CASE AUTH/3651/5/22 ***NO BREACH OF THE CODE***

COMPLAINANT v ROCHE

Allegations about an Ocrevus website

CASE SUMMARY

This case related to allegations that the claim 'generally well tolerated' used on the landing page of the Ocrevus (ocrelizumab) website was misleading, not balanced or accurate in view of clinical trial findings of serious adverse events.

The Panel ruled no breach of the following Clauses of the 2021 Code on the basis that the claim was qualified by a list of linked aspects of the safety and tolerability profile within the immediate visual field of the claim in question which were designed to catch the reader's eye such that it would be sufficiently clear that the claim was not unqualified and therefore not misleading or incapable of substantiation:

No Breach of Clause 2	**Requirement that material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 5.1	**Requirement to maintain high standards**
No Breach of Clause 6.1	**Requirement that claims must not be misleading**
No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**

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

FULL CASE REPORT

An anonymous, contactable health professional complained about the promotion of Ocrevus (ocrelizumab) by Roche Products Ltd. The material at issue was the landing page of the Roche Resources website.

COMPLAINT

The complainant alleged that the wording used around safety was misleading, not balanced or accurate, in view of the clinical trial findings around serious adverse events. The complainant alleged that Clauses 6.1, 6.2, 5.1 and 2 had been breached considering misleading information was a risk to patient management.

The complainant pointed out that underneath the safety profile of the product on the landing page of the Roche Resources website at issue it was claimed that Ocrevus was generally well tolerated by relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) patients. This claim was false as the following information in the summary of product

characteristics (SPC) mentioned a number of serious side-effects that took place during trials including even fatal side-effects. The claim of 'generally well tolerated' needed significant qualification which was not provided under the claim. The complainant referred to Section 4.8 of the SPC and the following information which confirmed the serious and fatal side-effects:

Infection

In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving Ocrevus vs 52.5% of patients receiving interferon beta 1a. Serious infections occurred in 1.3% of patients receiving Ocrevus vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving Ocrevus vs 69.9% of patients receiving placebo. Serious infections occurred in 6.2% of patients receiving Ocrevus vs 6.7% of patients receiving placebo. An increase in the rate of serious infections was observed in RMS between Years 2 and 3, but not in subsequent years. No increase was observed in PPMS.

Lymphocytes

In RMS, a decrease in lymphocyte < [lower limit of normal] [(LLN)] was observed in 20.7% of Ocrevus patients compared with 32.6% of patients treated with interferon beta-1a. In PPMS, a decrease in lymphocytes <LLN was observed in 26.3% of Ocrevus treated patients vs 11.7% of placebo-treated patients.

The majority of these decreases reported in Ocrevus treated patients were Grade 1 (<LLN - 800 cells/mm^3) and 2 (between 500 and 800 cells/mm^3) in severity. Approximately 1% of the patients in the Ocrevus group had a Grade 3 lymphopenia (between 200 and 500 cells/mm^3). None of the patients were reported with Grade 4 lymphopenia (< 200 cells/mm^3). An increased rate of serious infections was observed during episodes of confirmed total lymphocytes counts decrease in ocrelizumab treated patients.

Neutrophils

In the active-controlled (RMS) treatment period, a decrease in neutrophils < LNN was observed in 14.7% of Ocrevus patients compared with 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of Ocrevus patients presenting decreased neutrophils was higher (12.9 %) than placebo patients (10.0 %); among these a higher percentage of patients (4.3%) in the Ocrevus group had Grade 2 or above neutropenia vs 1.3% in the placebo group; approximately 1% of the patients in the Ocrevus group had Grade 4 neutropenia vs 0% in the placebo group.

Infusion-related reactions

In active-controlled (RMS) clinical trials, IRR (infusion-related reaction) was the most common adverse event [AE] in patients treated with Ocrevus with an overall incidence of 34.3% compared with an incidence of 9.9% in the interferon beta-1a treatment group (placebo infusion). The incidence of IRRs was highest during Dose 1, infusion 1 (27.5%) and decreased over time to <10% at Dose 4. The majority of IRRs in both treatment groups were mild to moderate. 21.7% and 10.1% of Ocrevus treated patients experienced mild and moderate IRRs respectively, 2.4% experienced severe IRRs and 0.1% experienced life-threatening IRRs.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves .

In other auto-immune conditions, use of Ocrevus concomitantly with immunosuppressive medications (eg chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of serious infections, including opportunistic infections. Infections included and were not limited to atypical pneumonia and *pneumocystis jirovecii* pneumonia, varicella pneumonia, tuberculosis, histoplasmosis. In rare cases, some of these infections were fatal. An exploratory analysis identified the following factors associated with risk of serious infections: higher doses of Ocrevus than recommended in MS, other comorbidities, and chronic use of immunosuppressants/corticosteroids.

