NOVARTIS

Regulatory Affairs

PAGENAX®
(brolucizumab)

120 mg/mL Solution for injection

International Package Leaflet

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Pagenax®

Ophthalmologicals, Antineovascularization agents.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Solution for injection

Pagenax® is supplied in a single-use vial.
Sterile, clear to slightly opalescent, colorless to slightly brownish-yellow and preservative-free aqueous solution.

Active substance(s)

Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa, produced in *Escherichia coli* cells by recombinant DNA technology.

One mL solution for injection contains 120 mg of brolucizumab.

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

Excipients

10 mM sodium citrate, 5.8% sucrose, 0.02% polysorbate 80 and water for injection and has a pH of approximately 7.2.

INDICATIONS

Pagenax is indicated for the treatment of:

- Neovascular (wet) age-related macular degeneration (AMD).
- Diabetic macular edema (DME).

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Single-use vial for intravitreal use only. Each vial should only be used for the treatment of a single eye.

Pagenax must be administered by a qualified physician.

General target population

Wet AMD

The recommended dose for Pagenax is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first three doses. Alternatively, Pagenax may be administered every 6 weeks for the first two doses, and a third dose may be administered 6 weeks later based on an assessment of disease activity. Thereafter, Pagenax is administered every 12 weeks (3 months). The physician may then individualize treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. The treatment interval could be as frequent as every 8 weeks (2 months) (see section CLINICAL STUDIES); however, the interval between two doses should not be less than every 8 weeks (2 months) (see section WARNINGS AND PRECAUTIONS).

Diabetic Macular Edema (DME)

The recommended dose for Pagenax is 6 mg (0.05 mL) administered by intravitreal injection every 6 weeks for the first five doses. Thereafter, Pagenax is administered every 12 weeks (3 months). Treatment intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomic parameters. In patients with disease activity, treatment every 8 weeks (2 months) could be considered (see section CLINICAL STUDIES).

Special populations

Renal impairment

No dosage regimen adjustment is required in patients with renal impairment (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

No dosage regimen adjustment is required in patients with hepatic impairment (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

The safety and efficacy of Pagenax in pediatric patients have not been established.

Geriatric patients (65 years or above)

No dosage regimen adjustment is required in patients 65 years or above.

Method of administration

As with all medicinal products for intravitreal use, Pagenax should be inspected visually prior to administration (see Instructions for use).

The injection procedure must be carried out under aseptic conditions, which include 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. Patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section CONTRAINDICATIONS). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

For information on preparation of Pagenax, see Instructions for use.

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 center of the globe. The injection volume of 0.05 mL is then delivered slowly; a different scleral site should be used for subsequent injections.

The safety and efficacy of Pagenax administered to both eyes concurrently have not been studied.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Active or suspected ocular or periocular infection.
- Active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis, retinal detachment, retinal vasculitis and/or retinal vascular occlusion

Intravitreal injections, including those with Pagenax, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection techniques must always be used when administering Pagenax.

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of Pagenax. These immune mediated adverse events may occur following the first intravitreal injection. Discontinue treatment with Pagenax in patients who develop these events. Patients treated with Pagenax who experience intraocular inflammation may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored (see sections CONTRAINDICATIONS and ADVERSE DRUG REACTIONS).

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

In a Phase IIIa clinical study (MERLIN), patients with nAMD who received Pagenax every 4 week maintenance dosing experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion than patients who received Pagenax every 8 or 12 week maintenance dosing in the pivotal Phase III clinical studies (HAWK and HARRIER). The interval between two Pagenax doses during maintenance treatment should not be less than 8 weeks (see section DOSAGE REGIMEN AND ADMINISTRATION).

Intraocular pressure increases

Transient increases in intraocular pressure have been seen within 30 minutes of injection, similar to those observed with intravitreal administration of other VEGF inhibitors (see section ADVERSE DRUG REACTIONS). Sustained intraocular pressure increases have also been reported with Pagenax. Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately.

Driving and using machines

Patients may experience temporary visual disturbances after an intravitreal injection with Pagenax and the associated eye examination, and should therefore be advised not to drive or use machinery until visual function has recovered sufficiently.

ADVERSE DRUG REACTIONS

Wet AMD population

A total of 1,088 patients treated with brolucizumab constituted the safety population in the two Phase III studies (HAWK and HARRIER) with a cumulative 96 weeks exposure to Pagenax and 730 patients treated with the recommended dose of 6 mg.

The most frequently reported adverse drug reactions in >5% of patients treated with Pagenax 6 mg were visual acuity reduced (7.3%), cataract (7.0%), conjunctival haemorrhage (6.3%), and vitreous floaters (5.1%).

Less common serious adverse drug reactions reported in <1% of the patients treated with Pagenax 6 mg were endophthalmitis, blindness, retinal artery occlusion and retinal detachment.

DME population

The safety of Pagenax was studied in two, Phase III active controlled studies (KESTREL and KITE) conducted respectively in 368 patients with visual impairment due to DME treated with the recommended dose of brolucizumab 6 mg for 52 weeks.

