CASE AUTH/3531/7/21

ANONYMOUS v NOVARTIS

Concerns about Lucentis advertised in UK ophthalmic journals

An anonymous non contactable complainant who described him/herself as an optometrist raised concerns around claims for Novartis Pharmaceutical UK Limited's product, Lucentis (ranibizumab).

The complainant alleged that claims of 'Powerful. Proven. Targeted.' were made with no context and no supporting data. 'Powerful' was meaningless and had no data to support it. 'Proven' was meaningless without context. Proven to do what? 'Targeted' was misleading without context. Targeted to the eye? Targeted to diabetes? Targeted to VEGF (vascular endothelial growth factor)? Targeted to a particular retinal layer? 'Treat DMO patients at the maximum possible interval' - what was that: a month, a year?

The detailed response from Novartis is given below.

The Panel noted that the complainant referred to two journal advertisements and a Novartis webpage, on its health professional website, which had the claim 'Powerful. Proven. Targeted.' beneath the Lucentis (ranibizumab) logo; the claim was referenced to the SPC. The Panel considered that the claim overall was a strong claim and each element needed to be capable of substantiation. Such substantiation did not need to be provided in the material.

The Panel considered that the strong claim 'Powerful' was ambiguous; it was not clear what was meant by it and it was not linked to any feature of the product. Novartis acknowledged this in its response and did not provide any substantiation. The Panel therefore ruled breaches of the Code in relation to each advertisement and the webpage at issue, as acknowledged by Novartis.

The Panel considered that as Lucentis had a marketing authorisation, it was 'proven' in relation to its use for the licensed indication being advertised. Although there was no detail about what was 'proven', the Panel did not consider that in these circumstances, the complainant had established, on the balance of probabilities, that its use was misleading as alleged. The Panel therefore ruled no breaches of the Code in relation to each advertisement and the webpage at issue.

The Panel further noted Novartis' submission that the claim 'Targeted' was a reference to the specific mechanism of action of Lucentis which was fully described within its summary of product characteristics (SPC). Whilst the Panel did not consider this was clear from the material at issue, it did not consider that in the particular circumstances of this case the complainant had established on the balance of probabilities that the use of 'targeted' was misleading as alleged. The Panel therefore ruled no breaches of the Code in relation to each advertisement and the webpage at issue.

With regard to the claim 'Lucentis allows you to treat your DMO patients at the maximum possible interval', which appeared beneath the heading 'Lucentis Treat and Extend', in one of the advertisements (ref MLR 114580), the Panel noted that further information was included in the advertisement. Directly below the claim it stated 'Treatment in adults is initiated with one injection per month until maximum visual activity is achieved and/or there are no signs of disease activity, after which you can extend the patient out by up to one month a time'. Below this, there was a diagram which set out possible dosing intervals for various months in either phase 1, loading dose or phase 2, treat and extend. This was described as a potential algorithm for a DMO patient using Lucentis treat and extend. The advertisement stated that this was not necessarily reflective of the treatment schedule for all patients as this would depend on their individual disease activity. The Panel considered that the advertisement included an explanation of the time interval and ruled no breach of the Code.

The Panel noted its comments and rulings of breaches of the Code above and considered that Novartis had failed to maintain high standards and a breach of the Code was ruled.

The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use and no breach was ruled.

An anonymous non contactable complainant who described him/herself as an optometrist in a named area, with an interest in pharmaceuticals and regulation, raised concerns around materials that he/she had recently seen in UK ophthalmic journals related to Novartis Pharmaceutical UK Limited's product, Lucentis (ranibizumab).

COMPLAINT

The complainant provided copies of the materials at issue, referring to them as two journal advertisements and a UK internet page. The complainant alleged that claims of 'Powerful. Proven. Targeted.' were made with no context and no supporting data. 'Powerful' was meaningless and had no data to support it. 'Proven' was meaningless without context. Proven to do what? 'Targeted' was misleading without context. Targeted to the eye? Targeted to diabetes? Targeted to VEGF (vascular endothelial growth factor)? Targeted to a particular retinal layer? 'Treat DMO patients at the maximum possible interval' - what was that: a month, a year?

The advertisements seemed to him/her to be inappropriate and wrong.

When writing to Novartis, the Authority asked it to consider the requirements of Clauses 2, 9.1, 7.2 and 7.4 of the Code.

RESPONSE

Background

Novartis stated that Lucentis (ranibizumab) received its first marketing authorisation for wet age related macular degeneration (wAMD) in January 2007, with a subsequent indication for visual impairment due to diabetic macular oedema (DMO) in January 2011.

NICE recommended Lucentis for wAMD in August 2008 and for a subset of DMO patients in February 2013. It was a first-in-class product for these therapeutic areas where treatment options were either limited or non- existent. Therefore, Lucentis could be described as a familiar, well known and established medicine to the medical retinal ophthalmologists who were required to prescribe and administer it.