When writing to Roche, the Authority asked it to consider the requirements of Clauses 6.1, 6.2, 5.1 and 2 of the 2021 Code as cited by the complainant.

RESPONSE

Roche stated that it was committed to the appropriate use of medicines, protecting the safety of patients and maintaining high standards in the ethical promotion of its medicines. It was therefore unfortunate to receive a complaint of this nature.

The complainant referred to the Ocrevus landing page on the Roche Resources website which highlighted the mode of action, prescribing information, indications, efficacy, safety profile and dosing administration for Ocrevus.

Ocrevus was a monoclonal antibody indicated for the treatment of adult patients with RMS with active disease defined by clinical or imaging features. It was also indicated for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. In UK clinical practice the majority of Ocrevus patients were treated for relapsing remitting multiple sclerosis.

The complainant alleged that the promotional safety 'wording' was misleading and not balanced or accurate in relation to the clinical trial safety findings and treatment-related serious adverse events (SAEs). The complainant failed to provide proof or clear examples of the specific misleading or inaccurate text that was not in accordance with the SPC or clinical trial safety findings, nor specified how said 'wording' was misleading and unbalanced. According to Section 4.3 of the Constitution and Procedure, '*a complainant has the burden of proving their complaint on the balance of probabilities*'. The complainant had not met this requirement in accordance with the Constitution and Procedure.

Roche recognised the special nature of the medicine (Clause 5.2) and had targeted the appropriate audience with tailored information in accordance with the SPC to encourage and support the rational use of the medicine. Particular care and attention was taken to clearly and separately elucidate the safety profile and warnings and precautions with more detailed text and information in accordance with the SPC. Access to this information was available through clearly labelled links provided on the webpage for health professionals.

The complainant alleged that the above mentioned points relating to misleading safety information constituted a risk to 'patient management'. The complainant failed to provide clear

examples or proof of the information that was specifically misleading and how this information specifically posed a risk to 'patient management'. The black triangle clearly indicated that the medicine was subject to additional monitoring and the indication statements clearly defined the target patient population most likely to benefit from this medicine: therefore, Roche had taken every reasonable action to minimise any risk to patient safety and to support the safe and rational use of the medicine.

The complainant alleged that the claim '*generally well tolerated*' was false in light of SAEs seen in the clinical trials. The complainant appeared to have conflated the concepts of *tolerability* and *safety profile*. Tolerability could be described as a cumulative summary of all-grade treatment-related AEs and rates of discontinuation *especially when compared to a known comparator with a known tolerability profile*. Safety profile could be described as the frequency distribution of all-grade treatment related AEs of a particular medicine *agnostic of a comparator*.

As per precedent set out in Cases AUTH/3231/7/19 and AUTH/3255/7/19, the Authority had a similar position regarding the use of the term '*tolerated*', previously noting that '*the number of adverse events do not necessarily mean that a medicine was not well tolerated*'. A medicine could be considered to be tolerable and yet still be associated with a defined risk of SAEs. This was not a logically incompatible or fundamentally misleading construct and health professionals were very sensitive to this clinical nuance. Indeed, it formed the basis of a risk-benefit conversation when the clinician and patient together decided on the most appropriate treatment option.

Assuming the inferred description of *'tolerability'* based on case precedent, the AE tables showed minimal differences between all-grade AEs and rates of discontinuation of Ocrevus and the known comparator arms of ß-IFN and placebo. The most commonly encountered treatment-related AEs had a broadly comparable incidence to that of the comparator arms. Where there was a higher incidence of an AE in favour of Ocrevus versus the comparator, more information was then provided, especially with regard to severity. It was further noted by NICE in its technology appraisal guidance for Ocrevus [TA533] that patient experts reported *'in their experience, adverse events such as fatigue and ability to concentrate experienced with other treatments, such as beta interferons, do not occur with ocrelizumab*'. This ratified the notion of tolerability relating to a patient's individual lived experience of their treatment. On the balance of probabilities, Ocrevus might be considered to be generally well tolerated.

The '*generally well tolerated*' claim was approved by the MHRA during pre-vetting. Whilst Roche acknowledged that MHRA pre-vetting and approval of material did not constitute ABPI compliance, Roche followed specific MHRA instructions to include the phrase '*generally well tolerated*' in the creation of this material. This demonstrated a genuine commitment from Roche to uphold the highest standards expected of the industry. However, to provide the complete picture of the AEs a patient could expect to encounter on Ocrevus treatment, particular care and attention was taken to clearly and separately elucidate the safety profile, IRRs, adverse drug reactions (ADRs) and warnings and precautions. Detailed text and information was provided in the links found below the statement, in accordance with the SPC specifically to encourage the rational use of the medicine.

