CASE AUTH/3460/1/21 ***NO BREACH OF THE CODE***

COMPLAINANT v NOVARTIS

Promotion of Beovu

A contactable complainant who later became non-contactable and who described him/herself as a health professional was concerned about the lack of safety information given in a journal advertisement (ref BRO20 – C053, November 2020) for Beovu (brolucizumab) placed in the December 2020 issue of the British Journal of Ophthalmology by Novartis Pharmaceuticals UK.

Beovu was presented as a pre-filled syringe for intravitreal injection, for use in adults for the treatment of neovascular (wet) age-related macular degeneration (nAMD).

The advertisement in question was headed 'For adults with wet AMD, their vision is a masterpiece' and included four claims for Beovu which were attributable to the HAWK and HARRIER trials. The first three claims were about the efficacy of Beovu and the fourth stated that in HAWK and HARRIER Beovu 'Exhibited an overall well-tolerated safety profile in treated patients.'

The complainant submitted that Beovu had been the subject of serious, sight-threatening complications which were noted in the pivotal trials, acknowledged as a safety signal by Novartis, and were subject to a mandated summary of product characteristics (SPC) update. The complainant considered that it was irresponsible to promote Beovu without providing safety information; it was worrying, misleading and risked patient safety.

The detailed response from Novartis is given below.

The Panel noted that the advertisement was placed in the British Journal of Ophthalmology and that the Beovu SPC stated that Beovu must be administered by a qualified ophthalmologist experienced in intravitreal injections. The Panel noted that this was a very specialist area.

The Panel noted that the complainant made no reference to any of the claims but was concerned about the lack of safety information in the advertisement given the serious, sight-threatening complications that had been noted with Beovu. The Panel noted Novartis' submission that adverse events of retinal vasculitis and/or retinal vascular occlusion were first seen in post-marketing reports and not in the pivotal trials as submitted by the complainant. A review of the post-marketing cases, with a comparison of inflammatory adverse events seen in the Beovu Phase 3 trials (HAWK and HARRIER) confirmed the safety signal. The Panel noted Novartis' submission that following confirmation of the signal, it informed all relevant health authorities globally; neither the Medicines and Healthcare products Regulatory Agency (MHRA) nor the European Medicines Agency (EMA) expedited processes or asked for further actions beyond the standard processes for safety notifications and label updates. In October 2020, the EMA approved an update to the Beovu SPC, sections 4.4 (special warnings and precautions)

and 4.8 (undesirable side effects), with no special conditions or requirements as part of its marketing authorisation. The Panel noted that the SPC stated that the frequency of retinal vascular occlusion and retinal vasculitis was 'not known'.

The Panel considered that it was not necessarily unacceptable not to include detailed safety data in an advertisement as long as the material complied with the Code and was not misleading in that regard. Material must not be inconsistent with the particulars in a medicine's current SPC. The Panel considered that whether specific safety data needed to be highlighted in promotional material, in addition to that which was required to be included within the prescribing information, depended on a consideration of all of the circumstances including the nature of the information, the therapy area and the content, context and layout of the material. The intended audience was also a relevant factor.

The Panel noted that the prescribing information at the base of the advertisement stated, under 'Warnings/Precautions', that retinal vasculitis and/or retinal vascular occlusion had been reported, typically in the presence of intraocular inflammation and that patients should be instructed to report any relevant symptoms without delay. The prescribing information also included 'retinal vascular occlusion' and 'retinal vasculitis' under the 'Undesirable effects' section with the frequency being unknown. The Panel further noted Novartis' submission that the prescribing information contained all relevant information for prescribers and there was no requirement to specifically address individual warnings or precautions, beyond inclusion in the prescribing information, particularly as there were no special/restricted conditions of use imposed by the EMA within the marketing authorisation and/or the SPC.

