Summary of the risk management plan for Beovu® (brolucizumab)

This is a summary of the risk management plan (RMP) for Beovu®. The RMP details important risks of Beovu®, how these risks can be minimized, and how more information will be obtained about Beovu's risks and uncertainties (missing information).

Beovu's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Beovu® should be used.

This summary of the RMP for Beovu® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Beovu's RMP.

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 SmPC for full indication).

It contains brolucizumab as the active substance and it is given by intravitreal injections.

Further information about the evaluation of Beovu's benefits can be found in Beovu's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/beovu

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 risks	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 and hypertension)
Missing information	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	For treatment emergent AEs in the study eye, the most pronounced numerical difference between brolucizumab and aflibercept was observed for intraocular inflammation and this was more pronounced in the Study RTH258-C001.
Risk factors and risk groups	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 (target posology long term S-db): brolucizumab 6 mg 5.3% in females vs. 3.2% in males.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8. PL Sections 2, 4. 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	A cluster of post-marketing events of retinal vasculitis, some of which were designated by the reporter as occlusive retinal vasculitis, have been reported to Novartis. Based on internal and independent external safety review committee assessments, it is concluded that there is a confirmed safety signal of rare adverse events of "retinal vasculitis and/or retinal vascular occlusion".
Risk factors and risk groups	There are no identified risk factors or risk groups.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.4, 4.8 PL Sections 2 and 4 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.
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: SmPC Sections 4.4, 4.8. PL Section 4. 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	In the two pivotal 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: SmPC Sections 4.4, 4.8, 4.9. PL Sections 2, 4. 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: SmPC Sections 4.4, 4.8 PL Sections 2, 4.

	Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 7 Important potential 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.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4 Additional Risk Minimization Measures: None
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: SmPC Sections 4.4. PL Section 2. Additional Risk Minimization Measures:

None

II C: Post-authorization development planII.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®.