

1. NAME OF THE MEDICINAL PRODUCT

Beovu 120 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution for injection contains 120 mg of brolocizumab*.

* Brolocizumab is a humanised monoclonal single-chain Fv (scFv) antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.

Beovu 120 mg/ml solution for injection in pre-filled syringe

Each pre-filled syringe contains 19.8 mg brolocizumab in 0.165 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6 mg of brolocizumab.

Beovu 120 mg/ml solution for injection (vial)

Each vial contains 27.6 mg brolocizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6 mg of brolocizumab.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to slightly opalescent, colourless to slightly brownish-yellow aqueous solution.

4. CLINICAL PARTICULARS

Patient Safety Information Guide

The marketing of Beovu is subject to a risk management plan (RMP) including 'Patient safety information guide'. The 'Patient safety information guide' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the guide before starting treatment.

4.1 Therapeutic indications

Beovu is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).

4.2 Posology and method of administration

Beovu must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Posology

The recommended dose is 6 mg brolocizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered (see sections 4.4 and 5.1).

If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment,

Beovu should be discontinued.

Special populations

Elderly

No dosage adjustment is required in patients aged 65 years or above (see section 5.2).

Renal impairment

No dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment

Brolucizumab has not been studied in patients with hepatic impairment. No dosage adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of brolucizumab in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

Beovu is for intravitreal use only.

The solution for injection should be inspected visually prior to administration (see section 6.6).

The intravitreal injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.3). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered slowly; a different scleral site should be used for subsequent injections.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Pre-filled syringe

The pre-filled syringe is for single use only. Each pre-filled syringe should only be used for the treatment of a single eye.

Since the volume contained in the pre-filled syringe (0.165 ml) is greater than the recommended dose (0.05 ml), a portion of the volume contained in the pre-filled syringe must be discarded prior to administration.

Injecting the entire volume of the pre-filled syringe could result in overdose. To expel the air bubble along with excess medicinal product, the plunger should be slowly depressed until the edge below the dome of the rubber stopper is aligned with the 0.05 ml dose mark (equivalent to 50 µl, i.e. 6 mg brolucizumab).

Vial

The vial is for single use only. Each vial should only be used for the treatment of a single eye.

Since the volume contained in the vial (0.23 ml) is greater than the recommended dose (0.05 ml), a portion of the volume contained in the vial must be discarded prior to administration.

Injecting the entire volume of the vial could result in overdose. To expel the air bubble along with excess medicinal product, the air should be carefully expelled from the syringe and the dose adjusted to the 0.05 ml mark (equivalent to 50 µl, i.e. 6 mg brolocizumab).

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with active or suspected ocular or periocular infections.

Patients with active intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Endophthalmitis, intraocular inflammation, traumatic cataract, retinal detachment, retinal tear, retinal vasculitis, and/or retinal vascular occlusion

Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, intraocular inflammation, traumatic cataract, retinal detachment and retinal tear (see section 4.8). Proper aseptic injection techniques must always be used when administering Beovu.

Patients should be instructed to report any symptoms suggestive of the above-mentioned events without delay.

Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion

Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, has been reported with the use of Beovu (see sections 4.3 and 4.8). A higher number of intraocular inflammation events were observed among patients with treatment-emergent antibodies. After investigation, retinal vasculitis and/or retinal vascular occlusion were found to be immune-mediated events. Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, may occur following the first intravitreal injection and at any time of treatment. These events were observed more frequently at the beginning of the treatment.

Based on clinical studies these events were more frequent in female patients treated with Beovu than male patients (e.g., 5.3% females vs. 3.2% males in HAWK and HARRIER) and in Japanese patients.

In patients developing these events, treatment with Beovu should be discontinued and the events should be promptly managed. Patients treated with Beovu with a medical history of intraocular inflammation and/or retinal vascular occlusion (within 12 months prior to the first brolocizumab injection) should be closely monitored, since they are at increased risk of developing retinal vasculitis and/or retinal vascular occlusion.