The ocular and non-ocular events in the KESTREL and KITE studies were reported with a frequency and severity similar to those seen in the wet AMD trials. Retinal vascular occlusion was reported in two patients (0.5%) treated with Pagenax and one patient (0.3%) treated with aflibercept 2 mg. Retinal vasculitis was reported in one patient (0.3%) treated with Pagenax and no patients treated with aflibercept 2 mg.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from the HAWK and HARRIER clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following

convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

Adverse drug reactions	Pagenax (N=730)	Aflibercept (N=729)	Frequency category
Eye disorders			
Visual acuity reduced	7.3	7.5	Common
Retinal haemorrhage	4.1	3.2	Common
Uveitis	1.6	0.1	Common
Iritis	1.2	0.3	Common
Vitreous detachment	4.0	3.3	Common
Retinal tear	1.2	0.7	Common
Cataract	7.0	11.1	Common
Conjunctival haemorrhage	6.3	7.0	Common
Vitreous floaters	5.1	2.9	Common
Eye pain	4.9	6.2	Common
Intraocular pressure increase	3.8	4.5	Common
Conjunctivitis	3.3	1.6	Common
Retinal pigment epithelial tear	2.7	1.1	Common
Vision blurred	1.9	1.6	Common
Corneal abrasion	1.5	2.2	Common
Punctate keratitis	1.4	2.3	Common
Endophthalmitis	0.7	0.1	Uncommon
Blindness	0.8	0.3	Uncommon
Retinal artery occlusion	0.8	0.1	Uncommon
Retinal detachment	0.7	0.4	Uncommon
Conjunctival hyperaemia	1.0	1.1	Uncommon
Lacrimation increased	1.0	1.1	Uncommon
Abnormal sensation in eye	0.8	1.8	Uncommon
Detachment of retinal pigment epithelium	0.5	0.4	Uncommon
Vitritis	0.4	0.4	Uncommon
Anterior chamber inflammation	0.4	0	Uncommon
Iridocyclitis	0.4	0.1	Uncommon
Anterior chamber flare	0.3	0	Uncommon
Corneal oedema	0.3	0	Uncommon
Vitreous haemorrhage	0.1	0.4	Uncommon
Immune system disorders			
Hypersensitivity[a]	1.8	1.4	Common

Adverse drug reactions	Pagenax (N=730)	Aflibercept (N=729)	Frequency category

[a] Including urticaria, rash, pruritus, erythema

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Pagenax via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Eye disorders
Retinal vascular occlusion, retinal vasculitis

Description of selected adverse drug reactions

Intraocular inflammation

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 Pagenax than male patients (e.g. 5.3% females vs. 3.2% males in HAWK and HARRIER).

The results of a retrospective real world evidence analysis in nAMD patients who were evaluated for up to 6 months after initiating treatment with Pagenax suggest that patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with Pagenax were more likely to present with similar events after Pagenax injection, as compared to nAMD patients with no history of these events.

Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with Pagenax. The immunogenicity of Pagenax was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Pagenax in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Pagenax with the incidence of antibodies to other products may be misleading.

Pre-treatment antibodies have been detected in drug-naïve subjects for a variety of biotechnology-derived therapeutic proteins including single-chain antibodies.

Wet AMD

The pre-treatment incidence of anti-brolucizumab antibodies was 35 – 52%. After dosing with Pagenax for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23 – 25% of patients.

DME

The pre-treatment incidence of anti-brolucizumab antibodies was 64%. After dosing with Pagenax for 52 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 12 to 18% of patients. In wet AMD and DME, anti-brolucizumab antibodies were not associated with an impact on clinical efficacy. Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed. Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, are immune mediated adverse events related to exposure to Pagenax. This treatment emergent antibody response may develop following the first intravitreal injection (see WARNINGS AND PRECAUTIONS).

INTERACTIONS

No formal interaction studies have been performed.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well-controlled studies of Pagenax administration in pregnant. The potential risk of use of Pagenax in pregnancy is unknown.

A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to pre- or postnatal development at approximately 6-times the human exposure based on serum C_{max} (see Animal data). However, based on the anti-VEGF mechanism of action, brolucizumab must be regarded as potentially teratogenic and embryo/fetotoxic. Therefore, Pagenax should not be used during pregnancy unless the expected benefits outweigh the potential risks to the fetus.

Animal data

In an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys, brolucizumab was administered to all animals by intravitreal (IVT) injection to one eye at doses of 3 or 6 mg once every 4 weeks until delivery. One additional injection was administered to a subset of animals 28 days post-partum and had blood and milk collected for toxicokinetic evaluations. There was no impact of IVT administration of brolucizumab on

embryo-fetal development, pregnancy or parturition, or on the survival, growth, or postnatal development of offspring. This represents an exposure approximately 6-times the human exposure (based on serum C_{max}) at the proposed clinical dose of 6 mg. However, 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 to female reproduction and to embryo-fetal development.

Lactation

It is unknown if brolucizumab is transferred into human milk after administration of Pagenax. There are no data on the effects of Pagenax on the breastfed child or on milk production. In an ePPND study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys. Because of the potential for adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with Pagenax.

