statement 'Promotional item produced by Leo Pharma'. Of concern was the statements 'Carefully examine nails for cutaneous disease' - Leo did not have any products indicated for this use or have data in their SPCs to reflect this specialist area, 'ask about joint stiffness as it may signal psoriatic arthritis' - Leo did not have products for psoriatic arthritis, 'ask about all your patients plaques as they can vary in severity across the body, including scalp and genital plaques' - Leo had products which were not suitable for these areas such as Dovobet ointment and Dovonex. The item then reproduced NICE guidance which was not allowed for promotional items.

The piece then recommends to the doctor that 'Treatment guidance for plaque psoriasis in a primary care setting is available from the Primary Care Dermatology Society, the leading Dermatology society for GPs'. This guideline was chosen and given priority by Leo over NICE or SIGN as their combination topical products were positioned more favourably with the Primary Care Dermatology Society (PCDS).

The promotion of PCDS guidance promoted the use of specific Leo products. The guidance from PCDS was written in promotional tone and listed products in Leo's preferred order, within the context of Leo's long time funding relationship with them. The complainant stated that he/she had taken the below guidance with respect to plaque psoriasis from the PCDS website to illustrate his/her point:

> **'Many GPs and GPSI use calcipotriol and betamethasone combination products first line** to encourage a rapid improvement and hence adherence in chronic plaque psoriasis: NB here our advice differs from the NICE psoriasis guideline which suggests starting with its individual components:
>
> - Such a combination product whether by Dovobet gel ®, Dovobet ointment ®, or the new spray foam version (Enstilar ®) is often considered a first line option for chronic plaque psoriasis on the body as an effective and cosmetically acceptable therapy. The apparent benefits of the foam formulation over the gel will be assessed as time goes by. Appropriate quantities (ie 2 x 60g) should be prescribed, and the patient should always be advised to shake the can well, before application. The foam preparation has a warning about flammability
> - Such therapy should be discontinued when the skin feels smooth even though still looking pink-red. Ongoing treatment with a vitamin D analogue (Calcipotriol or Calcitriol) or simple emollients is a logical follow on
> - Dovobet gel ® should be considered for the scalp, where it is also available in an applicator delivery mechanism that offers precise application to the affected area. The gel can also be used on the body if they prefer this over the foam (Enstilar ®). The Dovobet gel ® applicator offers the ability of no-touch application in addition to the pump delivering 0.05g with every squeeze.'

The complainant stated that the item did not contain prescribing information or a mandatory adverse events box, even though it promoted Enstilar, Dovobet gel, Dovonex and Dovobet ointment through direction to this guidance.

When writing to Leo, the Authority asked it to consider the requirements of Clause 9.6 and also Clauses 4.1 and 4.9 for each medicine.

RESPONSE

Leo did not agree that this document was in breach of the Code. This document was incorrectly labelled as 'promotional'. It was clearly labelled as a 'Plaque psoriasis diagnostic and monitoring tool'. As such, it was distinct from any management decisions or specific drugs/products. The only mention of 'treatment guidance' was a statement towards the end of the document, that guidance could be found on the PCDS website, NICE or SIGN, or through the healthcare practitioner's local CCG. This item was an educational tool primarily designed for use by GPs, which was why it was situated within the 'Resources' section of the website and not in a section relating to any particular product.

Leo submitted that the document outlined a rational approach to assessing patients with plaque psoriasis, including assessment of the nails and joints. This approach was aligned with NICE Clinical Guidance CG153 on Psoriasis assessment and management and reflected accepted clinical practice. For that reason, and in the context of a non-promotional document, it included the assessment of nails and questions about joint stiffness, even though Leo did not have products in these areas.

Leo stated that this item did not reproduce NICE guidance but provided a summary of the content of the guidance. The guidance was in the public domain and the context was non-promotional. Therefore, provided the summary met the Code quality standards, it was acceptable for Leo to produce it and share it with health professionals.