The interval between two Beovu doses during maintenance treatment should not be less than 8 weeks considering that a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion was reported in patients with nAMD who received Beovu every 4 week maintenance dosing in a clinical study compared to patients who received Beovu every 8 or 12 week

maintenance dosing in the pivotal Phase III clinical studies.

Intraocular pressure increases

Transient increases in intraocular pressure have been seen within 30 minutes of intravitreal injection with vascular endothelial growth factor (VEGF) inhibitors, including brolocizumab (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Beovu while the intraocular pressure is ≥ 30 mmHg). Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately.

Bilateral treatment

The safety and efficacy of brolocizumab administered in both eyes concurrently have not been studied.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with brolocizumab (see section 4.8). Patients should be instructed to inform their physician if they develop symptoms such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light (see section 4.8).

Concomitant use of other anti-VEGF

There are no data available on the concomitant use of Beovu with other anti-VEGF medicinal products in the same eye. Brolocizumab should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular).

Withholding treatment

In intravitreal anti-VEGF treatments, the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- a decrease in best-corrected visual acuity (BCVA) of ≥ 30 letters compared with the last assessment of visual acuity;
- a retinal break;
- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is $\geq 50\%$ of the total lesion area;
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD include a large and/or high pigment epithelial retinal detachment. When initiating brolocizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Rhegmatogenous retinal detachment or macular holes

Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

Systemic effects following intravitreal use

Systemic adverse events, including non-ocular haemorrhages and arterial thromboembolic events, have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with AMD with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 3 months. Caution should be exercised when treating such patients.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with brolocizumab and for at least one month after the last dose when stopping treatment with brolocizumab.

Pregnancy

There are no or limited amount of data from the use of brolocizumab in pregnant women. A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to reproductive toxicity. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Although the systemic exposure after ocular administration is very low due to its mechanism of action, there is a potential risk to embryofetal development. Therefore, brolocizumab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether brolocizumab is excreted in human milk. In a reproductive toxicity study, brolocizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys (see section 5.3). A risk to the breast-fed newborn/infant cannot be excluded. Brolocizumab is not recommended during breast-feeding and breast-feeding should not be started for at least one month after the last dose when stopping treatment with brolocizumab. A decision must be made whether to discontinue breast-feeding or to abstain from brolocizumab therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No reproductive or fertility studies have been conducted. VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VEGF inhibitors, there is a potential risk for female reproduction.

4.7 Effects on ability to drive and use machines

Beovu has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until visual function has recovered sufficiently.

4.8 Undesirable effects

For wet AMD, a total of 1 088 patients treated with brolocizumab constituted the safety population in two Phase III studies. Of these, 730 patients were treated with the recommended dose of 6 mg.

Summary of the safety profile

The most frequently reported adverse reactions were reduced visual acuity (7.3%), cataract (7.0%), conjunctival haemorrhage (6.3%) and vitreous floaters (5.1%).

The most serious adverse reactions were blindness (0.8%), endophthalmitis (0.7%), retinal artery occlusion (0.8%) and retinal detachment (0.7%).

Tabulated list of adverse reactions

The adverse reactions experienced following administration of Beovu in clinical studies are summarised in Table 1 below.

Adverse reactions (Table 1) are listed according to the MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Frequency categories for each adverse reaction are based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequencies of adverse reactions in clinical studies and post-marketing experience