The Panel noted that the only claim in the body of the advertisement with regard to safety was 'In HAWK & HARRIER, Beovu Exhibited an overall well-tolerated safety profile in treated patients'. The HAWK and HARRIER studies compared the safety and efficacy of Beovu vs aflibercept and in a *post hoc* analysis of the pivotal trials, a Novartis commissioned review noted that despite the vision loss associated with increased incidences of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion associated with Beovu, the overall rates of at least moderate vision loss were similar between the Beovu and aflibercept treatment arms (7.4% vs 7.7% respectively). The Panel noted that the *post hoc* review of HAWK and HARRIER (Monés *et al*, 2020) stated that it was critical that physicians appropriately monitored Beovu patients for this safety signal and that the findings would help to evaluate the risks and benefits of Beovu treatment. The Panel further noted Novartis' submission that the authors of the peer-reviewed HAWK and HARRIER manuscript (Dugel *et al*, 2021), which was published after post-marketing reports of retinal vasculitis and/or retinal vascular occlusion, stated that 'although numerical differences were found in some adverse events and serious adverse events ... brolucizumab exhibited an overall well-tolerated safety profile'.

The Panel noted that the National Institute for Health and Care Excellence (NICE) was aware that Beovu's SPC noted a risk of retinal vasculitis and retinal vascular occlusion. The evidence review group explained that because these adverse events were rare, it was not likely to affect the view that the overall impact on health of those associated with brolucizumab were similar to those of aflibercept and ranibizumab. The committee concluded that adverse events with brolucizumab were likely to be similar to aflibercept and ranibizumab.

The Panel considered that in the particular circumstances of this case, given the very specialist therapy area and the experience that prescribing opthalmologists would have with intravitreal injections, the advertisement did not imply that there were no safety concerns with Beovu. In the Panel's view, the complainant had not established that it was misleading to have not included additional safety data in the body of the advertisement. The Panel did not consider that the advertisement was misleading as alleged and did not consider that the complainant had established that the advertisement did not encourage the rational use of Beovu. No breaches of the Code were ruled.

The Panel noted its comments and rulings above and considered that the complainant had not shown that high standards had not been maintained. No breaches of the Code were ruled including of Clause 2.

A complainant who described him/herself as a health professional, complained about a journal advertisement (ref BRO20 – C053, November 2020) for Beovu (brolucizumab) placed in the December 2020 issue of the British Journal of Ophthalmology by Novartis Pharmaceuticals UK (copy provided).

Beovu was presented as a pre-filled syringe for intravitreal injection, for use in adults for the treatment of neovascular (wet) age-related macular degeneration (nAMD).

The advertisement in question was headed 'For adults with wet AMD, their vision is a masterpiece' and included four claims for Beovu which were attributable to the HAWK and HARRIER trials. The first three claims were about the efficacy of Beovu and the fourth stated that in Hawk and Harrier Beovu 'Exhibited an **overall well-tolerated safety profile** in treated patients'.

COMPLAINT

The complainant was particularly concerned about the lack of safety information, given that Beovu had been the subject of serious, sight-threatening complications which were noted in the pivotal trials, acknowledged as a safety signal by Novartis, and were subject to a mandated summary of product characteristics (SPC) update. The complainant noted that Novartis also had a dedicated website related to the safety concerns of Beovu (www.brolucizumab.info). The complainant considered that it was grossly irresponsible to promote Beovu in such a way that the safety information was not provided; it was worrying, misleading and a risk to patient safety.

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

RESPONSE

Novartis explained that Beovu was approved by the US Food and Drug Administration on 7 October 2019. The European Medicines Agency (EMA) issued the marketing authorisation on 13 February 2020.

On 23 February 2020, the American Society of Retina Specialists (ASRS) shared an update with its membership describing 14 reports of vasculitis – 11 of which were designated by the reporting provider as occlusive retinal vasculitis – which it had received since Beovu's approval the previous year. The ASRS was an academic society that collected safety information via its Research and Safety in Therapeutics Committee and kept its members updated with

information related to adverse events associated with all retina medicines and devices. The reports were initially restricted to the US at the time.

Prior to that, teams from Novartis Pharmaceuticals Corporation (Novartis US) and Novartis' global headquarters in Basel, Switzerland (Novartis AG) had already investigated the adverse events and followed the necessary regulatory and pharmacovigilance processes to validate and report those events. Novartis initiated its own internal review of those post-marketing safety case reports, including the establishment of an external Safety Review Committee (SRC) to provide an independent and objective review of the cases, with a comparison of inflammatory adverse events seen in the Beovu Phase 3 trials (HAWK and HARRIER).

