NOVARTIS

Regulatory Affairs

Drug generic name

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Brolucizumab*
Product(s) concerned (brand name(s)):	*Beovu*
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Beovu” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Beovu” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Beovu”.

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I. The medicine and what it is used for

Beovu® is authorized for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults (see www.swissmedicinfo.ch for full indication).
It contains brolucizumab as the active substance and it is given by intravitreal injections.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Beovu® together with measures to minimize such risks and the proposed studies for learning more about Beovu's risks, are outlined below.
Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.
In the case of Beovu®, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of Beovu® is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Beovu® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Beovu®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risk	Intraocular inflammation Retinal vasculitis and/or retinal vascular occlusion Endophthalmitis Transient intraocular pressure increased Retinal detachment/tear
Important potential risks	Non-ocular events (ATE, VTE, non-ocular haemorrhage

Missing information	and hypertension) Safety beyond two years of treatment Non-ocular safety after bilateral treatment

II B: Summary of important risks

Table 2 Important identified risk: Intraocular inflammation

Evidence for linking the risk to the medicine	The evidence comes from 4 pivotal trials in nAMD and DME indications and overall there is an imbalance between the brolucizumab and aflibercept arms.
Risk factors and risk groups	In nAMD clinical trials, a higher intraocular inflammation incidence was observed in Japanese patients treated with brolucizumab compared to non-Japanese patients. In Study RTH258-C001 the number of patients with an intraocular inflammation event was 7/60 (11.7%) in Japanese patients and 14/300 (4.7%) in non-Japanese patients. There is also a higher incidence of intraocular inflammation in females compared to males (long-term S-db): brolucizumab 6 mg 5.3% in females vs. 3.2% in males. In DME clinical trials, the above observations were not possible to make due to the smaller size of the Japanese cohort (approximately 20 per treatment arm). In clinical trials, among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed.
Risk minimization measures	Routine risk minimization: Prescribing information sections Dosage/Administration, Contraindication, Warnings and precautions, Undesirable effects. Prescribing information section Warnings and precautions where information is provided that treatment should be discontinued. Patient information sections “What you need to know before and while you receive Beovu”, “Possible side effects” Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 3 Important identified risk: Retinal vasculitis and/or retinal vascular occlusion

Evidence for linking the risk to the medicine	Current evidence is based on the 4 pivotal trials in nAMD and DME indications and on post-marketing data for nAMD indication.
Risk factors and risk groups	Patients at risk for intraocular inflammation or with active intraocular inflammation at the time of brolucizumab administration. Based on a retrospective real world evidence analysis, patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab were more likely to present with similar events after brolucizumab injection, as compared to nAMD patients with no history of these events.
Risk minimization measures	Routine risk minimization: Prescribing information sections Dosage/Administration, Undesirable effects. Prescribing information section Warnings and precautions, where information is provided that treatment should be discontinued and that these immune mediated adverse events may occur following the first intravitreal injection and at any time of treatment. They were observed more frequently at the beginning of the treatment. Patient information sections “What you need to know before and while you receive Beovu”, “Possible side effects” Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 4 Important identified risk: Endophthalmitis

Evidence for linking the risk to the medicine	The incidence of endophthalmitis after an intravitreal injection is low. Current evidence is based on the 4 pivotal trials in nAMD and DME indications.

Risk factors and risk groups	There is an increased risk of endophthalmitis if the intravitreal injection procedure is not carried out under aseptic conditions.
Risk minimization measures	Routine risk minimization: Prescribing information sections Dosage/Administration, Warnings and precautions, Undesirable effects. Patient information sections "Possible side effects" Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 5 Important identified risk: Transient intraocular pressure increased

Evidence for linking the risk to the medicine	Current evidence is based on the 4 pivotal trials in nAMD and DME indications. In the two pivotal nAMD trials for brolucizumab (Study RTH258-C001 and Study RTH258-C002), transient increases in intraocular pressure have been seen within 30 minutes of injection, similar to those observed with intravitreal administration of other VEGF inhibitors. These post-injection increases are self-limiting or can be treated with standard of care.
Risk factors and risk groups	Patients with intraocular pressure increased or glaucoma prior to the intravitreal injection.
Risk minimization measures	Routine risk minimization: Prescribing information sections Dosage/Administration, Warnings and precautions, Undesirable effects, overdosage. Patient information sections "What you need to know before and while you receive Beovu", "Possible side effects". Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 6 Important identified risk: Retinal detachment/ tear

Evidence for linking the risk to the medicine	Retinal detachment and tear is a well-known and well-characterized risk associated with the underlying disease and the aging of the eye.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, or severe high blood pressure.
Risk minimization measures	Routine risk minimization: Prescribing information sections Warnings and precautions, Undesirable effects. Patient information sections “What you need to know before and while you receive Beovu”, “Possible side effects”. Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 7 Important identified risk: Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)

Evidence for linking the risk to the medicine	Although there is an increased risk of ATEs, VTEs, non-ocular haemorrhage and hypertension after intravenously administered high doses of VEGF-inhibitors for the treatment of cancer, there is currently no evidence of increased incidences of ATEs, VTEs, non-ocular haemorrhage and hypertension for the much lower intravitreally administered doses of VEGF-inhibitors in patients with nAMD. After intravitreal administration in cynomolgus monkeys, the systemic maximal concentration of brolucizumab is approximately 1000-fold less than the trough concentration of a therapeutic dose of intravenously administered anti-VEGFs.
Risk factors and risk groups	Patients with cardiovascular risk factors or clotting disorders have a higher risk for ATEs, VTEs, non-ocular haemorrhage

	and hypertension. In DME patients, underlying disease (diabetes) is a risk factor.
Risk minimization measures	Routine risk minimization: Prescribing information sections Warnings and precautions, Undesirable effects. Patient information sections “What you need to know before and while you receive Beovu”, “Possible side effects”. Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 8 Missing information: Safety beyond two years of treatment

Risk minimization measures	Routine risk minimization: None Additional Risk Minimization Measures: None

Table 9 Missing information: Non-ocular safety after bilateral treatment

Risk minimization measures	Routine risk minimization: Prescribing information sections Warnings and precautions. Patient information sections “What you need to know before and while you receive Beovu”. Additional Risk Minimization Measures: None

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Beovu®.

II.C.2. Other studies in post-authorization development plan

There are no studies in post-authorization development plan for Beovu®.