| MedDRA System organ class | Frequency category |
|--|---------------------------|
| Immune system disorders | |
| Hypersensitivity (including urticaria, rash, pruritus, erythema) | Common |
| Eye disorders | |
| Visual acuity reduced | Common |
| Retinal haemorrhage | Common |
| Uveitis | Common |
| Iritis | Common |
| Vitreous detachment | Common |
| Retinal tear | Common |
| Cataract | Common |
| Conjunctival haemorrhage | Common |
| Vitreous floaters | Common |
| Eye pain | Common |
| Intraocular pressure increase | Common |
| Conjunctivitis | Common |
| Retinal pigment epithelial tear | Common |
| Vision blurred | Common |
| Corneal abrasion | Common |
| Punctate keratitis | Common |
| Blindness | Uncommon |
| Endophthalmitis | Uncommon |
| Retinal detachment | Uncommon |
| Conjunctival hyperaemia | Uncommon |
| Lacrimation increased | Uncommon |
| Abnormal sensation in eye | Uncommon |
| Detachment of retinal pigment epithelium | Uncommon |
| Vitritis | Uncommon |
| Anterior chamber inflammation | Uncommon |
| Iridocyclitis | Uncommon |
| Anterior chamber flare | Uncommon |
| Corneal oedema | Uncommon |

| | |
|----------------------------|----------|
| Vitreous haemorrhage | Uncommon |
| Retinal vascular occlusion | Uncommon |
| Retinal vasculitis | Uncommon |
| Scleritis** | Uncommon |

**including episcleritis

Description of selected adverse reactions

Immunogenicity

There is a potential for an immune response in patients treated with Beovu. After dosing with Beovu for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23–25% of patients. Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation adverse reactions were observed. After investigation, retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, were found to be immune-mediated adverse events related to exposure to Beovu (see section 4.4). Anti-brolucizumab antibodies were not associated with an impact on clinical efficacy.

Product-class-related adverse reactions

There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the brolucizumab clinical studies in patients with AMD. There were no major notable differences between the groups treated with brolucizumab and comparator.

Reporting of suspected adverse reactions

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>. and to Novartis using the following email address: safetydesk.israel@novartis.com

4.9 Overdose

Overdosing with greater than recommended injection volume may increase intraocular pressure. In the event of overdose, intraocular pressure should therefore be monitored and, if deemed necessary by the treating physician, appropriate treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antineovascularisation agents, ATC code: S01LA06

Mechanism of action

Brolucizumab is a humanised monoclonal single chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa.

Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathological ocular angiogenesis and retinal oedema. Brolucizumab binds with high affinity to VEGF-A isoforms (e.g. VEGF₁₁₀, VEGF₁₂₁, and VEGF₁₆₅), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.

effects

In the HAWK and HARRIER studies, anatomical parameters related to leakage of blood and fluid that characterise choroidal neovascularisation (CNV) were part of the disease activity assessments guiding treatment decisions. Reductions in central subfield thickness (CST) and in presence of intraretinal/subretinal fluid (IRF/SRF) or sub-retinal pigment epithelium (sub-RPE) fluid were observed in patients treated with Beovu as early as 4 weeks after treatment initiation and up to week 48 and week 96.

At week 16, the reduction in CST was statistically significant on Beovu versus aflibercept in both studies (HAWK: -161 vs. -134 microns; HARRIER: -174 vs. -134 microns). This decrease from baseline in CST was also statistically significant at week 48 (HAWK: -173 vs. -144 microns; HARRIER: -194 vs. -144 microns), and maintained to the end of each study at week 96 (HAWK: -175 vs. -149 microns; HARRIER: -198 vs. -155 microns).

At week 16, the percentage difference in patients with IRF and/or SRF fluid was statistically significant on Beovu versus aflibercept in both studies (HAWK: 34% vs. 52%; HARRIER: 29% vs. 45%). This difference was also statistically significant at week 48 (HAWK: 31% vs. 45%; HARRIER: 26% vs. 44%), and maintained to the end of each study at week 96 (HAWK: 24% vs. 37%; HARRIER: 24% vs. 39%).

At week 16, the percentage difference in patients with sub-RPE fluid was statistically significant on Beovu versus aflibercept in both studies (HAWK: 19% vs. 27%; HARRIER: 16% vs. 24%). This difference was also statistically significant at week 48 (HAWK: 14% vs. 22%; HARRIER: 13% vs. 22%), and maintained to the end of each study at week 96 (HAWK: 11% vs. 15%; HARRIER: 17% vs. 22%).

