CASE AUTH/3765/4/23

COMPLAINANT v TAKEDA

Allegations related to Takeda's rare disease website

CASE SUMMARY

This case was in relation to Takeda's 'Rare Disease Hub' website. The complainant's allegations related to:

- **the use of a white border around the black triangle symbol**
- **the absence of an explanation of the black triangle symbol's meaning**
- **the absence of the adverse event reporting statement**
- **the potential for the 'disease awareness' section of the website to promote medicines to patients**
- **the provision of prescribing information for multiple medicines via a single webpage**
- **the inclusion of prescribing information for a medicine that the complainant alleged was not licensed in Northern Ireland**
- **the presentation of information about adverse reactions in prescribing information.**

The outcome under the 2021 Code was:

Breach of Clause 12.9	**Failing to include the adverse event reporting statement**

No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 5.6 (x2)	**Requirement to tailor material to the audience to whom it is directed**
No Breach of Clause 6.1	**Requirement that information must be accurate, up to date and not misleading**
No Breach of Clause 11.1	**Requirement that a medicine must not be promoted prior to the grant of its marketing authorisation**
No Breach of Clause 12.1 (x2)	**Requirement to include up-to-date prescribing information**
No Breach of Clause 12.10	**Requirement to include the black triangle in promotional material**
No Breach of Clause 15.6	**Requirement that promotional materials and activities must not be disguised**
No Breach of Clause 26.4	**Requirement to include the black triangle in material which relates to a medicine subject to additional monitoring and that is intended for patients taking that medicine**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint about Takeda was received from an anonymous, contactable complainant who described themself as a UK health professional.

COMPLAINT

The complaint wording is reproduced below with typographical errors corrected. The clauses in square brackets indicate the clauses of the Code that the case preparation manager asked Takeda to consider in relation to each allegation.

> "I am a UK HCP and would like to remain anonymous. I would like to make a complaint about Takeda's website - [website link provided].
>
> Until about several weeks ago, when I clicked on the bleeding disorders tab, there was a tile for Adynovi and how to use it. This had a black triangle next to it with a white border. Is this acceptable as I was under the impression this should be totally black and there should be a statement explaining what this means. [Clause 12.10 and Clause 26.4]
>
> Also, when I clicked on this tile, I noticed there was no adverse event reporting statement as part of the page where the tile was located or upon clicking the tile itself. [Clause 12.9]
>
> Also, I noted on the page that there was a section on disease awareness. I was under the impression that disease awareness is very specific to patients and not clinicians. Hence, whilst the site is dedicated to HCPs, is the purpose for us to use it with patients and thereby inadvertently promote other medicines to them - as other medicines like Advate are mentioned on this page. [Clause 5.1, Clause 5.6 and Clause 15.6]
>
> Also, I note that when I click the prescribing information tab on the top left of the website, all of Takeda's drugs are listed in detail. I thought that promotion should be to a targeted audience (as it includes brand name and indication). Hence, why would a haematologist need to know about Takhzyro for HAE or an immunologist need to know about Obizur for AHA? [Clause 5.6]
>
> Also, there are some drugs which are not licensed in Northern Ireland e.g. Rixubis, but the PI is there. Whilst I note this is not for Northern Ireland, I still feel as if Takeda want me to know about this drug. Is this not unlicensed promotion? [Clause 11.1]
>
> Also, when I read the prescribing information, I am concerned about the undesirable effects section. There is a subheading within this section which states "Other serious undesirable effects" which implies that the side effects that precede this statement are also serious which is misleading e.g. for Advate, it states headache and pyrexia before it states "other serious undesirable effects" which implies that headache and pyrexia are serious. This is the case for all of the PIs that have been listed. Also I note that some PIs do not have "serious" events listed merely a list of side effects which I don't

believe is correct e.g. Takhzyro. Please can the PMCPA investigate. [Clause 6.1 and Clause 12.1]."