Lucentis had a SPC requirement (Section 4.2) that this intravitreal injection was administered by a qualified ophthalmologist; such administration must be performed aseptically in a clean room, usually to be found in hospital medical retina departments. Because of the highly specialised nature of administration, a detailed knowledge of the product would only be expected in those healthcare professionals involved in this process. It was of significance in the context of this complaint, that the complainant described him/herself as an optometrist, and therefore not the primary target for the information presented within the journals.

The journal advertisements were reviewed and approved to be printed in UK Ophthalmic Journals and designed to be read by a target audience of ophthalmologists. The advertisement (MLR ID 116486) was printed in the British Journal of Ophthalmology (accessed July 2021) which described itself as 'a leading international journal for ophthalmologists and vision scientists' and the advertisement (MLR ID 114580) was printed in the Eye Journal (accessed July 2021) which described itself as 'The official journal of The Royal College of Ophthalmologists'.

Given the nature of the described readers of both journals, both journals were predominantly aimed at ophthalmologists who were the only health professionals who could prescribe and administer Lucentisand would therefore be familiar with Lucentis and what the terms Powerful, Proven and Targeted meant in the context of this veteran intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

Clauses 7.2 and 7.4

(i) Clinical Context

Novartis stated that in order to appropriately and systematically respond to the use of the terms subject to the complaint, the clinical landscape must first be understood. Prior to the availability of Lucentis in 2011, the only treatment available for visual impairment due to DMO was a non-pharmacological intervention – laser treatment – which at best, merely halted visual deterioration, at the cost of permanent retinal scarring.

As a first-in-class product, the initial registration studies demonstrating Lucentis safety and efficacy (RESOLVE (Massin P, Bandello F, Mitchell P et al (2010) and RESTORE, (Mitchell P, Bandello F, Schmidt-Erfurth U et al T (2011) and RESTORE Extension Study (2014) were against placebo and laser respectively, and showed significant mean visual gains in patients receiving Lucentis when compared to those receiving placebo or laser:

RESOLVE: At 12 months mean change in visual acuity
Lucentis = +10.3 letters Placebo (SHAM) = -1.4 letters $p<0.0001$

RESTORE: At 12 months mean change in visual acuity
Lucentis = +6.8 letters Laser = +0.9 letters $p<0.0001$

A third study also detailed in the SPC, RETAIN (Prünte C, Fajnkuchen F, Mahmood S et al (2016) described the use of a more convenient Lucentis dosing regimen and also demonstrated similar visual gains.

Novartis submitted that ophthalmologists agreed that a Visual Acuity (VA) outcome of a gain of 5 or more letters was deemed clinically meaningful (Beck RW, Maguire MG, Bressler NM et al (2007) and the mean visual gain by those patients receiving Lucentis in these DMO studies all substantially exceeded this number, demonstrating clinically meaningful efficacy for patients.

(ii) The claim POWERFUL:

Novartis submitted that the use of 'powerful', was made within the context set out in (i), above, and in particular, the clinically meaningful efficacy in the treatment of visual impairment due to DMO. Notwithstanding, Novartis recognised that the context behind the use of the word 'powerful' remained ambiguous. On this occasion, therefore, Novartis accepted a breach of Clauses 7.2 and 7.4 for the use of the word 'powerful'. As a result, Novartis would remove use of the word 'powerful' from its marketing materials forthwith.

(iii) The claim PROVEN:

Novartis submitted that the data set out in (i), above, together with the length of time since the marketing authorisation during which anti-VEGF therapy had been established as standard of care in DMO (numerous independent treatment guidelines, copies provided) meant that Lucentis could justifiably be described as 'proven'. Accordingly, Novartis did not accept a breach of Clause 7.2 and 7.4 for use of the word 'proven'.

(iv) The claim TARGETED:

Novartis submitted that the use of the word 'targeted' was a reference to the specific mechanism of action of Lucentis which was fully described within its SPC.
Lucentis was a humanised recombinant monoclonal antibody fragment targeted against human VEGF-A. It binded with high affinity to the VEGF-A isoforms (eg VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Prevention of VEGF-A binding moderated the pathophysiological processes such as endothelial cell proliferation, neovascularisation and vascular leakage – which played a role in diabetic eye disease.

Novartis submitted that such a specific mode of action, together with the SPC explanation justified the use of the word 'targeted'. Accordingly, Novartis did not accept a breach of Clause 7.2 and 7.4 for use of the word 'targeted'.

(v) The claims on dosing in DMO

With regard to the claim in the journal advertisement 'Lucentis allowed you to treat your DMO patients at the maximum possible interval', the complainant queried if this interval was a month or a year. Novartis submitted that the sentence below the claim clearly explained that treatment was initiated with one injection per month until maximum visual acuity was achieved and/or there were no signs of disease activity after which the physician could

extend the interval period of when the patient would next receive an injection by up to one month at a time.