In these studies, for patients treated with Beovu, reductions in CNV lesion size were observed as early as 12 weeks, and at weeks 48 and 96 after treatment initiation.

Clinical efficacy and safety

The efficacy and safety of Beovu were assessed in two randomised, multicentre, double-masked, active-controlled Phase III studies (HAWK and HARRIER) in patients with neovascular (wet) AMD. A total of 1,817 patients were treated in these studies for two years (1,088 on Beovu and 729 on comparator aflibercept). Patient ages ranged from 50 to 97 years, with a mean age of 76 years.

In both studies, after the first three monthly doses (weeks 0, 4 and 8), brolucizumab patients were treated every 12 weeks, with the option of adjusting to a dosing interval every 8 weeks based on disease activity. Disease activity was assessed by a physician during the first 12-week interval (at weeks 16 and 20) and at each subsequent scheduled 12-weekly treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased CST and/or presence of IRF/SRF or sub-RPE fluid) at any of these visits were adjusted to an 8-weekly treatment interval. The comparator aflibercept was administered every 8 weeks after the first 3 monthly doses.

Results

The primary efficacy endpoint for the studies was the change from baseline in best corrected visual acuity (BCVA) to week 48, as measured by the early treatment diabetic retinopathy study (ETDRS) letter score, with the primary objective being to demonstrate non-inferiority of Beovu versus aflibercept. In both studies, Beovu (administered in an every 12 weeks or an every 8 weeks regimen) demonstrated non-inferior efficacy to aflibercept 2 mg (administered every 8 weeks). The visual acuity gains observed in the first year were maintained in the second year.

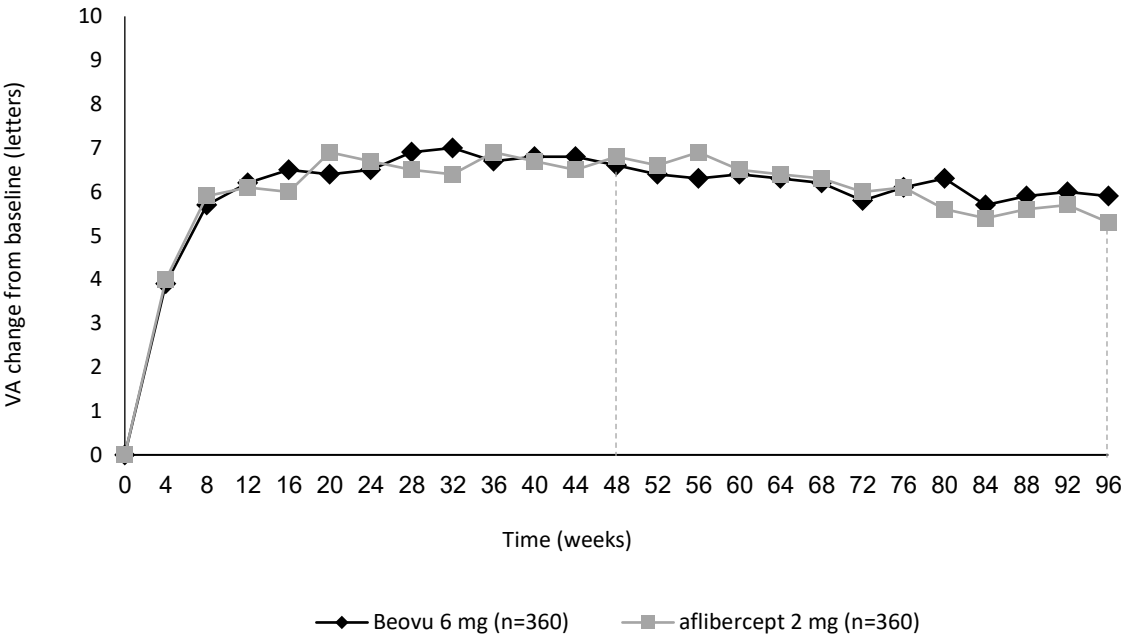
Detailed results of both studies are shown in Table 2 and in Figure 1 below.