Leo submitted, therefore, in the context of an accurate summary of NICE guidelines, provided in a non-promotional context, it did not agree that the document breached Clause 9.6 of the Code.

Leo noted that the complainant appeared to be suggesting that the PCDS guidance itself was promotional in nature. The document in question, from the Resources section of the website, did not link directly to the PCDS guidance – it simply listed the PCDS website in the references. The PCSD was an independent forum for GPs to exchange views on primary care dermatology. It was organised as a charity and received sponsorship by at least 15 pharmaceutical companies including Leo. The PCSD website stated:

> 'It is supported by the majority of Pharma companies, with dermatological interests, by annual subscriptions which reduces the risk of individual bias. This allows the society to subsidise and develop educational meetings all over the UK and to keep the membership fee low which encourages a wide membership take-up.'

Leo submitted, in summary, no mention was made in the document on the website of any product or products, and therefore there was no requirement to include prescribing information or adverse event reporting information. Simply including a reference in the document to guidance produced by an independent third party which referred to Leo products, did not make the original document promotional or require inclusion of prescribing information or adverse

event reporting in accordance with Clause 4.1 or Clause 4.9 of the Code. This applied to all of the products listed by the complainant.

PANEL RULING

The Panel noted that the document in question was entitled 'Plaque psoriasis diagnostic and monitoring tool'. The webpage which hosted the document encouraged health professionals to download the document, therefore the document as a standalone item needed to comply with the requirements of the Code.

The Panel noted that the document made no direct or indirect reference to a specific medicine. The bottom of the document stated that it was a promotional item produced by Leo. The Panel noted Leo's submission that the document had been labelled incorrectly in that regard.

The Panel noted that the document stated:

> 'Treatment guidance for plaque psoriasis in a primary care setting is available from the Primary Care Dermatology Society, the leading dermatology society for GPs. Further guidance is available from NICE or SIGN clinical guidelines, or your local CCG.'

The Panel noted the complainant's allegation that the material promoted Enstilar, Dovobet gel, Dovonex and Dovobet ointment through direction to the PCDS guidance which was given priority by Leo over NICE or SIGN as their combination topical products were positioned more favourably within PCDS guidelines. The Panel noted, from the extract provided by the complainant, that the PCDS guidelines stated that its advice differed from the NICE psoriasis guideline.

The Panel did not have a copy of the PCDS guidelines which were available from the URL cited in the reference section of the material at the time of the complaint, but based on the extract provided by the complainant, it appeared that the PCDS guidelines referred to and positioned Leo medicines favourably.

The Panel noted Leo's submission that the material in question did not link directly to the PCDS guidance. However, the Panel noted that whilst there was no link to the guidelines in the main body of the document, the references section had a URL link to the Primary Care Dermatology Society guidelines on the pcds.org.uk website.

The Panel considered that the 'Plaque psoriasis diagnostic and monitoring tool' not only referenced the PCDS guidelines but also, in the main body of the document, directed readers to view the PCDS guidelines. In the Panel's view, the 'Plaque psoriasis diagnostic and monitoring tool' therefore promoted Leo medicines and therefore required prescribing information and an adverse event reporting statement.

The Leo material in question, which could be downloaded as a standalone item, did not have prescribing information or the adverse event reporting statement as required by the Code and a breach of Clause 4.1 was ruled in relation to each of Enstilar, Dovobet gel, Dovonex and Dovobet ointment as alleged. The material contained no adverse event reporting statement as required by the Code and a breach of Clause 4.9 was ruled.

The Panel noted that Clause 9.6 stated that reproductions of official documents must not be used for promotional purposes unless permission had been given in writing by the appropriate body.

The Panel considered that the material in question was not a reproduction of the NICE Psoriasis Clinical Guideline; the material gave recommendations on when to consider referral for a patient with plaque psoriasis and listed a number of clinical factors which was referenced to the NICE Psoriasis Clinical Guideline. The material referred to the NICE Psoriasis Clinical Guideline, and gave a URL to this guideline in the references section. In the Panel's view, the material was not covered by Clause 9.6 and therefore no breach of Clause 9.6 was ruled.