The complainant alleged that the '*generally well tolerated*' claim needed significant qualification which was not provided. The claim was substantiated by both the broadly comparable frequency distributions of all-grade treatment related AEs, and rates of discontinuation due to treatment emergent AEs versus known comparator. It remained challenging to consider what

else could have been provided to further substantiate the claim over and above the industry gold standard references of the pivotal registration Phase III clinical trials and SPC.

In light of the above, Roche concluded that the information provided on the Ocrevus Roche Resources page was accurate, balanced, fair, objective, unambiguous, reflected the SPC, did not mislead the reader, and enabled the reader to make an independent, informed decision regarding the use of ocrelizumab. That the complainant had been able to easily locate and include the relevant information in the product SPC referenced throughout the Roche Resources page, suggested a sufficient degree of accessibility of said information. Roche therefore denied a breach of Clauses 6.1 and 6.2.

Considering all of the above, high standards expected of the industry had been maintained, with full consideration for patient safety. In conclusion, Roche denied a breach of Clauses 5.1 and Clause 2 fully acknowledging the reservation of the aforementioned clause for situations of particular censure.

PANEL RULING

The complaint concerned the landing page of the Ocrevus website and the complainant's allegation that the claim 'generally well tolerated' was misleading, and was not balanced and accurate in view of clinical trial findings around safety and serious adverse events. The complainant stated that misleading information was a risk to patient management and that the claim required significant qualification which was not provided.

The Panel considered the layout and the overall impression created by the landing webpage which was intended for health professionals. The menu at the top of the page stated 'If you are an HCP, register free to access the full content'. It was unclear to the Panel whether the complainant had so registered. The Panel made its ruling on the version of the webpage provided by the complainant. The complainant did not refer to any linked material. A banner advertisement which referred to when to consider Ocrevus appeared above a menu which had links to GB and NI Prescribing Information, and adverse event reporting and additional monitoring. The relevant part of the webpage sat beneath the licensed indications and was segmented into six sections: MOA (mechanism of action), RMS, PPMS, Safety Profile, Dosing and Roche in Neuroscience. The Panel did not have access to the linked content within these sections. The RMS section included links to the Ocrevus core data in RMS and Ocrevus OLE (open label extension) data in RMS and the PPMS sections included links to the Ocrevus study design in PPMS, Ocrevus efficacy in PPMS and Ocrevus safety in PPMS.

The claim in question was within a section titled 'Safety Profile' which appeared above a blue cross (+) within an outlined circle that was followed by the claim in question 'Ocrevus was generally well tolerated by RMS and PPMS patients' in black font. Beneath the claim was the phrase 'Find out more about' and a list of four links which referred to aspects of the safety profile: Ocrevus Safety Profile, Ocrevus ADRs, Ocrevus IRRs and Ocrevus Warnings and Precautions. The claim that 'Ocrevus was generally well tolerated by RMS and PPMS patients' was referenced to the Ocrevus SPC, Hauser *et al* 2017 and Montalban *et al* 2017.

The Panel considered that the landing page helped health professionals navigate the Ocrevus website by signposting and directing them to where detailed information could be found. Nonetheless, whilst context was important, the Panel noted that any claims on the landing page should be capable of standing alone in relation to the requirements of the Code.

The Panel noted that there were differences between a medicine's tolerability and safety profiles. The Panel also noted Roche's submission that the complainant appeared to have conflated the concepts of tolerability and safety profile. Tolerability could be described as a cumulative summary of all-grade treatment-related AEs and rates of discontinuation especially when compared to a known comparator with a known tolerability profile. Safety profile could be described as the frequency distribution of all-grade treatment related AEs of a particular medicine agnostic of a comparator.

The Panel noted that the webpage was directed to a broad health professional audience and queried whether all health professionals would truly understand the differences between safety and tolerability. The Panel noted Roche's submission that the 'generally well tolerated' claim had been approved by MHRA during pre-vetting and its acknowledgement that MHRA pre-vetting and approval did not constitute ABPI Code compliance.

The Panel noted Roche's submission that the claim was substantiated by both the broadly comparable frequency distributions of all-grade treatment related AEs, and rates of discontinuation due to treatment emergent AEs versus known comparator (both provided with references to the SPC and the two peer-reviewed Phase III clinical trials published in the New England Journal of Medicine). The Panel noted that as referred to by the complainant the SPC included a number of special warnings and precautions for use including infusion related reactions, infections, and the treatment of severely immunocompromised patients. Section 4.8 of the SPC – Undesirable effects, included descriptions of selected adverse reactions including infusion-related reactions, infection, and laboratory abnormalities in respect of lymphocytes and neutrophils. The Panel considered the nature, frequency and severity of adverse reactions was relevant to tolerability.