Table 2 Visual acuity outcomes at weeks 48 and 96 in Phase III - HAWK and HARRIER studies

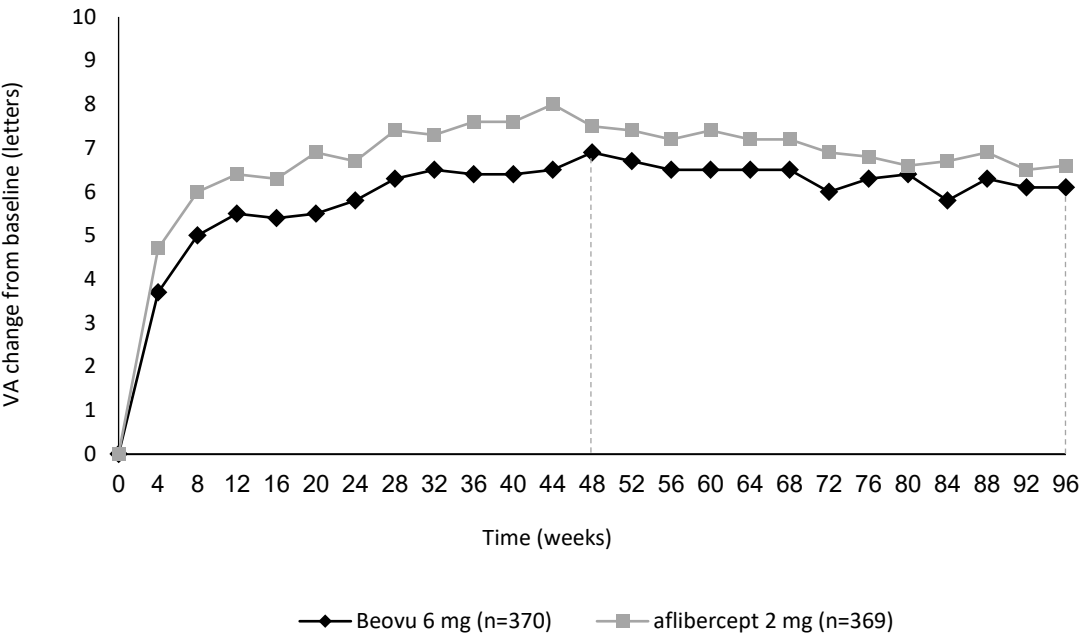
| Efficacy outcome | Week | HAWK | | | HARRIER | | |
|--|--------------------------|--------------------------|--------------------------------|---|--------------------------|--------------------------------|---|
| | | Beovu 6 mg (n=360) | Aflibercept 2 mg (n=360) | Difference (95% CI) brolucizumab – aflibercept | Beovu 6 mg (n=370) | Aflibercept 2 mg (n=369) | Difference (95% CI) brolucizumab – aflibercept |
| Mean change from baseline in BCVA (measured by ETDRS letters score) | 48 | 6.6 (SE=0.71) | 6.8 (SE=0.71) | -0.2 (-2.1, 1.8) P<0.0001 ^{a)} | 6.9 (SE=0.61) | 7.6 (SE=0.61) | -0.7 (-2.4, 1.0) P<0.0001 ^{a)} |
| | 36 – 48 ^{b)} | 6.7 (SE=0.68) | 6.7 (SE=0.68) | 0.0 (-1.9, 1.9) P<0.0001 ^{a)} | 6.5 (SE=0.58) | 7.7 (SE=0.58) | -1.2 (-2.8, 0.4) P=0.0003 ^{a)} |
| | 96 | 5.9 (SE=0.78) | 5.3 (SE=0.78) | 0.5 (-1.6, 2.7) | 6.1 (SE=0.73) | 6.6 (SE=0.73) | -0.4 (-2.5, 1.6) |
| % of patients who gained at least 15 letters of vision | 48 | 33.6 | 25.4 | 8.2 (2.2, 15.0) | 29.3 | 29.9 | -0.6 (-7.1, 5.8) |
| | 96 | 34.2 | 27.0 | 7.2 (1.4, 13.8) | 29.1 | 31.5 | -2.4 (-8.8, 4.1) |
| % of patients who lost visual acuity (%) (≥15 letters of BCVA loss) | 48 | 6.4 | 5.5 | 0.9 (-2.7, 4.3) | 3.8 | 4.8 | -1.0 (-3.9, 2.2) |
| | 96 | 8.1 | 7.4 | 0.7 (-3.6, 4.6) | 7.1 | 7.5 | -0.4 (-3.8, 3.3) |
| BCVA: best corrected visual acuity; missing data are imputed using last observation carried forward (LOCF) method ETDRS: early treatment diabetic retinopathy study SE: standard error ^{a)} P-value referring to the non-inferiority hypothesis with a non-inferiority margin of 4.0 letters. ^{b)} Key secondary endpoint, accounting for differences in timing of Beovu and aflibercept treatments. | | | | | | | |