Females of reproductive potential

Females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) during treatment with Pagenax and for at least one month after the last dose when stopping treatment with Pagenax.

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Increased levels of signaling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathologic ocular angiogenesis and retinal edema. Brolucizumab binds with high affinity to VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$, and $VEGF_{165}$), 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 pathologic neovascularization and decreasing vascular permeability.

Pharmacodynamics (PD)

Wet AMD

In the HAWK and HARRIER studies, related anatomical parameters 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 Pagenax as early as 4 weeks after treatment initiation and up to Week 48 and Week 96. Statistically significant greater reductions in CST and in presence of IRF/SRF relative to aflibercept were demonstrated at Weeks 16 and 48 (see section CLINICAL STUDIES).

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

DME

In the KESTREL and KITE studies, related anatomical parameters 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) were observed in patients treated with Pagenax as early as 4 weeks after treatment initiation and up to Week 52.

Pharmacokinetics (PK)

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

Absorption/Distribution

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

Metabolism/Elimination

Brolucizumab is a monoclonal antibody fragment and no drug metabolism studies have been conducted. As a single-chain antibody fragment, free brolucizumab 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, brolucizumab was eliminated with an apparent systemic half-life of 4.4 days. Concentrations were generally near or below the quantitation limit (<0.5 ng/mL) approximately 4 weeks after dosing in most patients. Pagenax did not accumulate in the serum when administered intravitreally every 4 weeks.

Special populations

Geriatric patients (65 years or above)

In the HAWK and HARRIER clinical studies, approximately 90% (978/1088) of patients randomized to treatment with Pagenax were ≥65 years of age and approximately 60% (648/1088) were ≥75 years of age. In the KESTREL and KITE clinical studies, approximately 45% (164/368) of patients randomized to treatment with Pagenax were ≥ 65 years of age and approximately 10% (37/368) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

Race/Ethnicity

There were no ethnic differences in systemic pharmacokinetics following intravitreal injection in a study with 24 Caucasian and 26 Japanese patients.

Renal impairment

Mild to severe renal impairment should have no impact on the overall systemic exposure to brolucizumab, because the systemic concentration of brolucizumab is driven by the distribution from the eye rather than the elimination rate and because the systemic exposure of free brolucizumab is low.

The systemic clearance of brolucizumab was evaluated in nAMD patients who had both serum brolucizumab pharmacokinetic and creatinine clearance data available. Subjects with mild (50 to 79 mL/min (n=13)) renal impairment had mean systemic clearance rates of brolucizumab which were within 15% of the mean clearance rate for subjects with normal renal function (≥80 mL/min (n=25)). Patients with moderate (30 to 49 mL/min (n=3)) renal impairment had mean systemic clearance rates of brolucizumab which were lower than patients with normal renal function but the number of patients was too low to make definitive conclusions. No patients with severe (<30 mL/min) renal impairment were studied.

Hepatic impairment

Mild to severe hepatic impairment should have no impact on the overall systemic exposure to brolucizumab, because metabolism occurs via proteolysis and does not depend on hepatic function.

CLINICAL STUDIES

Treatment of wet AMD

The safety and efficacy of Pagenax were assessed in two randomized, multi-center, 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 Pagenax and 729 on aflibercept). Patient ages ranged from 50 to 97 years with a mean age of 76 years.

In HAWK, patients were randomized in a 1:1:1 ratio to the following dosing regimens:

- brolucizumab 3 mg administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses,
- brolucizumab 6 mg administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses,
- aflibercept 2 mg administered every 8 weeks (q8w) after the first 3 monthly doses.

In HARRIER, patients were randomized in a 1:1 ratio to the following dosing regimens:

- brolucizumab 6 mg administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses,
- aflibercept 2 mg administered every 8 weeks (q8w) after the first 3 monthly doses.

In both studies, after the first three monthly doses (Week 0, 4 and 8), brolucizumab patients were treated q12w, with the option of adjusting to q8w dosing interval based on disease activity. Disease activity was assessed by a physician during the first q12 week interval (at Week 16 and 20) and at each subsequent scheduled q12w treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased central subfield thickness (CST), and/or presence of retinal fluids (IRF/SRF, sub-RPE)) at any of these visits were adjusted to a q8w treatment interval.

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 to demonstrate non-inferiority of Pagenax vs. aflibercept. In both studies, Pagenax (administered in a q12w/q8w regimen) demonstrated non-inferior efficacy to aflibercept 2 mg (administered q8w). The visual acuity gains observed in the first year were maintained in the second year.

Detailed results of both studies are shown in Table 3 and Figure 1 below.