TAKEDA'S RESPONSE

The response from Takeda is reproduced below:

"Takeda has very carefully considered the concerns raised in your letter and has addressed all of the allegations made by the complainant in accordance with the applicable clauses. As the complainant stated in their letter, some of the material alleged to be in breach of the Code is no longer live on the website. In order to provide a satisfactory response, Takeda has reviewed the site, as it was on the day the complaint was received, in addition to reviewing specific material that is no longer on the site and to which the complainant may be referring.

For context, Takeda developed the Rare Disease Hub as a resource for UK healthcare professionals (HCPs) interested in a range of rare diseases, covering a number of different clinical specialities. The site is intended for HCPs with varying levels of experience and contains a wide range of educational materials which we believe UK HCPs will find valuable. These includes educational resources on disease awareness, diagnosis and general management approaches pertaining to a number of rare disease therapy areas which align with Takeda's interests. As part of this overall educational package, where relevant, the Rare Disease hub includes information about Takeda medicines. Owing to the presence of content relating to Takeda medicines, and in line with the definition of promotion in the Code, the site has been certified as promotional and visitors to the site must attest to being a UK HCP before being permitted entry. In the event that non-HCPs attempt to access the Rare Disease Hub, they are directed to an alternative website which is entirely non-promotional and suitable for a non-HCP audience.

Allegation 1: Concerns about black triangle on Adynovi (rurioctocog alfa pegol) material

The complainant had issue with (1) the use of a black triangle with a white border as well as (2) the need for a statement explaining the meaning of the triangle. On the day the complaint was received, there were no items live on the website displaying a black triangle with a white border. We were, however, able to identify an item which had previously been removed from the website where the Adynovi name was accompanied by a black triangle with a white border.

The Code stipulates: "Digital communication are [also] covered by this requirement [to clearly show, when required by the licensing authority, an inverted black equilateral triangle to denote that additional monitoring is required in relation to adverse reactions] located adjacent to the first mention of the product as this is likely to be the most prominent display of the name of the product. The size must be that it is easily noticed" (Clause 12.10). On this item the background was dark grey and without a white border, the legibility, and therefore prominence, of the triangle would be reduced. It is Takeda's view that increasing the legibility of the black triangle by providing a white background is in line with the requirements of the Code and is not an alteration of the triangle itself.

Takeda do not believe that clause 12.10 of the Code has been breached.

Regarding the need for an explanatory statement for material with a black triangle, clause 12.10 states "*No written explanation of the symbol is necessary*". Clause 26.4 does refer to the need for such an explanatory statement where material is intended for patients. However, this is not applicable to the Rare Disease Hub which is intended for a UK HCP audience only. The statement *"Rare Disease Hub is for UK healthcare professionals only. This website has been initiated and developed by Takeda. This educational website includes content that may mention Takeda products"* is clearly present on all pages. Furthermore, positive attestation of a user's status as a UK HCP is required before they are able to access any content.

Takeda do not believe that clause 26.4 has been breached.

Allegation 2: Adverse Event reporting on main page of the website

The complainant alleged that a lack of an adverse reporting statement on the main page of the site was in breach of the Code. A clear statement at the top of the page stated where prescribing information and adverse event reporting information could be found.

At the time this site was created, Takeda held the view that a statement directing HCPs to where adverse event reporting information could be found, at one click away, was acceptable. Following recent Code cases and advice issued by the PMCPA on the 18th November 2022, Takeda recognised that this approach was no longer acceptable and put a plan in place to update all relevant digital materials. The Rare Disease Hub website was due to be updated on the 2nd May 2023, and indeed since 2nd May 2023 has had the full adverse event reporting statement displayed prominently on the main homepage and on each page where Takeda products are referenced.

Since this update had not been made on the day the complaint was received, Takeda accept that a breach of Clause 12.9 has occurred.