APPEAL BY LEO

Leo submitted that the conclusion of the Panel that the D&M Tool was promotional was incorrect. A copy was provided:

- While the D&M Tool included a statement at the bottom of the document that this was a 'Promotional item produced by Leo Pharma', Leo explained, in response to the complaint, that the document had been incorrectly labelled as promotional.
- The D&M Tool was an educational document directed principally towards GPs, which provided information regarding the general assessment of patients with plaque psoriasis:
    - The approach was consistent with NICE's Clinical Guideline (CG153) on Psoriasis: Assessment and Management; and
    - The fact that the document was intended as an educational tool was reflected in the fact that it was located in the Resources section of the website and not in a section dealing with specific products.
- There was no mention of any specific products in the D&M Tool.
- The Panel's conclusion that the D&M Tool promoted Leo Pharma medicinal products was based on its conclusion that the PCDS guidelines positioned Leo Pharma products favourably, however:
    - The PCDS was an independent charity which issued its own guidance on dermatological issues in primary care and aimed to provide a forum for support of GPs and discussion on dermatological issues;
    - PCDS guidance 'Psoriasis: an overview and chronic plaque psoriasis' was prepared independently of Leo Pharma and without any input from the company.
    - While the complainant had quoted a single section of the PCDS guidance which referred to certain LEO Pharma products, this was not representative of the guidance overall, which also recommended use of treatments manufactured and supplied by other companies including Silkis ointment (Galderma), Exorex lotion (Teva), Zorac gel (Allergan), Diprosalic ointment (Organon Pharma) and Eumovate cream (GlaxoSmithKline),
    - While Leo Pharma provided funding for PCDS, the charity also received funding from at least 15 other pharmaceutical companies; the PSDS website stated:

'[PCDS] is supported by the majority of Pharma companies, with dermatological interests, by annual subscriptions which reduces the risk of individual bias.'

- The D&M Tool directed readers to the PCDS guidelines because these were specifically intended for use in primary care by GPs, but also referenced other guidance issued by NICE and SIGN which had a broader application.

In summary, therefore, Leo submitted that the D&M Tool was an educational resource which did not mention or promote any individual medicinal product. It referenced the independently produced PCDS guidelines as being of use to GPs interested in dermatology and these guidelines, in turn, referred to a range of treatments manufactured and supplied by various pharmaceutical companies. The reference to the PCDS guidelines did not have the effect that the D&M Tool promoted any Leo Pharma product and there was no requirement to include prescribing information or an adverse event reporting statement.

APPEAL BOARD RULING

The Appeal Board noted that the material at issue was entitled 'Plaque psoriasis diagnostic and monitoring tool'. The webpage which hosted the material encouraged health professionals to download it, therefore the material as a standalone item needed to comply with the requirements of the Code.

The Appeal Board noted that the material at issue stated:

> 'Treatment guidance for plaque psoriasis in a primary care setting is available from the Primary Care Dermatology Society, the leading dermatology society for GPs.
>
> Further guidance is available from NICE or SIGN clinical guidelines, or your local CCG.'

The Appeal Board noted that the PCDS was an independent organisation that received funding from a number of pharmaceutical companies including Leo.

The Appeal Board noted that the material at issue was in relation to assessing psoriasis and consideration of when referral to secondary care might be appropriate; it made no direct or indirect reference to any specific medicine. However, the bottom of the material stated that it was a promotional item produced by Leo and the material's certificate referred to Leo's medicine Enstilar. The Appeal Board noted Leo's submission that the material and certificate had been labelled incorrectly in that regard.

The Appeal Board considered that company material could mention independent organisation guidelines and websites which included references to the company's medicines without necessarily rendering the company material promotional. Much would depend on how the guideline/website was referred to in the company's material.

The Appeal Board noted that there was no link to the PCDS guidelines in the main body of the material at issue, only in the references section. The references section also contained links to other sites including the National Psoriasis Foundation and the NICE Psoriasis Clinical Guideline CG153.