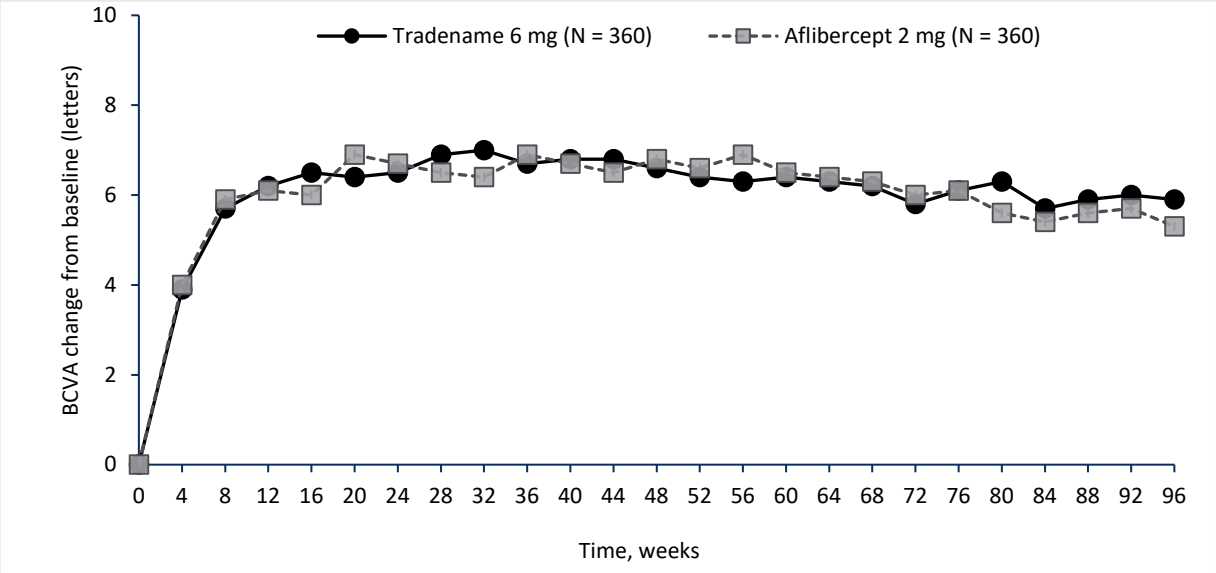
Table 3 Visual acuity outcomes at Week 48 and 96 in Phase III - HAWK and HARRIER studies

		HAWK			HARRIER		
Efficacy outcome	**At week**	**Pagenax (n=360)**	**Aflibercept 2 mg (n=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Pagenax (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)]
% 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)
% 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)

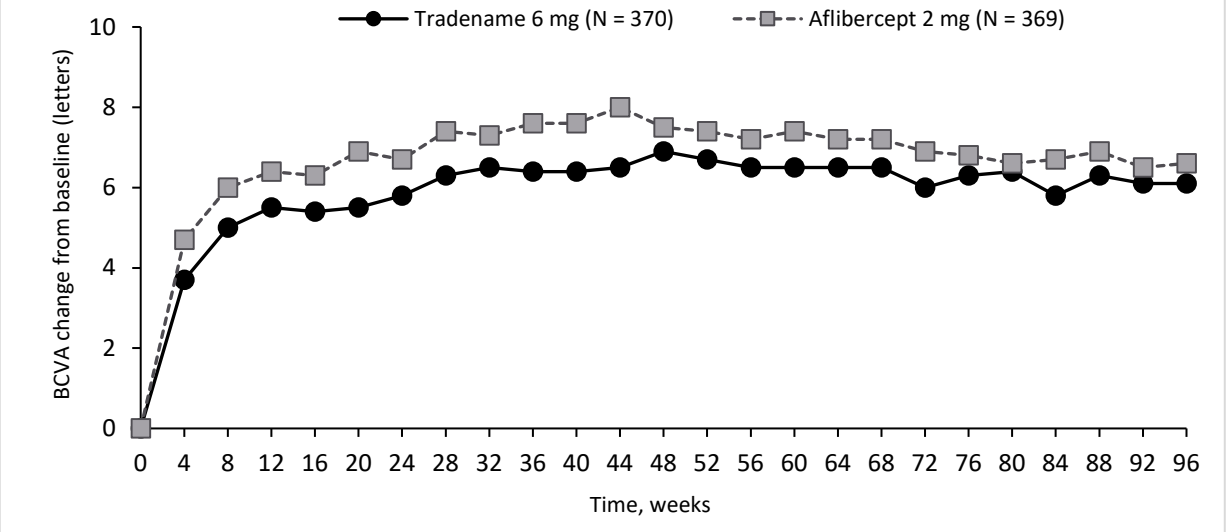
BCVA: Best Corrected Visual Acuity; missing data are imputed using last observation carried forward (LOCF) method
ETDRS: Early Treatment Diabetic Retinopathy Study
[a)] P-value referring to the non-inferiority hypothesis with a non-interiority margin of 4.0 letters

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% patients treated with Pagenax on q12w 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 q12w interval during the first 12 week interval, 85% and 82% remained on the q12w dosing interval up to Week 48. Of patients on the q12w interval at Week 48, 82% and 75% remained on the 12 week dosing interval through 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 population.

Disease activity was assessed by changes in visual acuity and/or anatomical parameters, including central subfield thickness (CST) and/or presence of retinal fluids (IRF/SRF, sub-RPE). At Week 16, when disease activity was first assessed for determining the treatment interval, statistically fewer patients showed disease activity on Pagenax compared to aflibercept 2 mg. Disease activity was assessed throughout the studies. Anatomical parameters of disease activity were decreased at Week 48 for Pagenax compared to aflibercept (Table 4).

