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Direct Healthcare Professional Communication

Novartis, Aug, 2021

To: All Healthcare professionals treating patients with brolucizumab (VSIQQ™)

- **URGENT SAFETY COMMUNICATION: Brolucizumab (VSIQQ™) - 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 VSIQQ™ in patients who develop events of RV and/or RO.**

Dear Healthcare Professional,

Novartis in agreement with Scientific center of medicine and medical technology expertise of MOH of Armenia would like to inform you of the following:

Summary

- **The results of the mechanistic study BASICHR0049, of blood samples from nAMD patients exposed to VSIQQ™ 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 VSIQQ™ and the VSIQQ™ related "retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI".**
- **Considering this finding, you should discontinue treatment with VSIQQ™ 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 VSIQQ™ 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 VSIQQ™ related "retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI". **This finding supports the requirement to discontinue treatment with VSIQQ™ 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 occlusion, 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 SmPC, the Special warnings and precautions for use section states "Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of Vsiqq (see sections 4.3 and 4.8). In patients developing these events, treatment with Vsiqq 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."

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 VSIQQ™ in patients who develop adverse events of retinal vasculitis and/or retinal vascular occlusion.**

Novartis considers that the benefit-risk ratio for VSIQQ™ in nAMD remains unchanged.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online to the Scientific Centre of Drug and Medical Technology Expertise after academician E. Gabrielyan of MoH of RA via www.pharm.am or call the hotline numbers: (+374 0) 20 05 05 and (+374 96) 22 05 05.

You may also contact Novartis Pharma AG via drugsafety.cis@novartis.com.

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