Allegation 3: Concerns about Disease Awareness section of site

The complainant suggested that part of the website in fact constituted a disease awareness campaign intended for the public. The Rare Disease Hub website has a section titled 'Disease Awareness' where information on specific conditions is given without mentioning any treatments for those conditions. The materials in the section are intended to educate HCPs, not the public, on the relevant disease states. Due to the rarity of the conditions covered by the Rare Disease Hub, it is our expectation that many HCPs who visit the website will have limited knowledge of some of these conditions and that the materials contained in this section of the site will be a valuable educational resource for them.

The section was named Disease Awareness simply to differentiate it from areas of the website which include materials which discuss Takeda medicines. As previously stated, Takeda had taken reasonable measures to minimise the chance of non-HCPs accessing the Rare Disease Hub, including the requirement for visitors to the site to positively confirm that they are UK-registered HCPs before being able to access the

site. Takeda therefore refute the suggestion that any part of the Rare Disease Hub constitutes a disease awareness campaign intended for the public.

Takeda do not believe that Clauses 5.6 or 15.6 have been breached, and therefore reject the suggestion that high standards have not been maintained, and consequently that Clause 5.1 has been breached.

Allegation 4: Concerns about promotion to the wrong audience by providing prescribing information for all Takeda medicines listed somewhere on the site

The fourth concern alleges that the way in which prescribing information is presented within the website promoted individual medicines to an inappropriate audience. The Rare Disease Hub was developed for a wide variety of HCPs, not limited to those who specialise in particular therapy areas. This is because (i) Takeda's rare disease portfolio spans a number of different therapeutic areas and (ii) it is important for healthcare professionals outside of these areas to have some understanding of rare disease which may present in their clinical practice.

Since users are very likely to view web pages which discuss a number of medicines, Takeda have taken the view that providing a 'one click' link on every page to a page which includes prescribing information for all Takeda medicines mentioned within the Rare Disease Hub is the most practical and user-friendly way of complying with the Code requirement to have prescribing information readily available and no more than 'one click away' when viewing promotional material online. Takeda do not believe that this approach constitutes the promotion of individual medicines to an inappropriate audience. Takeda also consider the approach taken here to be entirely consistent with the panel's views as expressed in Case AUTH/3451/1/21.

Takeda do not believe that clause 5.6 has been breached.

Allegation 5: Concerns about promotion of an unlicenced medicine in Northern Ireland

The complainant alleged that Rixubis is not licenced in Northern Ireland. Rixubis has a UK marketing authorisation (UK Summary of Product Characteristics [SmPC] provided). Takeda does not actively promote Rixubis in Northern Ireland for commercial reasons. However, the marketing authorisation for this product clearly includes Northern Ireland.

Takeda do not believe that Clause 11.1 has been breached.

Allegation 6: Concerns about prescribing information

The sixth concern alleges that the prescribing information (PI) contained within the rare disease hub was not accurate. Takeda has reviewed all PIs and is confident each one has been prepared in line with the requirements of the Code. The complainant specifies 2 particular PIs, Takhzyro (landelumab) and Advate (octocog alpha). Table 1 shows all the adverse events listed in section 4.8 of the SmPC for Takhzyro. All these adverse events are included within the *Undesirable Effects* section of the prescribing information. As there are no serious adverse effects stated within the SmPC,

prescribing information accordingly reflects this.

Table 1

System organ class	Adverse drug reaction	Frequency
Immune system disorders	Hypersensitivity*	Common
Nervous system disorders	Dizziness	Common
Skin and subcutaneous tissue disorders	Rash maculo-papular	Common
Musculoskeletal and connective tissue disorders	Myalgia	Common
General disorders and administration site conditions	Injection site reactions**	Very common
Investigations	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common

The PI for Advate has listed the common and very common adverse effects described in the SmPC in the first sentence of the *Undesirable Effects* section. In a new sentence, *Other serious undesirable effects,* adverse events which although less common are required to be included within the PI are listed. It is Takeda's view that both these PIs, and indeed all other PIs included within the Rare Disease Hub, have been prepared in accordance with the requirements of the Code and reflect each products' up-to-date SmPC.