Table 4 Disease Activity Evaluation in HAWK and HARRIER studies up to Week 96

		HAWK			HARRIER		
Efficacy outcome (pre-specified secondary endpoints)	**At Week**	**Pagenax (N=360)**	**Aflibercept 2mg (N=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Pagenax (N=370)**	**Aflibercept 2mg (N=369)**	**Difference (95% CI) brolucizumab – aflibercept**
% of patients with disease activity [c)]	16 [d)]	24.0	34.5	-10.5 (-17.1, -3.5) P=0.0013 [a)]	22.7	32.2	-9.5 (-15.8, -3.1) P=0.0021 [a)]
Mean change in CST from baseline (µm)	16 [d)]	-161.4 (SE=6.2)	- 133.6 (SE=6.2)	-27.8 (-45.1, -10.5) P=0.0008 [a)]	-174.4 (SE=6.7)	-134.2 (SE=6.7)	-40.2 (-58.9, -21.6) P<0.0001 [a)]
	48	-172.8 (SE=6.7)	-143.7 (SE=6.7)	-29.0 (-47.6, -10.4) P=0.0012 [a)]	-193.8 (SE=6.8)	-143.9 (SE=6.8)	-49.9 (-68.9, -30.9) P<0.0001 [a)]
% of patients with IRF and/or SRF fluid	16 [d)]	33.9	52.2	-18.2 (-25.3, -10.9) P<0.0001 [a)]	29.4	45.1	-15.7 (-22.9, -9.0) P<0.0001 [a)]
	48	31.2	44.6	-13.5 (-20.7, -6.1) P=0.0001 [a)]	25.8	43.9	-18.1 (-24.9, -11.8) P<0.0001 [a)]
% of patients with sub- RPE fluid	16 [d)]	18.7	27.3	-8.6 (−14.4, −2.9) P=0.0030[b)]	16.0	23.8	-7.8 (−13.0, −2.7) P=0.0041[b)]
	48	13.5	21.6	-8.1 (−13.6, −2.7) P=0.0035[b)]	12.9	22.0	-9.1 (−13.8, −3.9) P=0.0007[b)]

CST: Central subfield thickness; IRF/SRF: Intraretinal/subretinal fluid; RPE: Retinal pigment epithelium;

[a)] Secondary endpoint in HARRIER, confirmatory analysis in HAWK. 1-sided p-values for superiority of brolucizumab

[b)] Secondary endpoints in HAWK and HARRIER; 2-sided p-values

[c)] Disease activity assessments were based on the physician's judgment supported by protocol guidance at Week 16: Decrease in BCVA of ≥ 5 letters compared with baseline, decrease in BCVA of ≥ 3 letters and CST increase ≥75 µm compared with Week 12, decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12 or new or worse intraretinal cysts (IRC)/intraretinal fluid (IRF) compared with Week 12

[d)] Up to Week 16, treatment exposure was identical, allowing a matched comparison of Pagenax and aflibercept

In both studies, Pagenax 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 Best Corrected Visual Acuity (BCVA). Patient reported outcomes benefits were maintained in the second year.

No clinically meaningful differences were found between Pagenax 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, color vision, and peripheral vision).

Treatment of DME

The safety and efficacy of Pagenax were assessed in two randomized, multi-center, double-masked, active controlled, Phase III studies (KESTREL and KITE) in patients with diabetic macular edema (DME).

A total of 926 patients were treated in these studies for 1 year (558 on brolucizumab and 368 on aflibercept 2 mg). Patient ages ranged from 23 to 87 years with a mean of 63 years.

In KESTREL, patients were randomized in a 1:1:1 ratio to the following dosing regimens:

- brolucizumab 6 mg administered once every 6 weeks (q6w) for first 5 doses, followed by brolucizumab 6 mg every 12 or 8 weeks (q12w/q8w).
- brolucizumab 3 mg administered once every 6 weeks (q6w) for first 5 doses, followed by brolucizumab 3 mg every 12 or 8 weeks (q12w/q8w).
- aflibercept 2 mg administered once every 4 weeks (q4w) for first 5 doses, followed by aflibercept 2 mg every 8 weeks (q8w).

In KITE, patients were randomized in a 1:1 ratio to the following dosing regimens:

- brolucizumab 6 mg administered once every 6 weeks (q6w) for first 5 doses, followed by brolucizumab 6 mg every 12 or 8 weeks (q12w/q8w).
- aflibercept 2 mg administered once every 4 weeks (q4w) for first 5 doses, followed by aflibercept 2 mg every 8 weeks (q8w).

In both studies, after the first five doses (Weeks 0, 6, 12, 18 and 24), brolucizumab patients were treated q12w, with the option of adjusting to a q8w dosing interval based on disease activity. Disease activity was assessed by a physician during the first q12 week interval (at Weeks 32 and 36) and at each subsequent scheduled q12w treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased central subfield thickness) at any of these visits were adjusted to a q8w treatment interval. The comparator aflibercept was administered every 8 weeks after the first 5 monthly doses.

