NOVARTIS

2nd November 2021

**Direct Healthcare Professional Communication:**

**Beovu® ▼ (brolucizumab) - Updated recommendations to minimise the known risk of intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion.**

Dear Healthcare Professional,

In agreement with European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA), Novartis would like to inform you of the following:

***Summary***

- **Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion may occur following the first intravitreal injection with brolucizumab and at any time of treatment. These events were observed more frequently early on during treatment.**
- **More intraocular inflammation events were seen among patients who developed anti-brolucizumab antibodies during treatment. Retinal vasculitis and/or retinal vascular occlusion are immune-mediated events.**
- **In patients developing intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, treatment with brolucizumab should be discontinued and the events should be promptly managed.**
- **Maintenance doses of brolucizumab (after the first 3 doses) should not be administered at intervals less than 8 weeks. This is based on findings from the MERLIN study (see further details in the Background section below).**
- **Patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab are at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored.**
- **Female sex has been identified as an additional risk factor. A higher incidence was also observed in Japanese patients.**
- **Patients should be instructed in how to recognise early signs and symptoms of intraocular inflammation, retinal vasculitis and retinal vascular occlusion and be advised to seek medical attention without delay, if these side effects are suspected.**

***Background on the safety concern***

Brolucizumab is a humanised monoclonal antibody indicated for the treatment of neovascular (wet) age-related macular degeneration (nAMD).

Immune-mediated event

Results of the mechanistic study BASICHR0049 based on an analysis of blood samples from five nAMD patients exposed to brolucizumab who subsequently developed retinal vasculitis (RV) and/or retinal vascular occlusion (RO), taken together with accumulated data regarding the association of treatment-emergent immunogenicity and intraocular inflammation (IOI), indicate a causal link between the treatment-emergent immune reaction against brolucizumab and brolucizumab related “retinal vasculitis and/or retinal vascular occlusion, typically in presence of IOI”.

In this study, blood samples were collected from the five case patients and from six control patients who had no signs/symptoms of IOI while still receiving brolucizumab treatment. The presence of RV and/or RO was confirmed by the independent Safety Review Committee that had been setup by Novartis when the safety signal emerged and/or by the practicing ophthalmologists / retinal specialists who were caring for these subjects.

The samples were tested for the potential activation of immune response factors against brolucizumab, including identification of anti-drug antibodies (ADA) and neutralising antibody response, ADA isotyping and epitope mapping, identification of an immune T cell response to brolucizumab and in vitro stimulation of platelet aggregation in whole blood in presence of brolucizumab and VEGF-A. In the samples from five patients who experienced the RV and/or RO adverse events a humoral and cellular immune response against brolucizumab was identified 3-5 months after the last brolucizumab dose and occurrence of the event. Data showed the presence of high titre ADAs, with a polyclonal and diverse IgG-driven response against multiple B cell epitopes on the brolucizumab molecule, as well as memory T cell activation induced by unstressed and heat- or mechanically-stressed brolucizumab preparations.

In the samples from patients from the control group, ADAs, when present, had lower titres.

Increased risk with 4-week dose intervals during maintenance phase

Novartis has also recently generated the first interpretable results (FIR) of the CRTH258AUS04 (MERLIN) study.

The MERLIN study is a *2-year multicenter, randomized, double-masked Phase 3a study to assess the safety and efficacy of brolucizumab 6mg q4 week compared to aflibercept 2mg q4 week in patients with neovascular age related macular degeneration (nAMD) with persistent retinal fluid.* The study is conducted only in the US and recruited pre-treated nAMD patients with frequent treatment need.

- IOI including RV and RO were reported with a higher frequency in the brolucizumab 6 mg q4 week arm (9.3%) compared with the brolucizumab 6 mg q8/q12 week arms (4.4%) in the pivotal Phase 3 nAMD clinical studies.

Risk factors identified

Novartis conducted non-interventional retrospective real-world evidence studies in patients with neovascular (wet) age-related macular degeneration (nAMD) to better understand the incidence of adverse events/safety signal after initiating treatment with brolucizumab for up to 6 months. Each of the two studies consisted of retrospective analysis of large United States real-world databases, the IRIS Registry® [Study HEORUSV201342] and Komodo Healthcare Map™ [Study HEORUSV201368], respectively. Both assessments were conducted in parallel and were nearly identical to the extent the data permitted.

The results of this retrospective analysis in nAMD patients suggest that patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab were more likely to present with similar events after brolucizumab injection, as compared to nAMD patients with no history of these events.

In addition, a gender difference with a higher risk for IOI (including RV) and/or RO in females has been observed in the two retrospective studies but also in clinical trials. A higher incidence was also observed in Japanese patients.

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The product information of brolucizumab will be updated to reflect the most recent evidence and the new recommendations.

***Call for reporting***

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

You can report via:

- the Yellow Card website www.mhra.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, investigation results, treatment dates, and product brand name.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Beovu (brolucizumab)▼ is subject to additional monitoring. This will allow quick identification of new safety information.
Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card Scheme.

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com.

Further copies of this letter can be obtained via the electronic medicines compendium (eMC) website by visiting https://www.medicines.org.uk/emc.

***Company contact point***

If you have any questions or require further information, please contact Novartis Medical Information department on 01276 698370 or email medinfo.uk@novartis.com.

Yours faithfully,

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