In addition, and as described above, Lucentis was a specialised medicine for use by a qualified specialist within a specialist setting. As such, it would be expected that the prescriber would be familiar with the SPC before using the medicine. This dosing methodology was clearly described within the SPC. Novartis therefore believed that this dosing query was without merit; accordingly, Novartis did not accept a breach of Clauses 7.2 and 7.4.

(vi) Website

Novartis stated that the screenshot included by the complainant only captured the header of the health professional portal page which was not a fair representation of the website in its totality.

Further down the site page, it could be seen that there were tabs and options for the visiting healthcare professional to view further information on Lucentis efficacy data and other details on the usage of Lucentis. Thus, if there were any confusion about the justifiable claims made in the strapline – these could be informed by means of the data available in the website in its entirety.

Novartis did not accept a breach of Clauses 7.2. and 7.4

Clause 9.1

Novartis submitted that throughout the development, review and approval of these materials, in accordance with the Code requirements and Novartis standard operating procedures, due process was followed. Notwithstanding the acknowledgment of inappropriate use of the term 'powerful' in these materials, Novartis submitted that they were otherwise accurate, appropriately substantiated, high quality and within both the spirit and the letter of the Code.

Novartis therefore submitted that the materials maintained high standards and were not in breach of Clause 9.1.

Clause 2

Regarding a potential breach of Clause 2, Novartis saw no evidence that its materials could bring discredit upon, or reduce confidence in, the pharmaceutical industry. Accordingly, Novartis did not accept a breach of Clause 2.

In summary, the complainant had raised a number of issues related to the advertising and promotion of Lucentis. Novartis believed that there was a legitimate defence to the alleged breaches of Clauses 2, 7.2, 7.4 and 9.1. Notwithstanding, only with regard to the use of the term 'powerful', Novartis conceded a breach of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that the complainant referred to two journal advertisements and a Novartis webpage, on its health professional website, which had the claim 'Powerful. Proven. Targeted.'

beneath the Lucentis (ranibizumab) logo; the claim was referenced to the SPC. The Panel considered that the claim overall was a strong claim and each element needed to be capable of substantiation. Such substantiation did not need to be provided in the material.

The Panel noted Novartis' submission that the health professional website had tabs and options to view further information on Lucentis' efficacy data and other details on the usage of Lucentis and if there was any confusion about the justifiable claims made in the strapline, these could be informed by means of the data available on the website in its entirety. The Panel noted that claims in promotional material must be capable of standing alone as regards accuracy etc. In general, claims should not be qualified by the use of footnotes and the like.

The Panel considered that the strong claim 'Powerful' was ambiguous; it was not clear what was meant by it and it was not linked to any feature of the product. Novartis acknowledged this in its response and did not provide any substantiation. The Panel therefore ruled breaches of Clauses 7.2 and 7.4 of the Code in relation to each advertisement and the webpage at issue, as acknowledged by Novartis.

The Panel considered that as Lucentis had a marketing authorisation, it was 'proven' in relation to its use for the licensed indication being advertised. Although there was no detail about what was 'proven', the Panel did not consider that in these circumstances, the complainant had established, on the balance of probabilities, that its use was misleading as alleged. The Panel therefore ruled no breach of Clauses 7.2 and 7.4 of the Code in relation to each advertisement and the webpage at issue.

The Panel further noted Novartis' submission that the claim 'Targeted' was a reference to the specific mechanism of action of Lucentis which was fully described within its SPC. Whilst the Panel did not consider this was clear from the material at issue, it did not consider that in the particular circumstances of this case the complainant had established on the balance of probabilities that the use of 'targeted' was misleading as alleged. The Panel therefore ruled no breach of Clauses 7.2 and 7.4 of the Code in relation to each advertisement and the webpage at issue.

With regard to the claim 'Lucentis allows you to treat your DMO patients at the maximum possible interval', which appeared beneath the heading 'Lucentis Treat and Extend', in one of the advertisements (ref MLR 114580), the Panel noted that further information was included in the advertisement. Directly below the claim it stated 'Treatment in adults is initiated with one injection per month until maximum visual activity is achieved and/or there are no signs of disease activity, after which you can extend the patient out by up to one month a time'. Below this, there was a diagram which set out possible dosing intervals for various months in either phase 1, loading dose or phase 2, treat and extend. This was described as a potential algorithm for a DMO patient using Lucentis treat and extend. The advertisement stated that this was not necessarily reflective of the treatment schedule for all patients as this would depend on their individual disease activity. The Panel considered that the advertisement included an explanation of the time interval and ruled no breach of Clause 7.2.

The Panel noted its comments and rulings of breaches of the Code above and considered that Novartis had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use and no breach was ruled.

Complaint received **1 July 2021**

Case completed **23 February 2022**