Results

The primary efficacy endpoint for both studies was the change from baseline at Week 52 in Best Corrected Visual Acuity (BCVA) as measured by the Early Treatment Diabetic

Retinopathy Study (ETDRS) Letter Score with the primary objective to demonstrate non-inferiority of Pagenax versus aflibercept 2 mg. In both studies, Pagenax (administered in a q12w/q8w regimen) demonstrated non-inferior efficacy to aflibercept 2 mg (administered q8w).

The results of KESTREL and KITE also demonstrated non-inferiority of Pagenax versus aflibercept 2 mg for the key secondary endpoint (average change from baseline in BCVA over the period Week 40 through Week 52).

The median number of injections given over 12 months was 7 in patients treated with Pagenax versus 9 in patients treated with aflibercept 2 mg.

Detailed results of both studies are shown in Table 5 and Figure 2 below.

Table 5 Efficacy outcomes at Week 52 in Phase III - KESTREL and KITE studies

		KESTREL			KITE		
Efficacy outcome	**At Week**	**Pagenax (n=189)**	**aflibercept 2 mg (n=187)**	**Difference (95% CI) Pagenax – aflibercept**	**Pagenax (n=179)**	**aflibercept 2 mg (n=181)**	**Difference (95% CI) Pagenax – aflibercept**
Change from baseline in BCVA (measured by ETDRS letters score) – LS mean (SE)	52	9.2 (0.57)	10.5 (0.57)	-1.3 (-2.9, 0.3) P <0.001[a]	10.6 (0.66)	9.4 (0.66)	1.2 (-0.6, 3.1) P <0.001[a]
	40-52	9.0 (0.53)	10.5 (0.53)	-1.5 (-3.0, 0.0) P <0.001[a]	10.3 (0.62)	9.4 (0.62)	0.9 (-0.9, 2.6) P <0.001[a]
Gain of at least 15 letters in BCVA from baseline or BCVA ≥84 letters (%)	52	36.0	40.1	-4.1 (-13.3, 5.9)	46.8	37.2	9.6 (-0.4, 20.2)
Average change from baseline in CST (micrometers) – LS mean (SE)	40-52	-159.5 (5.88)	-158.1 (5.91)	-1.4 (-17.9, 15.0)	-187.1 (6.91)	-157.7 (6.89)	-29.4 (-48.6, -10.2) P =0.001[b]
Presence of IRF and/or SRF (%)	52	60.4	73.5	-13.2 (-23.2, -3.8)	54.5	72.9	-18.4 (-28.5, -8.3)

BCVA: Best Corrected Visual Acuity; BCVA assessments after start of alternative DME treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment

CST: Central subfield thickness

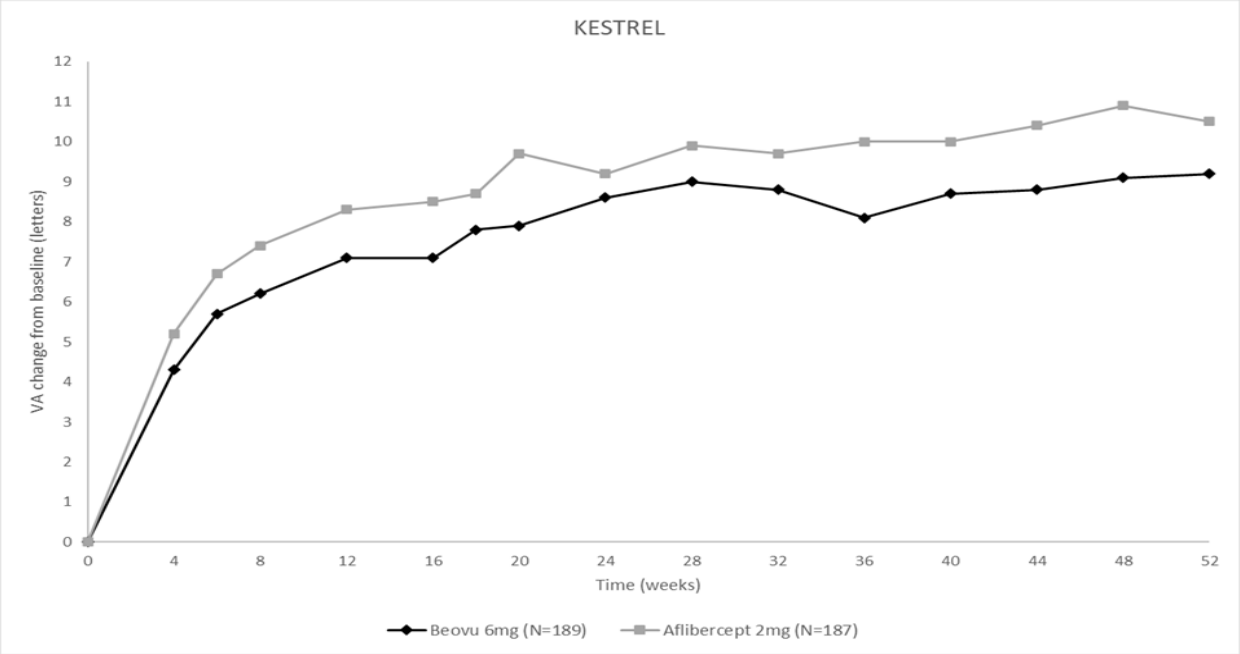
IRF: Intraretinal fluid; SRF: Subretinal fluid

