Direct Healthcare Professional Communication

XX Oct, 2021

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

Dear Healthcare Professional,

Novartis in agreement with the European Medicines Agency and the <National Competent Authority> 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 Beovu® 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 Beovu® should be discontinued and the events should be promptly managed.
- Maintenance doses of Beovu® (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 Beovu® 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 (Beovu®) 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 Beovu® 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 Beovu® and Beovu® 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 Beovu® 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 Beovu® 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 multicentre, randomised, double-masked Phase 3a study to assess the safety and efficacy of brolucizumab 6 mg q4 weeks compared to aflibercept 2 mg q4 weeks 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 Beovu® were more likely to present with similar events after Beovu 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.

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

Call for reporting

Novartis would like to remind you to continue to report adverse reactions in accordance with the national spontaneous reporting system, <include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>.

Beovu® is subject to additional monitoring as a standard practice as it is a biological medicine and newly placed on the EU market in early 2020.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>.

You are also kindly requested to report the batch details for the product

concerned. Should you need any further information, please do not

hesitate to contact us.

Sincerely,

{insert name}

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Beovu® (brolucizumab) 120 mg/ml solution for injection in pre-filled syringe
Marketing authorisation holder(s)	Novartis Europharm Limited Vista Building, Elm Park, Merion Road, Dublin, Ireland
Safety concern and purpose of the communication	URGENT SAFETY COMMUNICATION: Brolucizumab (Beovu®)- Emerging safety issue on the identification of a causal immune-mediated mechanism of the previously identified risk of – retinal vasculitis (RV), and/or retinal vascular occlusion (RO), typically in the presence of intraocular inflammation (IOI) – indicating a requirement to discontinue treatment with Beovu® in patients who develop events of RV and/or RO.
DHPC recipients	Ophthalmologists, pharmacists; final list of recipients to be agreed at national level including professional societies and national associations, depending on the national healthcare system.
Member States where the DHPC will be distributed	Member States of the European Union (EU) and the European Economic Area (EEA)

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP	14-Oct-2021
Submission of translated DHPCs to the national competent authorities for review	4 days* after CHMP opinion.
Agreement of translations by national competent authorities	4-5 days* after submission of translated DHPCs to the national competent authorities for review
Dissemination of DHPC	6 days* after national competent authorities approval

*days are working days
** Estimated based on Guideline on good pharmacovigilance practices (GVP) – Module XV (Rev 1)