Takeda do not believe that Clauses 12.1 or 6.1 have been breached.

Conclusion

Takeda has thoroughly investigated all points raised by the complainant. The company acknowledges that the adverse event reporting statement mandated by the Code was not properly displayed on either the main page or pages where Takeda medicines were mentioned within the Rare Disease Hub and therefore accepts that a breach of Clause 12,9 has occurred, though this situation has now been remedied.

Takeda are, however, of the view that the Code has not in any way been breached in respect of any of the other matters raised by the complainant."

FURTHER INFORMATION FROM TAKEDA

After giving preliminary consideration to the case, the Panel asked Takeda to clarify the status of Rixubis in Northern Ireland at the time of the complaint.

The response from Takeda is reproduced below:

> "Takeda would like to apologise for the confusion. Takeda erroneously stated the SmPC was for both Great Britain and Northern Ireland.
>
> Rixubis has held a National PLGB licence, covering Great Britian, since 1st January 2021. Takeda also holds a Centralised licence which covers the EU including Northern Ireland, first authorised on 19th December 2014. Supply of Rixubis to Northern Ireland was discontinued on 01st July 2022 therefore it would not have been available to Northern Irish prescribers on the 25th April 2023. This discontinuation of supply was for commercial reasons.
>
> Takeda would also like to clarify that the only mention of Rixubis on the Rare Disease Hub website is in the Prescribing Information tab and there are no corresponding promotional items hosted on the site."

PANEL RULING

The complaint was regarding Takeda's 'Rare Disease Hub' website. The Panel noted Takeda's submission that the website was intended for UK health professionals and was certified as promotional. The Panel further noted Takeda's submission that visitors to the site must attest to being a UK health professional before being permitted entry; non-health professionals that attempted to access the site were directed to an alternative non-promotional website.

Black triangle

The complainant expressed concern that the black triangle for Adynovi was presented with a white border round it on a tile within the 'Bleeding Disorders' section of the website and that there was no explanation of the symbol's meaning. The case preparation manager had asked Takeda to consider the requirements of Clause 12.10 and Clause 26.4 in relation to this part of the complaint.

Clause 12.10 of the Code specified, among other things, that, when required by the licensing authority, all promotional material must clearly show an inverted black equilateral triangle to denote that additional monitoring is required in relation to adverse reactions. The symbol should always be black and, in digital communications, should be located adjacent to the first mention of the product and at a size such that it is easily noticed. Clause 12.10 further stated that no written explanation of the symbol is necessary.

The Panel noted the complainant had stated that the tile at issue was present "until about several weeks ago". Takeda submitted that on the day the complaint was received, there were no items on the website displaying a black triangle with a white border. Takeda provided material (C-APROM/GB/ADYN/0029, certified March 2022), which had been removed from the website prior to the complaint, where the Adynovi name was accompanied by a black triangle with a white border. The Panel thus made its determination in relation to this material provided by Takeda.

The Panel noted that the Bleeding Disorders webpage at issue had three main sections headed "materials for use with patients", "disease awareness" and "all content". Under each headed section were numerous labelled tiles.

The Panel noted that C-APROM/GB/ADYN/0029 was the PDF certified in relation to a tile labelled “Adynovi (rurioctocog alfa pegol) BAXJECT III: reconstitution system” located under the “all content” section and for the webpage that users were taken to when the tile was clicked. Within that same certified PDF there was a tile with identical appearance present under the “materials for use with patients” section. The Panel assumed that both tiles, when clicked, led to the same webpage.

On the tile, a black triangle was present adjacent to the name of the medicine, against a dark-coloured background. The triangle symbol had a white border. There was no explanation of the symbol.