The Appeal Board considered that it was regrettable that Leo had in error classified the 'Plaque psoriasis diagnostic and monitoring tool' as promotional. Whilst this material had mentioned the PCDS guidelines which included reference to Leo's medicines by brand name and positioned

them favourably, it also mentioned NICE and SIGN. There was no link to PCDS in the main body of the Leo material, only in the references section, which referred to a number of other independent organisations. Although there had been errors in the certification of the material, the Appeal Board did not consider that in the particular circumstances of this case the 'Plaque psoriasis diagnostic and monitoring tool' was promotional as alleged, and consequently it did not need to include prescribing information for Enstilar, Dovobet gel, Dovonex and Dovobet ointment or an adverse event reporting statement. The Appeal Board ruled no breaches of Clauses 4.1 and 4.9. The appeal on this point was successful.

102 Events

COMPLAINT

The complainant alleges that the events tab on this website was not up to date and was last updated in February 2020 (MAT/21424v2 February 2020). Information to health professionals should be kept up to date and accurate.

When writing to Leo, the Authority asked it to consider the requirements of Clause 7.2.

RESPONSE

Leo did not agree that this page was in breach of the Code. Clause 7.2 dealt with Information, Claims and Comparisons. In the supplementary information for Clause 7, it stated 'The application of the clause is not limited to information or claims of a medical or scientific nature. It includes, *inter alia*, information or claims relating to pricing and market share'. These categories of information were all product related. Leo did not consider that this clause was intended to cover information about meeting event dates.

In summary, Leo did not believe that Clause 7.2 was applicable to the Events tab on the website or that this tab breached the Code in any way.

PANEL RULING

The Panel noted, from the PDF provided by Leo, that the Events page listed a number of national and international learned society meetings, including dates and location, with what appeared to be links to further information. It was not clear to the Panel what these links took the reader to. The Panel considered, based on the limited information provided, that even if some of these events had already taken place, the complainant had not established that references to those events on the webpage in question constituted a breach of Clause 7.2 and no breach was ruled in that regard.

Overall in the context of Clauses 9.1 and 2

When writing to Leo, the Authority asked it to consider the requirements of the clauses cited above (Clauses 2, 3.2, 4.1, 4.6, 4.9, 4.10, 7.2, 7.3, 7.4, 7.6, 7.9, 7.10, 9.1, 9.2, 9.6, 26.1 and 26.2) and to respond cumulatively to Clauses 2 and 9.1 of the Code.

RESPONSE

Leo submitted that this complaint involved multiple allegations in relation to a total of 103 documents or issues. There was substantial duplication of the matters raised and the overwhelming majority of allegations were unsubstantiated. In the context of the allegations raised by the complainant, there had been a small number of areas where the Code had not been complied with. In this context, Leo partially acknowledged there were allegations that were substantiated, namely that the safety data provided had been incomplete. Leo took such matters extremely seriously and for that reason Leo had taken the website down pending comprehensive review and correction. Leo was also conducting a full audit of all Kyntheum materials and undertaking a thorough investigation into the process for uploading newly approved content onto websites.

Leo submitted, nevertheless, in general, it believed high standards had been maintained and that the website which was the subject of this complaint did not bring the industry into disrepute contrary to Clause 2.

PANEL RULING

The Panel had considered each of the 102 points above in relation to the clauses raised by the case preparation manager, which had included rulings of breaches of Clause 9.1 at Points 35, 64, 65, 86 and 92 and rulings of breaches of Clause 2 at Points 35, 64, 65 and 92 above. The Panel did not consider that a further cumulative ruling in relation to all points was warranted and ruled no breach of Clauses 9.1 and 2 in that regard.

* * * * *

During the consideration of this case, the Panel was extremely concerned regarding Leo's response in relation to certification and control of the website at issue. In the Panel's view, certification underpinned self-regulation.

Complaint received **13 April 2021**

Case completed **8 December 2022**