The SPC stated that the most important and frequently reported adverse drug reactions (ADRs) were IRRs and infections. It further stated that the overall safety profile of Ocrevus was based on data from patients from pivotal clinical trials in MS (RMS and PPMS) and included a summary of the ADRs reported in association with the use of Ocrevus during the controlled treatment periods of MS clinical trials. The pivotal studies referred to in the SPC were the same as those cited as references supporting the claim in question.

The SPC further stated that in active-controlled (RMS) clinical trials, IRR was the most common adverse event in patients treated with Ocrevus with an overall incidence of 34.3% compared with an incidence of 9.9% in the interferon beta-1a treatment group (placebo infusion). The majority of IRRs in both treatment groups were mild to moderate. 21.7% and 10.1% of Ocrevus treated patients experienced mild and moderate IRRs respectively, 2.4% experienced severe IRRs and 0.1% experienced life-threatening IRRs.

In the placebo-controlled (PPMS) clinical trial IRR was the most common adverse event in patients treated with Ocrevus with an overall incidence of 40.1% compared with an incidence of 25.5% in the placebo group. The majority of IRRs were mild to moderate. 26.7% and 11.9% of Ocrevus treated patients experienced mild and moderate IRRs respectively, 1.4% experienced severe IRRs. There were no life-threatening IRRs.

The SPC further stated that the overall proportion of patients experiencing a serious infection was similar to comparators. The frequency of grade 4 (life-threatening) and grade 5 (fatal) infections was low in all treatment groups, but in PPMS it was higher with Ocrevus compared with placebo for life-threatening (1.6% vs 0.4%) and fatal (0.6% vs 0%) infections. All life-threatening infections resolved without discontinuing ocrelizumab.

The Panel considered the rates of adverse events and discontinuation identified in the pivotal clinical trials for the two indications (RMS and PPMS).

In the OPERA I and OPERA II RMS trials 80.1% and 86.3% of patients (Opera 1) treated with Ocrevus and 80.9% and 85.6% of patients (Opera II) treated with Interferon Beta-1a had an adverse event (of any grade). The rates of adverse events that lead to treatment discontinuation in OPERA I and OPERA II respectively were 3.2% and 3.8% of patients treated with Ocrevus and 6.4% and 6.0% of patients treated with Interferon Beta-1a.

In the ORATORIO-PPMS trial 95.1% of patients treated with Ocrevus and 90.0% of patients treated with placebo had an adverse event (of any grade) while the rates of adverse events leading to discontinuation of treatment were 4.1% of patients treated with Ocrevus and 3.3% of patients treated with placebo.

The Panel noted the adverse event and discontinuation data in the SPC and the clinical studies and in addition noted Roche's submission about the broadly comparable frequency distributions of all grade treatment-related adverse events and rates of relevant discontinuations. It also noted that the studies highlighted that further long-term assessment of the safety profile of ocrelizumab was required in order to fully characterise the risk of uncommon adverse events, including progressive multifocal leukoencephalopathy (PML). In addition, the Panel noted that Ocrevus was a black triangle medicine subject to additional monitoring to allow quick identification of new safety information and that this was explained immediately below the safety profile section.

The Panel noted its description above of the section within which the claim 'Ocrevus was generally well tolerated by RMS and PPMS patients' appeared and which the complainant alleged required significant qualification. In the Panel's view, the claim was immediately qualified by the subsequent list of linked aspects of the safety profile. The location of the subsequent list was such that itemised links were within the immediate visual field of the claim in question and, in the Panel's view, were designed to catch the reader's eye. The linked list included Ocrevus ADRs, Ocrevus IRRs and Ocrevus Warnings and Precautions.

In the Panel's view, taking account of its comments above and the cumulative effect of the qualifying term 'generally' and the location (within the immediate visual field of the claim in question), and description of the of the listed links relevant to both tolerability and safety, the phrase 'well-tolerated' had been sufficiently qualified. On balance, the Panel considered that it was made sufficiently clear to the reader that the claim 'well tolerated' was not unqualified and therefore did not consider the claim in question was misleading or incapable of substantiation on the narrow ground alleged. The Panel therefore ruled **no breach of Clauses 6.1 and 6.2** and accordingly, **no breach of Clauses 5.1 and 2.**

Complaint received **30 May 2022**

Case completed **23 May 2023**