Important Safety Information
BEOVU (brolucizumab) – Risk of Intraocular Inflammation, Retinal Vasculitis and/or Retinal Vascular Occlusion

NOVARTIS

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Audience
Healthcare professionals including ophthalmologists (retina specialists and general ophthalmologists) and specialty pharmacists.

Key messages

- **An increased incidence of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, was observed in patients who received BEOVU 6 mg with every 4 weeks (q4 week) dosing beyond the first 3 doses, compared to aflibercept 2 mg every 4 weeks, in neovascular (wet) age-related macular degeneration in the MERLIN study.**

- **More intraocular inflammation events were seen among patients who developed anti-brolucizumab antibodies during treatment. Retinal vasculitis and retinal vascular occlusion are immune-mediated events (BASICHR0049 study).**

- **Healthcare professionals are advised of the following:**

  - **Treatment with BEOVU is contraindicated in patients with active intraocular inflammation.**
  - **Patients should not be treated with BEOVU 6 mg at intervals less than 8 weeks beyond the first 3 doses.**
  - **Treatment with BEOVU should be discontinued in patients who develop retinal vasculitis and/or retinal vascular occlusion.**
  - **Based on clinical studies, intraocular inflammation related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with BEOVU than in male patients.**
  - **Patients with a history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with BEOVU are at increased risk and should be closely monitored.**

- **The product monograph for BEOVU will be updated to reflect the most recent evidence and the new recommendations.**

What is the issue?
An increased incidence of intraocular inflammation (IOI), including retinal vasculitis (RV) and retinal vascular occlusion (RO), was observed in patients who received BEOVU 6 mg with every 4 weeks (q4 week) dosing beyond the first 3 doses compared to aflibercept 2 mg every 4 weeks, in neovascular age-related macular degeneration (nAMD) in the MERLIN study.

A causal link was observed between the treatment-emergent immune reaction against BEOVU and the BEOVU related "retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation" (BASICHR0049 study).

Products affected
BEOVU, brolucizumab injection, 6 mg/0.05 mL solution for intravitreal injection. Drug Identification Number (DIN): 02496976

Background information
BEOVU is a humanized monoclonal single-chain Fv (scFv) antibody fragment directed against human vascular endothelial growth factor (hVEGF) and is indicated for the treatment of neovascular (wet) age-related macular degeneration (nAMD).

<u>Increased risk with 4-week dosing intervals during maintenance phase</u>

After one year of treatment, in a Phase IIIa clinical study (MERLIN), patients with nAMD who received BEOVU 6 mg every 4 week maintenance dosing experienced a higher incidence of IOI (including RV) and RO, when compared with patients who received aflibercept 2 mg every 4 weeks (IOI: 9.3% vs 4.5%, of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%). The incidences of IOI and RO were also higher than what was previously observed in patients who received BEOVU every 8 or 12 week maintenance dosing in the pivotal Phase III clinical studies (HAWK and HARRIER).

The interval between two BEOVU doses during maintenance treatment (after the first 3 doses) should not be less than 8 weeks.

<u>Immune-mediated events</u>

In the BASICHR0049 mechanistic study, blood samples were collected from 5 patients with independently confirmed retinal vasculitis and/or retinal vascular occlusion and from 6 control patients who had no signs/symptoms of intraocular inflammation while still receiving BEOVU.

In the samples from the 5 patients who experienced retinal vasculitis and/or retinal vascular occlusion, a humoral and cellular immune response against brolucizumab was identified 3 to 5 months after the last BEOVU dose and occurrence of the event. Data showed that there was a presence of high titre anti-drug antibodies (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. An

increase in *in vitro* platelet aggregation in the presence of brolucizumab and VEGF-A was also observed.

In samples from the control group, ADAs, when present, had lower titres and only marginal responses were detected when inducing T cell activation. In addition, *in vitro* platelet aggregation was lower compared to patients who had experienced retinal vasculitis and/or retinal vascular occlusion.

Taken together with accumulated data regarding the association of treatment-emergent immunogenicity and intraocular inflammation, 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 intraocular inflammation".

This finding supports the requirement to discontinue treatment with BEOVU in patients who develop these adverse events.

Other Risk Factors

Two non-interventional, retrospective US real-world databases consisting of the IRIS Registry [Study HEORUSV201342] and Komodo Healthcare Map [Study HEORUSV201368], respectively, were evaluated to better understand the incidence of adverse events after initiating treatment with brolucizumab for up to 6 months in patients with nAMD. The results of this retrospective analysis suggest that patients with a 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 conditions.

In addition, a higher risk for intraocular inflammation (including retinal vasculitis) and/or retinal vascular occlusion in females has been observed in the 2 retrospective studies as well as in clinical trials (e.g., 5.3% females vs. 3.2% males in the HAWK and HARRIER studies).

While some of this information has been added to the BEOVU product monograph, additional updates will be made to reflect the most recent evidence and the new recommendations.

Information for consumers

BEOVU is used to treat an eye disorder called neovascular (wet) age-related macular degeneration in adults. The recommended dose is 6 mg of BEOVU given by injection into the eye every 4 weeks (monthly) for the first 3 months. Following that, patients may get one injection every 12 weeks (3 months) or every 8 weeks (2 months). The doctor will determine the treatment interval based on the condition of the eye. The treatment interval between two doses of BEOVU should not be less than every 8 weeks (2 months).

Patients who received an injection of BEOVU and who develop redness of the eye or worsening eye redness, eye pain, increased discomfort, sudden vision loss, blurred

or decreased vision, increased number of small particles in the vision, or increased sensitivity to light should inform their doctor immediately. All of these signs and symptoms could be an indication of a serious side effect of treatment and may result in the doctor stopping treatment with BEOVU.

Information for healthcare professionals
Healthcare professionals are advised of the following:

- Treatment with BEOVU is contraindicated in patients with active intraocular inflammation.
- Patients should not be treated with BEOVU 6 mg at intervals less than 8 weeks beyond the first 3 doses.
- Treatment with BEOVU should be discontinued in patients who develop retinal vasculitis and/or retinal vascular occlusion.
- Based on clinical studies, intraocular inflammation related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with BEOVU than in male patients (e.g., 5.3% females vs. 3.2% males in the HAWK and HARRIER studies).
- Patients with a history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with BEOVU are at increased risk and should be closely monitored.

While some of this information has been added to the BEOVU product monograph, additional updates will be made to reflect the most recent evidence and the new recommendations.

Action taken by Health Canada
Health Canada, in collaboration with Novartis Pharmaceuticals Canada Inc., is working on updating the BEOVU product monograph.

Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database (https://recalls-rappels.canada.ca/en) on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media channels, including LinkedIn and Twitter.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any case of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, or other serious or unexpected side effects in patients receiving BEOVU should be reported to Novartis Pharmaceuticals Canada Inc. or Health Canada.

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Telephone: 1-877-631-6775 ext 3425
Fax: 1-877-636-3175

https://www.novartis.ca/our-products/pharmaceuticals

To correct your mailing address or fax number, contact Novartis Pharmaceuticals Canada Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: mhpd-dpsc@hc-sc.gc.ca
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