Using the terminology defined by the SRC, Novartis' review of post-marketing events confirmed a safety signal of rare adverse events termed as 'retinal vasculitis' and/or 'retinal vascular occlusion' that might result in severe vision loss. Typically, those events occurred in the presence of intraocular inflammation (IOI). That signal was confirmed on 6 April 2020.

Following confirmation of the signal, Novartis informed all relevant health authorities globally including the Medicines and Healthcare products Regulatory Agency (MHRA) and the EMA neither of which expedited processes or asked for further actions beyond the standard processes for safety notifications and label updates. On 15 October 2020, the EMA approved an update to the Beovu SPC section 4.4 (special warnings and precautions) and section 4.8 (undesirable side effects; Table 1 frequencies of adverse events and post-marketing experience), with no special conditions or requirements as part of its marketing authorisation.

Novartis noted that the complainant was concerned about the lack of safety information provided in the journal advertisement and that Beovu had been the subject of a serious, sight-threatening adverse event. Novartis submitted that the advertisement contained four accurate statements that described the benefit/risk profile of Beovu from the results of the HAWK and HARRIER registration trials, including one that described the safety profile of Beovu as having 'an overall well-tolerated safety profile in treated patients'.

The complainant implied that the adverse events of retinal vasculitis and/or retinal vascular occlusion were noted in the initial results of the pivotal trials and acknowledged by Novartis but this was not so; the events were first seen in post-marketing reports. This initiated a number of actions by Novartis that led to the SRC performing a *post hoc* analysis of the pivotal trials and, in addition to the identification of a safety signal, the SRC concluded on the overall safety of the two products:

> 'Of note, despite the vision loss associated with increased incidences of IOI, retinal vasculitis and/or retinal vascular occlusion associated with brolucizumab, the overall rates of at least moderate vision loss (≥15 ETDRS letter loss) are similar between the brolucizumab and aflibercept treatment arms: 7.4% or 81/1088 in brolucizumab and 7.7% or 56/729 in aflibercept.'

Even with the emergence of retinal vasculitis and/or retinal vascular occlusion as an adverse event, the SRC conclusion was independent acknowledgement that the overall rates of vision loss – the most important potential adverse event with the use of these medicines – were similar between the two medicines. This was pertinent and important when considering the overall safety profiles of each medicine.

Novartis submitted that this was a view shared by the authors of the peer-reviewed HAWK and HARRIER manuscript, which was published after post-marketing reports of retinal vasculitis and/or retinal vascular occlusion. They stated that 'although numerical differences were found in some adverse events and serious adverse events ... brolucizumab exhibited an overall well-tolerated safety profile'. Novartis acknowledged that although author comments did not automatically permit for their use as claims, Novartis had included that information as part of the supporting evidence.

Novartis noted that the National Institute for Health and Care Excellence (NICE), following the safety update, had subsequently recommended Beovu for the treatment of wet age-related macular degeneration on 3 February 2021. After the emergence of the post-marketing safety reports, Novartis promptly informed NICE to ensure it was aware throughout the appraisal process. Reassuringly, as part of the technology appraisal guidance, NICE commented on the safety profile of Beovu compared with aflibercept and ranibizumab, and concluded:

> 'The committee was aware that brolucizumab's summary of product characteristics notes a risk of retinal vasculitis and retinal vascular occlusion. The [evidence review group] explained that because these adverse events were rare, it was not likely to affect the view that the overall impact on health of those associated with brolucizumab are similar to those of aflibercept and ranibizumab. The committee concluded that adverse events with brolucizumab are likely to be similar to aflibercept and ranibizumab.'

This was further independent acknowledgement of the overall similar safety profiles of brolucizumab and the other two approved medicines in the same class.

Novartis noted that Clause 7.2 required material to be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine and in that regard the company considered that the prescribing information, which occupied approximately half of the advertisement, provided the required context to appropriately support a single page advertisement. The prescribing information contained the most relevant safety information to allow prescribers to make informed decisions. Novartis noted that the complainant stated that there was a mandated SPC update. That SPC update came after Novartis notified regulatory authorities once the post-marketing signal was confirmed as per responsible safety reporting. As a result, the prescribing information contained information on the updated SPC which included the adverse events of retinal vasculitis and retinal vascular occlusion. In the context of a single page advertisement, Novartis considered that that was sufficiently complete for readers to form their own opinion of the therapeutic value of the medicine. Novartis, of course, acknowledged that the prescribing information alone would not be sufficient for a more substantial piece of material and the company would continue to create and certify material based on its individual merits in line with the requirements of the Code.