It appeared that when this tile was clicked, it would lead to a webpage that included, among other things, a static display of the first frame of a video. This video frame had a black triangle adjacent to the first mention of Adynovi and included the text “This video demonstrates, step-by-step, how to use the BAXJECT III system, to support patients prescribed Adynovi to self-infuse” and “This video has been developed by Takeda and is intended only for patients who have been prescribed Adynovi.”

In the Panel’s view, the promotional website was for health professionals and needed to comply with the requirements of the Code for promotional material. However, any materials within the website that were intended for health professionals to show their patients, such as a video, needed to comply with the requirements of the Code for patient material, including Clause 26.4.

Clause 26.4 stated, among other things, that for any material which relates to a medicine and is intended for patients taking that medicine, and when such a medicine is subject to additional monitoring, an inverted black equilateral triangle must be included on it together with the following statement or a similar one: “This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See [a website address which links directly to the MHRA Yellow Card site] for how to report side effects.”

Given that the video was intended to be shown to patients, the Panel was concerned that the explanatory statement was not provided with the black triangle that was present in the first frame of the video. However, the Panel considered that the video was not the subject of the allegation. The Panel considered that the allegation was about the display of the tile located on the previous webpage, which, in the Panel’s view, was a webpage for health professionals – on that narrow ground, the Panel ruled **no breach of Clause 26.4**.

Regarding the tile, Takeda submitted that the black triangle had a white border to ensure its legibility and prominence against a dark grey background.

The Panel noted that neither Clause 12.10 nor its supplementary information specified how the black triangle should be presented when displayed against a dark-coloured background. The Panel considered that the Code required that, among other things, the symbol in digital material must be clearly shown, should always be black and the size must be such that it is easily noticed.

The Panel considered that, while it was preferable for the black triangle to be on a light-coloured background, where it was necessary to present the black triangle against a dark-coloured

background, the use of a white border was not necessarily unacceptable, provided the requirements of Clause 12.10 were met and the company was confident that the display would not cause confusion.

The Panel considered that the complainant had not established, on the balance of probabilities, that the use of a white border around the black triangle symbol on the tile in question would confuse health professionals or was unacceptable as alleged, nor that a written explanation of the symbol was required on the tile, and the Panel ruled **no breach of Clause 12.10**.

Adverse events reporting statement

The complainant alleged that there was no adverse event reporting statement present on either the webpage where the tile in question was located, or on the webpage reached after clicking on the tile.

The case preparation manager had raised Clause 12.9 in relation to this allegation.

The Panel noted that Clause 12.9 required that all promotional material must include the prominent statement: "Adverse events should be reported. Reporting forms and information can be found at [website address which links directly to the MHRA Yellow Card site]. Adverse events should also be reported to [relevant pharmaceutical company]."

Takeda submitted that, at the time of the complaint, there was a statement on the Bleeding Disorders main webpage (material reference C-APROM/GB/RDG/0075, certified 6 April 2023) directing users to where the adverse event reporting statement could be found and that the statement itself was one click away, which Takeda acknowledged did not meet the requirements of the Code.

The Panel considered that the website did not meet the requirements of Clause 12.9 at the time of the complaint and ruled **a breach of Clause 12.9**, as acknowledged by Takeda.

'Disease Awareness' section of the website

The complainant alleged that if the purpose of the 'disease awareness' section of the website was for it to be used by health professionals with patients, it could inadvertently promote "other medicines" to patients. The complainant expressed the opinion that 'disease awareness' referred to information intended for patients, not health professionals.

The Panel understood the complainant's wording of "other medicines" to mean medicines other than that which the patient was prescribed.

The Panel noted, from the screenshots provided by the case preparation manager and the material provided by Takeda contemporaneous to the complaint (reference C-APROM/GB/RDG/0075, certified 6 April 2023), that the webpage at issue had three main sections headed "materials for use with patients", "disease awareness" and "all content". Under each headed section were numerous labelled tiles which referred to videos, articles, and information to be downloaded.