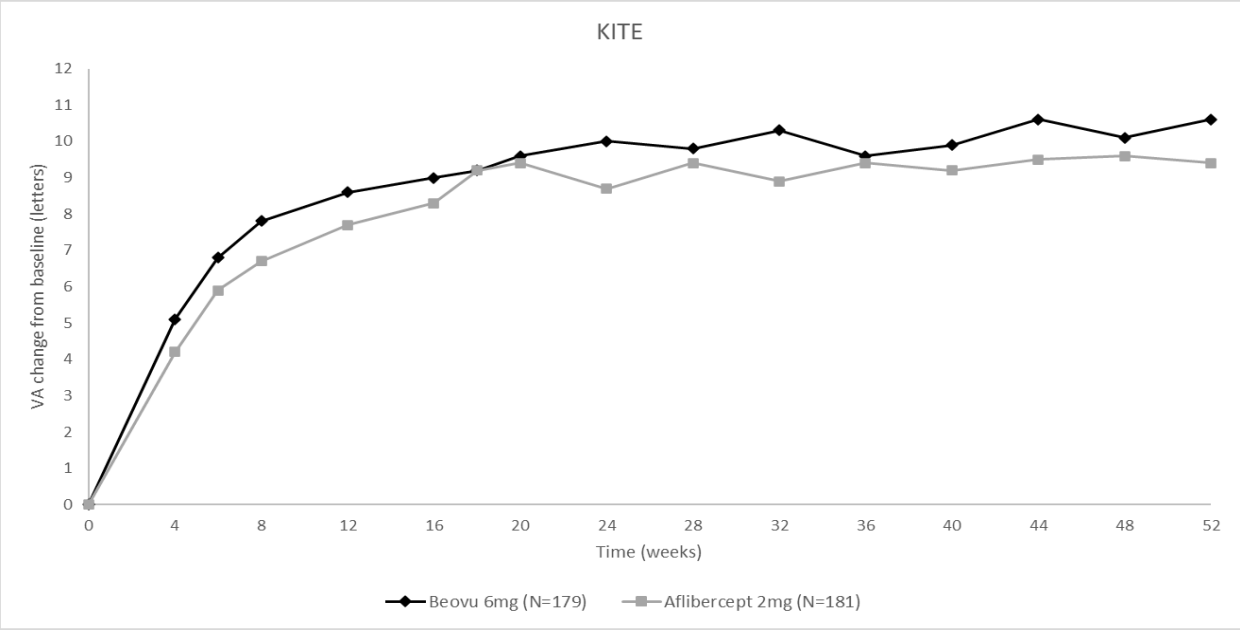
CST and fluid status assessments after start of alternative DME treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment

[a] P-value referring to the non-inferiority hypothesis with a non-inferiority margin of 4 letters

[b] P-value referring to the superiority testing at one-sided type I error of 0.025

Figure 2 Mean change in visual acuity from baseline to Week 52 in KESTREL and KITE studies





These visual acuity gains were achieved with 55% and 50% of patients treated with Pagenax on a q12w dosing interval at Week 52 in KESTREL and KITE, respectively. Among patients identified as eligible for q12w dosing during the first 12-week interval, 88% and 95% remained on the q12w dosing interval at Week 52.

Treatment effects in evaluable subgroups (i.e. age, gender, baseline HbA1c, baseline visual acuity, baseline central subfield thickness, DME lesion type, duration of DME since diagnosis,

retinal fluid status) in each study were generally consistent with the results in the overall population.

Disease activity (DA) was assessed by changes in visual acuity and/or anatomical parameters, including CST and/or presence of IRF/SRF. Disease activity was assessed throughout the studies. At the first assessment at Week 32, disease activity was observed in 20.1% and 24.2% of patients treated with Pagenax (5 injections received) and 27.8% and 39.8% of patients treated with aflibercept 2 mg (6 injections received) in KESTREL and KITE, respectively.

In both studies, Pagenax demonstrated a significant reduction from baseline in CST starting at Week 4 and continuing up to Week 52. In KITE, the average reduction from baseline over the period Week 40 to Week 52 with Pagenax was statistically superior to that observed with aflibercept 2 mg. From Week 40 to Week 52, the proportion of patients with IRF/SRF was lower in patients treated with Pagenax (range 54% to 65%) compared to patients treated with aflibercept 2 mg (range 71% to 80%).

In both studies, Pagenax demonstrated 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 Best Corrected Visual Acuity (BCVA).

No differences were found between Pagenax and aflibercept 2 mg in changes from baseline to Week 52 in NEI VFQ-25 total score and subscales (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision).