Novartis noted that Clause 4.2 stated that prescribing information consisted of any warnings issued by the Medicines Commission, the Commission on Human Medicines, the Committee on the Safety of Medicines or the licensing authority. Currently, retinal vasculitis and/or retinal vascular occlusion appeared under the special warnings section of the SPC alongside a number of adverse events including endophthalmitis and intraocular inflammation, amongst others, that all appeared in the prescribing information. Novartis considered that the prescribing information contained all relevant information for prescribers and there was no requirement to specifically address individual warnings or precautions, beyond inclusion in the prescribing information, particularly as there were no special/restricted conditions of use imposed by the EMA within the marketing authorisation and/or the SPC.

Novartis noted the complainant's reference to a global Beovu safety website. Novartis acknowledged there was a dedicated website (brolucizumab.info) that was created by Novartis AG, which aimed to provide information and guidance for health professionals who prescribed Beovu from a global perspective. That website included, amongst others, information on the post-marketing data which reported estimated rates of retinal vasculitis and/or retinal vascular occlusion.

Whilst the intention was to provide transparency to prescribers from a global perspective, Novartis noted that that was not a regulatory-approved source of information and there were limitations to the methodology used. For example, the website did not undergo regulatory review by the MHRA and/or EMA so the information could neither be validated nor substantiated for use in the UK. Additionally, the data did not include a significant proportion of patients from the UK, changed on a regular basis due to regular updates and was based on sales data (as opposed to definitive information on the number of patients treated or injections administered). For those reasons, Novartis had not used the information contained on the website in materials in the UK. Additionally, the website was neither UK approved, nor did Novartis direct UK health professionals to the website and, therefore, was not in scope of the Code.

Accordingly, Novartis submitted there was no breach of Clause 7.2 as the information provided complied with the Code and was sufficiently complete to provide readers with enough information to form their own opinion of the therapeutic value of Beovu.

Novartis reiterated that all of the claims in the journal advertisement were capable of substantiation and provided an accurate description of Beovu data from the HAWK and HARRIER studies which was consistent with the terms of the marketing authorisation. In addition, there were no exaggerated or all-embracing claims made and no superlatives were made in relation to Beovu. The claims also did not imply there was special merit, quality or property of Beovu. Novartis thus denied a breach of Clause 7.10.

Novartis also denied a breach of Clause 9.1. The company sought to operate at the highest standards when creating journal advertisements and did so by creating an advertisement that was objective, capable of substantiation and consistent with the SPC as detailed above.

Novartis denied a breach of Clause 2 and stated that it always sought to ensure that its promotion was of the highest standards and did not prejudice patient safety and thus did not bring discredit upon, or reduce confidence in, the pharmaceutical industry.

PANEL RULING

The Panel noted that the advertisement was placed in the British Journal of Ophthalmology and that the Beovu SPC stated that Beovu must be administered by a qualified ophthalmologist experienced in intravitreal injections. The Panel noted that this was a very specialist area.

The Panel noted that the complainant made no reference to any of the claims but was concerned about the lack of safety information in the advertisement given the serious, sight-threatening complications that had been noted with Beovu. The Panel noted Novartis' submission that adverse events of retinal vasculitis and/or retinal vascular occlusion were first seen in post-marketing reports and not in the pivotal trials as submitted by the complainant. A review of the post-marketing cases, with a comparison of inflammatory adverse events seen in the Beovu Phase 3 trials (HAWK and HARRIER) confirmed the safety signal. The Panel noted

Novartis' submission that following confirmation of the signal, it informed all relevant health authorities globally including the MHRA and the EMA, neither of which expedited processes or asked for further actions beyond the standard processes for safety notifications and label updates. On 15 October 2020, the EMA approved an update to the Beovu SPC section 4.4 (special warnings and precautions) and section 4.8 (undesirable side effects; Table 1 frequencies of adverse events and post-marketing experience), with no special conditions or requirements as part of its marketing authorisation. The Panel noted that Table 1 in the SPC stated that the frequency of retinal vascular occlusion and retinal vasculitis was 'not known'.