Takeda submitted that the disease awareness section contained information on specific conditions without mentioning any treatments. According to Takeda, the section was named

"disease awareness" to differentiate it from other areas of the website that had materials which discussed Takeda medicines.

The Panel took account of Takeda's submission that due to the rarity of the conditions covered by the website, it expected that many health professional visitors of the site would have limited knowledge of some of these conditions.

The Panel noted that the Code made reference to 'disease awareness' under the supplementary information to Clause 26.2, in relation to campaigns to encourage members of the public to seek treatment for their symptoms, while in no way promoting the use of a specific medicine.

The Panel considered that while the Code referred to 'disease awareness' in relation to members of the public, it did not prohibit use of the terminology in relation to materials or activities intended to increase health professionals' awareness of a disease.

The Panel took account of the layout of the webpage and the three distinct sections that were clearly labelled as "materials for use with patients", "disease awareness" and "all content". While it could have been made clearer that the materials in the "disease awareness" section were for health professionals only, the Panel considered, on the balance of probabilities, that health professionals would likely understand that all materials appropriate for use with patients would be found in the "materials for use with patients" section.

The case preparation manager had asked Takeda to consider the requirements of Clause 5.6 (requirement to tailor material to the audience to whom it is directed and to only make material available to people whose need for or interest in it can be reasonably assumed), Clause 15.6 (requirement that promotional materials must not be disguised) and Clause 5.1 (requirement to maintain high standards) in relation to this part of the complaint.

As noted above, Takeda submitted that visitors to the site must attest to being a UK health professional before being permitted entry; non-health professionals that attempted to access the site were directed to an alternative non-promotional website. Furthermore, it appeared to the Panel that while health professionals may show patients certain materials held within the "materials for use with patients" section, it was not expected that the patient would navigate the website themselves, and therefore patients would not see what other content was on the "Bleeding Disorders" webpage in question.

The Panel considered that the complainant had not established that this webpage promoted medicines to patients. The Panel therefore ruled **no breach of Clauses 5.1, 5.6 and 15.6**.

Provision of prescribing information

The complainant alleged that by providing prescribing information in the form of a link to a single webpage with prescribing information for all Takeda medicines detailed meant that the promotion of Takeda medicines was not to a targeted audience.

The Panel noted Takeda's submission that providing a 'one click' link on every page to a page which includes prescribing information for multiple Takeda medicines mentioned within the Rare Disease Hub was a practical and user-friendly way of complying with the requirements of the Code for a website where individual webpages were likely to make mention of multiple Takeda

medicines and where the intended audience was a wide variety of health professionals who might need some understanding of a range of rare diseases.

The screenshot of the prescribing information webpage contemporaneous to the complaint (C-APROM/GB/RDG/0073, certified February 2023) provided as part of Takeda's submission showed that the webpage contained prescribing information for 16 Takeda medicines. These were presented, one after the other, in the main body of the webpage. At the top of the page, there was a box, which appeared to contain 'jump links' to enable the user to navigate to the medicine of interest more quickly.

The case preparation manager had raised Clause 5.6 in relation to this part of the complaint.

Clause 5.6 required that material should only be provided or made available to those groups of people whose need for or interest in it can reasonably be assumed and that material should be tailored to the audience to whom it is directed. The Panel considered that the layout of the webpage was such that it would be clear to the user how to navigate to the prescribing information for their medicine of interest. Bearing in mind the very narrow allegation, the Panel considered that the complainant had not established that the information constituted promotion to people whose need for or interest in it could not be reasonably assumed. The Panel therefore ruled **no breach of Clause 5.6**.

Promotion of Rixubis in Northern Ireland

The complainant alleged that the provision of prescribing information for medicines that were not licensed in Northern Ireland constituted unlicensed promotion. The complainant gave only Rixubis as an example and therefore the Panel ruled in relation to this medicine alone.

The case preparation manager had raised Clause 11.1 which required that a medicine must not be promoted prior to the grant of its marketing authorisation.

