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IMPORTANT MEDICINE SAFETY INFORMATION

04 November 2021

Dear HealthCare Professional

RE: VSIQQ® (BROLUCIZUMAB) - A REQUIREMENT TO DISCONTINUE TREATMENT WITH VSIQQ® IN PATIENTS WHO DEVELOP RETINAL VASCULITIS AND/OR RETINAL VASCULAR OCCLUSION, TYPICALLY IN THE PRESENCE OF INTRAOCULAR INFLAMMATION

Novartis, as directed by the South African Health Products Regulatory Authority (SAHPRA), would like to inform you about the requirement to discontinue treatment with Vsiqq® in patients who develop retinal vasculitis and/or retinal vascular occlusion. Retinal vasculitis and retinal vascular occlusion are immune-mediated events, which typically occur in the presence of intraocular inflammation.

The Professional Information (PI) of Vsiqq® will be amended to reflect the above safety information.

Summary

- 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 intraocular inflammation” has been identified following the results of the mechanistic study BASICHR0049 and taken together with accumulated data regarding the association of treatment-emergent immunogenicity and intraocular inflammation. Retinal vasculitis and/or retinal vascular occlusion events were found to be immune mediated.

- The BASICHR0049 was a mechanistic study which was aimed to elucidate the immune response to brolucizumab (Vsiqq®) in patients with neovascular age-related macular degeneration who developed retinal vasculitis and/or retinal vascular occlusion.

Background to the Safety concern

In the BASICHR0049 mechanistic study, blood samples have been collected from five patients with retinal vasculitis and/or retinal vascular occlusion and from six control patients who had no signs or symptoms of intraocular inflammation while still receiving Vsiqq® treatment. The presence of retinal vasculitis and/or retinal vascular occlusion was confirmed by the independent Safety Review Committee that had been setup by Novartis when the safety signal emerged.

The blood samples from the BASICHR0049 mechanistic study 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 the presence of brolucizumab and vascular endothelial growth factor A (VEGF-A).

In samples from patients who experienced adverse events of retinal vasculitis and/or retinal vascular occlusion, a humoral and cellular immune response against brolucizumab was identified. Data showed the presence of high ADA, with a polyclonal and diverse Immunoglobulin G (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 the presence of brolucizumab and VEGF-A was also observed to be significantly higher when compared to the control group.

Taken together with accumulated data regarding the association of treatment-emergent immunogenicity and intraocular Inflammation, the BASICHR0049 mechanistic study 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 intraocular inflammation”. This finding supports the requirement to discontinue treatment with Vsiqq® in patients who develop these adverse events.

Advice to Healthcare Professionals

- Healthcare professionals are urged to advise patients to report any symptoms suggestive of the above mentioned events without delay (e.g. redness of the eye or worsening of eye redness, eye pain, increased discomfort, sudden vision loss, blurred or decreased vision, an increased number of small particles in vision, increased sensitivity to light).
- Healthcare professionals are advised to discontinue treatment with Vsiqq® in patients who develop adverse events of retinal vasculitis and/or retinal vascular occlusion.

Healthcare professionals are urged to report adverse drug reactions (ADRs) or product quality issues (including batch details) related to Vsiqq® to Novartis on the following email patientsafety.sacg@novartis.com or via the website https://www.report.novartis.com. Alternatively, please complete the ADR reporting form accessible via the SAHPRA website at www.sahpra.org.za and email it to adr@sahpra.org.za. Healthcare professionals may also use the Med Safety App [accessible from the Apple store (for iOS devices) and Google Play (for android devices)] or the National Department of Health Mobile Application accessible from the Essential Medicines List (EML) Clinical Guide to report ADRs or product quality issues.

Should you need any further information, please do not hesitate to contact us.

Sincerely,

Padayachee Kumeshnie

Digitally signed by Padayachee Kumeshnie
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