The Panel considered that it was not necessarily unacceptable not to include detailed safety data in an advertisement as long as the material complied with the Code and was not misleading in that regard. Material must not be inconsistent with the particulars in a medicine's current SPC. The Panel considered that whether specific safety data needed to be highlighted in promotional material, in addition to that which was required to be included within the prescribing information, depended on a consideration of all of the circumstances including the nature of the information, the therapy area and the content, context and layout of the material. The intended audience was also a relevant factor.

The Panel noted that the prescribing information at the base of the advertisement included, under 'Warnings/Precautions', 'Retinal vasculitis and/or retinal vascular occlusion typically in the presence of intraocular inflammation, have been reported with the use of Beovu. In patients developing these events, treatment with Beovu should be discontinued and the events should be promptly managed. Patients should be instructed to report any symptoms suggestive of the above-mentioned events without delay'. The prescribing information also included 'retinal vascular occlusion' and 'retinal vasculitis' under the 'Undesirable effects' section with the frequency being unknown. The Panel further noted Novartis' submission that the prescribing information contained all relevant information for prescribers and there was no requirement to specifically address individual warnings or precautions, beyond inclusion in the prescribing information, particularly as there were no special/restricted conditions of use imposed by the EMA within the marketing authorisation and/or the SPC.

The Panel noted that the only claim in the body of the advertisement with regard to safety was 'In HAWK & HARRIER, Beovu Exhibited an **overall well-tolerated safety profile** in treated patients'. The Panel noted that the HAWK and HARRIER studies compared the safety and efficacy of Beovu vs aflibercept and in a *post hoc* analysis of the pivotal trials, a Novartis commissioned Safety Review Committee noted that despite the vision loss associated with increased incidences of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion associated with Beovu, the overall rates of at least moderate vision loss were similar between the Beovu and aflibercept treatment arms (7.4% vs 7.7% respectively). The Panel noted that the *post hoc* review of HAWK and HARRIER (Monés *et al*, 2020) stated that it was critical that treating physicians monitored appropriately for this safety signal during Beovu treatment and concluded that the findings would help physicians to evaluate the risks and benefits of Beovu treatment for nAMD. The Panel further noted Novartis' submission that the authors of the peer-reviewed HAWK and HARRIER manuscript (Dugel *et al*, 2021), which was published after post-marketing reports of retinal vasculitis and/or retinal vascular occlusion, stated that 'although numerical differences were found in some adverse events and serious adverse events ... brolucizumab exhibited an overall well-tolerated safety profile'.

The Panel noted that NICE was aware that Beovu's SPC noted a risk of retinal vasculitis and retinal vascular occlusion. The evidence review group explained that because these adverse events were rare, it was not likely to affect the view that the overall impact on health of those

associated with brolucizumab were similar to those of aflibercept and ranibizumab. The committee concluded that adverse events with brolucizumab were likely to be similar to aflibercept and ranibizumab.

The Panel considered that in the particular circumstances of this case, given the very specialist therapy area and the experience that prescribing opthalmologists would have with intravitreal injections, the advertisement which included claims regarding the efficacy and safety results observed in HAWK and HARRIER did not imply that there were no safety concerns with Beovu. In the Panel's view, the complainant had not established that it was misleading to have not included additional safety data in the body of the advertisement at issue. The Panel did not consider that the advertisement was misleading as alleged and based on the complainant's narrow allegation ruled no breach of Clause 7.2. The Panel further did not consider that the complainant had established that the advertisement did not encourage the rational use of Beovu. No breach of Clause 7.10 was ruled.

The Panel noted the complainant's reference to the website www.brolucizumab.info and Novartis' comments in that regard but did not consider that it was the subject of complaint and so it made no ruling in that regard.

The Panel noted its comments and rulings above and considered that the complainant had not shown that high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel consequently ruled no breach of Clause 2.

Complaint received **21 January 2021**

Case completed **24 August 2021**