The Panel noted that the website was for UK health professionals. The Panel noted from the screenshot of the prescribing information webpage contemporaneous to the complaint (C-APROM/GB/RDG/0073) that Rixubis prescribing information for only Great Britain was provided.

Takeda submitted that Rixubis had held a PLGB licence, covering Great Britain, since 1 January 2021.Takeda further submitted that Rixubis was unavailable to prescribers in Northern Ireland at the time of the complaint due to discontinuation of supply for commercial reasons; however, Rixubis was still licensed in Northern Ireland at the time of the complaint through a Centralised licence that covered the EU including Northern Ireland.

The Panel rejected the complainant's allegation that Rixubis was not licensed within Northern Ireland and therefore ruled **no breach of Clause 11.1**.

Presentation of information about adverse reactions in prescribing information

The complainant raised a concern about the use of the subheading 'Other serious undesirable effects' within the prescribing information. The complainant alleged that this misleadingly implied that the side effects listed before this subheading were all serious. The complainant gave the Advate prescribing information as an example and alleged that it implied that headache and pyrexia were serious. The complainant further alleged that this was the case for all of the

prescribing information on the website. The complainant had only named Advate and therefore the Panel ruled on this allegation in relation to Advate prescribing information only.

The complainant also alleged that some prescribing information, citing Takhzyro as an example, did not list 'serious' side effects – it just provided a list of side effects. The complainant had only named Takhzyro and therefore the Panel ruled on this allegation in relation to Takyzyro prescribing information only.

The case preparation manager had asked Takeda to consider the requirements of Clause 6.1 and Clause 12.1 in relation to this part of the complaint.

Clause 12.1 required that the prescribing information listed in Clause 12.2 must be provided in a clear and legible manner. Clause 12.2 required that the prescribing information included, among other things, "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 Code did not specify the exact subheadings to be used in prescribing information; however, the Panel considered that the information should be displayed in a manner that was clear, legible and not misleading.

The Panel noted that both the Great Britain and Northern Ireland prescribing information for Advate stated, among other things:

> "**Undesirable effects:** *Very common (≥1/10)*: FVIII inhibition (PUPs, previously untreated patients). *Common (≥1/100 to <1/10):* Headache, pyrexia. Other serious undesirable effects: *Uncommon (≥1/1,000 to <1/100)*: Post-procedural haemorrhage, lymphangitis, FVIII inhibition (PTPs, previously treated patients), syncope, haematoma, dyspnoea, peripheral oedema; *Unknown frequency*: Anaphylactic reaction, hypersensitivity."

The Panel had no details before it regarding Takeda's methodology for deciding which undesirable effects in the SPC it considered as 'serious' for inclusion in the prescribing information in addition to the requirement to include all of the 'very common' and 'common' undesirable effects. Nonetheless, the Panel considered that such a matter was not the subject of this complaint. In the Panel's view, the complainant's allegation was very narrow. The complainant alleged that the phrasing "Other serious undesirable effects" in the prescribing information implied that headache and pyrexia, which preceded this statement, were also serious. The Panel accepted that it might be interpreted in that way. However, the Panel considered, particularly given that the frequency categories were stated, that, on the balance of probabilities, "Other serious undesirable effects" would be interpreted as side effects that although not 'very common' or 'common' were considered to be 'serious'. The Panel considered that the complainant had not established that the use of the subheading 'Other serious undesirable effects' was misleading as alleged and ruled **no breach of Clauses 6.1 and 12.1** in this regard.

In relation to the allegation that the Takhzyro prescribing information did not have 'serious' undesirable effects listed, the Panel noted that all the adverse reactions listed in section 4.8 of the Takhzyro SPC were either frequency 'very common' or 'common' and all had been included in the prescribing information under their respective frequency category. The Panel therefore ruled **no breach of Clause 12.1**.

Complaint received **25 April 2023**

Case completed **27 June 2024**