Figure 1 Mean change in visual acuity from baseline to week 96 in HAWK and HARRIER studies

HAWK



HARRIER



These visual acuity gains were achieved with 56% and 51% of patients treated with Beovu 6 mg on a 12-weekly dosing interval at week 48, and with 45% and 39% of patients at week 96 in HAWK and HARRIER, respectively. Among patients identified as eligible for the 12-weekly regimen during the first 12-week interval, 85% and 82% remained on the 12-weekly dosing interval up to week 48. Of patients on the 12-weekly interval at week 48, 82% and 75% remained on the 12-weekly dosing interval up to week 96.

Treatment effects in evaluable subgroups (e.g. age, gender, race, baseline visual acuity, baseline retinal thickness, lesion type, lesion size, fluid status) in each study were generally consistent with the

results in the overall populations.

Disease activity was assessed by changes in visual acuity and/or anatomical parameters, including CST and/or presence of IRF/SRF or sub-RPE. Disease activity was assessed throughout the studies. Anatomical parameters of disease activity were decreased at week 48 and at week 96 for Beovu compared to aflibercept (see “Pharmacodynamic effects”).

The percentage difference in patients with disease activity at week 16 was statistically significant on Beovu versus aflibercept (24% vs 35% in HAWK, $p=0.0013$; 23% vs 32% in HARRIER, $p=0.0021$).

In both studies, Beovu demonstrated clinically meaningful increases from baseline in the pre-specified secondary efficacy endpoint of patient-reported outcomes, reported through the National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in BCVA. Patient-reported outcome benefits were maintained in the second year.

No clinically meaningful differences were found between Beovu and aflibercept in changes from baseline to week 48 in NEI VFQ-25 total score and subscales (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision and peripheral vision).

Paediatric population

Beovu is not indicated for use in paediatric population.

5.2 Pharmacokinetic properties

Beovu is administered directly into the vitreous to exert local effects in the eye.

Absorption and distribution

After intravitreal administration of 6 mg brolocizumab per eye to patients with nAMD, the geometric mean C_{max} of free brolocizumab in the plasma was 49.0 ng/ml (range: 8.97 to 548 ng/ml) and was attained in 1 day.

Biotransformation and elimination

Brolocizumab is a monoclonal antibody fragment and no metabolism studies have been conducted. As a single-chain antibody fragment, free brolocizumab is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF, passive renal elimination and metabolism via proteolysis.

After intravitreal injections, brolocizumab was eliminated with an apparent systemic half-life of 4.3 ± 1.9 days. Concentrations were generally near or below the quantitation limit (<0.5 ng/ml) approximately 4 weeks after dosing in most patients. Brolocizumab did not accumulate in the serum when administered intravitreally every 4 weeks.

