Novartis Pharma AG
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4056 Basel
Switzerland

Direct Healthcare Professional Communication

18 Aug, 2021

- **Brolucizumab (Beovu®) - 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.**

Dear Healthcare Professional,

Novartis in agreement with Saudi FDA would like to inform you of the following:

Summary

- **The results of the mechanistic study BASICHR0049, of blood samples from nAMD patients exposed to Beovu® and having subsequently developed RV and/or RO, taken together with accumulated data regarding the association of treatment-emergent immunogenicity and IOI indicate a causal link between the treatment-emergent immune reaction against Beovu® and the Beovu® related "retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI".**
- **Considering this finding, you should discontinue treatment with Beovu® in patients who develop events of retinal vasculitis and/or retinal vascular occlusion.**

Background to the Urgent Safety Communication and specific details

As per the Novartis Core Data Sheet (CDS) for neovascular age-related macular degeneration (nAMD), the 'Description of selected adverse drug reactions' section states "*Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed.* (See section 7 Adverse drug reactions)"

In the BASICHR0049 mechanistic study, blood samples have been collected from 5 case patients with RV and/or RO and from 6 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.

The samples from these patients were tested for the potential activation of immune response factors against brolucizumab, including identification of anti-drug antibodies (ADA) and neutralizing 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 samples from patients who experienced the RV and/or RO adverse events a humoral and cellular immune response against brolucizumab was identified. Data showed the presence of high titer ADA,

with a polyclonal and diverse IgG-driven response against multiple B cell epitopes on the brolucizumab molecule, as well as regulatory and memory T cell activation induced by unstressed and heat- or mechanically-stressed brolucizumab preparations. An increase in in vitro platelet aggregation in presence of brolucizumab and VEGF-A was also observed.

In samples from patients from the control group, ADAs, when present, had lower titers and only marginal responses were seen when inducing T cell activation. In addition, in vitro platelet aggregation was significantly lower compared to patients who had experienced the events of interest.

These emerging results from BASICHR0049 mechanistic study represent an additional characterization of an already described adverse drug reaction. Taken together with accumulated data regarding the association of treatment-emergent immunogenicity and IOI, these results indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the Beovu® related "retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI". **This finding supports the requirement to discontinue treatment with Beovu® in patients who develop these adverse events.**

As per the Novartis CDS for nAMD, the warning and precautions section states "*Retinal vasculitis and/or retinal vascular* o*cclusion, typically in the presence of intraocular inflammation, have been reported with the use of Beovu (see sections 5 Contraindications and 7 Adverse drug reactions).*

Patients should be instructed to report any symptoms suggestive of the above mentioned events without delay."

In the SPC, the recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. The physician may further individualise treatment intervals based on disease activity.

Novartis is working with the health authorities to reflect the findings from the BASICHR0049 study results in revised prescribing information.

In light of the newly available data on the mechanism of this known risk, **you should discontinue treatment with Beovu® in patients who develop adverse events of retinal vasculitis and/or retinal vascular occlusion.**

Novartis considers that the benefit-risk ratio for Beovu® in nAMD remains unchanged.

This letter has been approved by the SFDA

Call for reporting

Novartis would like to remind you to continue to report adverse reactions in accordance with the national spontaneous reporting system:

Novartis Pharma AG Patient Safety Department - Saudi Arabia -.

Toll Free Number: 8001240078
Phone: +966112658100
Fax: +966112658107
Email: adverse.events@novartis.com
Or by online: https://report.novartis.com/

Saudi Food and Drug Authority National Pharmacovigilance Center

Unified Contact Center: 19999
Fax: +966112057662
Email: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

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,

Hajer Alsaleh

Country Patient Safety Manager / Novartis QPPV