Diabetic retinopathy severity score (DRSS) was assessed in the KESTREL and KITE studies. At baseline, 98.1% of patients in both KESTREL and KITE had gradable DRSS scores. Based on the pooled analysis, 28.9% of patients treated with Pagenax experienced a ≥2 step improvement from baseline to Week 52 in the DRSS score compared to 24.9% of patients treated with aflibercept 2 mg. The estimated difference between Pagenax and aflibercept 2 mg was 4.0% (95% CI: [-0.6, 8.6]).

In silico study

The results of the Pagenax arms of the HAWK and HARRIER studies, where Pagenax was administered every 4 weeks (monthly) for the first 3 doses followed by dosing every 12 or 8 weeks (q12w/q8w), were replicated in a population PK/PD model simulation study where Pagenax was administered every 6 weeks (q6w) for the first 2 doses followed by dosing every 12 or 8 weeks (q12w/q8w).

NON-CLINICAL SAFETY DATA

Carcinogenicity and mutagenicity

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

Repeat dose toxicity

Non-clinical data reveal no special hazard for humans based on 3- and 6-month repeated dose toxicity studies. Intravitreal injections of brolucizumab to cynomolgus monkeys at doses up to 6 mg per eye every 4 weeks for 26 weeks resulted in no ocular or systemic effects and were well-tolerated.

Evaluations included daily observations for morbidity and mortality, clinical observations (including abnormal respiration and behavior), body weight determinations, biomicroscopic and indirect ophthalmoscopic examinations, intraocular pressure measurements, electroretinograms, clinical pathology, toxicokinetic and anti-drug antibody analysis of the serum and vitreous, and macroscopic and microscopic examinations.

The ocular and systemic no observed adverse effect level (NOAEL) with brolucizumab 6 mg per eye every 4 weeks provides a 2-fold margin of ocular safety (based on comparative ocular volume) for the recommended human dose.

INCOMPATIBILITIES

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

STORAGE

Special precautions for storage

See folding box.

Vial

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hours.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Pagenax should not be used after the date marked “EXP” on the pack.

Pagenax must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Instructions for use of the Pagenax vial kit

Storage and inspection

Store Pagenax in the refrigerator (2°C to 8°C/36°F to 46°F); do not freeze. Keep the vial in the outer carton to protect from light.

Prior to use, the unopened vial of Pagenax may be kept at room temperature (below 25°C/77°F) for up to 24 hours. After opening the vial, proceed under aseptic conditions.

Pagenax is a clear to slightly opalescent and colorless to slightly brownish-yellow solution.

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 followed.

The contents of the vial and filter needle are sterile and for single use only. Do not use if the packaging, vial and/or filter needle are damaged or expired.

How to prepare and administer Pagenax

The intravitreal injection procedure must 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) and the availability of sterile paracentesis equipment (if required). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

For preparation and intravitreal injection the following single use medical devices are needed:

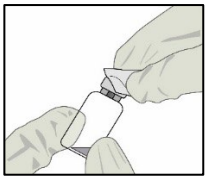
- A 30G x ½" injection needle, sterile.
- A 1 mL syringe with a 0.05 mL dose mark, sterile
- The 5 µm blunt filter needle (18G x 1½", 1.2 mm x 40 mm), sterile

The injection needle and the syringe are not included in the Pagenax vial kit.

Note: The dose must be set to 0.05 mL.

Ensure that the injection is given immediately after preparation of the dose (Step 8).

Injection procedure

1 

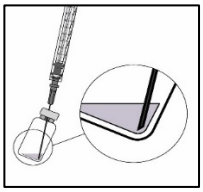
Remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).

2

Assemble the **filter needle** onto a **1 mL syringe** using aseptic technique.

3

Push **the filter needle** into the center of the vial septum until the needle touches the bottom of the vial.

4 

To withdraw the liquid, hold the vial **slightly inclined and slowly withdraw** all the liquid from the vial and filter needle.

Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

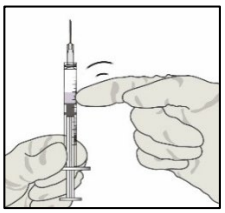
5

Disconnect the filter needle from the syringe in an aseptic manner and dispose of it.

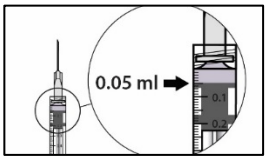
The filter needle is not to be used for intravitreal injection.

6

Aseptically and **firmly assemble a 30G x ½" injection needle** onto the syringe.

7 

To check for air bubbles, hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

8 

Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark. The syringe is ready for the injection.

9

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. **Confirm delivery of the full dose** by checking that the rubber stopper has reached the end of the syringe barrel.

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

Commonly asked questions and answers

Q: What if I have difficulty withdrawing sufficient liquid from the vial?

A: Do not shake the vial before withdrawal but let the liquid settle to the bottom of the vial. Ensure the vial is in an upright, slightly inclined position. **Slowly withdraw** the plunger and wait for the liquid to appear in the syringe barrel. Continue to withdraw slowly to completely empty the vial and the filter needle.

Q: What if I cannot remove all the air bubbles from the liquid?

A: It is important that the liquid is air free. However, tiny air bubbles that are attached to the stopper usually do not detach from the stopper during the injection and therefore do not affect the dose volume.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: July 2022

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