Special populations

Elderly

There were no relevant differences in systemic pharmacokinetics following intravitreal injection in a study with 22 patients aged 65 to 74 years, 18 patients aged 75 to 84 years and 3 patients aged ≥ 85 years.

Renal impairment

The systemic pharmacokinetics of brolocizumab was evaluated in nAMD patients with normal renal function (≥ 90 ml/min [$n=21$]), with mild (60 to <90 ml/min [$n=22$]) or moderate (30 to <60 ml/min

[n=7]) renal impairment. While the mean systemic clearance values for patients with mild or moderate renal impairment were generally lower than patients with normal renal function, no significant impact of mild and moderate renal impairment on the overall systemic exposure to brolocizumab was observed. No patients with severe (<30 ml/min) renal impairment were studied.

Hepatic impairment

Brolocizumab has not been studied in patients with hepatic impairment. Mild to severe hepatic impairment should have no impact on the overall systemic exposure to brolocizumab, because metabolism occurs via proteolysis and does not depend on hepatic function.

5.3 Preclinical safety data

No studies have been conducted on the carcinogenic or mutagenic potential of brolocizumab.

In pregnant cynomolgus monkeys, brolocizumab was administered once every 4 weeks by intravitreal injection at dose levels resulting in maximal systemic exposures 6-fold higher than those in humans at the maximum recommended dose (based on serum C_{max}). There was no impact on embryofoetal development, pregnancy or parturition, or on the survival, growth or postnatal development of offspring. Nevertheless, based on its pharmacological effect, brolocizumab should be regarded as potentially teratogenic and embryo-foetotoxic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sucrose
Sodium citrate
Polysorbate 80
Sodium Hydroxide (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Pre-filled syringe

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the pre-filled syringe in its sealed blister and in the outer carton in order to protect from light.
Prior to use, the unopened blister may be kept at room temperature (below 25°C) for up to 24 hours.

Vial

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Prior to use, the unopened vial may be kept at room temperature (below 25°C) for up to 24 hours.

6.5 Nature and contents of container

Pre-filled syringe

0.165 ml sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap including a Luer lock adapter. The pre-filled syringe has a plunger rod and a purple finger grip, and is packed in a sealed blister.

Pack size of 1 pre-filled syringe.

Vial

0.230 ml sterile solution in a glass vial with a coated rubber stopper sealed with an aluminium cap with a purple plastic flip-off disk.

Pack size of 1 vial and 1 blunt filter needle (18G x 1½", 1.2 mm x 40 mm, 5 µm).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Pre-filled syringe

The pre-filled syringe contains more than the recommended dose of 6 mg. The extractable volume of the pre-filled syringe (0.165 ml) is not to be used in total. The excess volume should be expelled prior to injection. Injecting the entire volume of the pre-filled syringe could result in overdose. To expel the air bubble along with the excess medicinal product, slowly push the plunger until the edge below the dome of the rubber stopper is aligned with the black dosing line on the syringe (equivalent to 0.05 ml, i.e., 6 mg brolocizumab).

The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, the pre-filled syringe must not be used and appropriate replacement procedures followed.

The pre-filled syringe is sterile and for single use only. Do not use if the packaging, or pre-filled syringe are damaged or expired. Detailed instructions for use are provided in the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

Vial

The vial contains more than the recommended dose of 6 mg. The extractable volume of the vial (0.23 ml) is not to be used in total. The excess volume should be expelled prior to injection. Injecting the entire volume of the vial could result in overdose. The injection dose must be set to the 0.05 ml dose mark, i.e. 6 mg brolocizumab.

The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, the vial must not be used, and appropriate replacement procedures must be followed.

The content of the vial and the filter needle are sterile and for single use only. Do not use if the packaging, vial and/or filter needle are damaged or expired. Detailed instructions for use are provided in the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local

requirements.

7. REGISTRATION HOLDER AND IMPORTER

Novartis Israel Ltd., POB 7126, Tel-Aviv

8. REGISTRATION NUMBER(S)

166-75-36377

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