**PRESCRIBING INFORMATION**

RANIBIZUMAB

For use of a Registered Ophthalmologist Only

## 1 GENERIC NAME

Ranibizumab

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL contains 10 mg ranibizumab. Each single use vial of 0.23 mL contains 2.3 mg of ranibizumab.

List of excipients: trehalose dihydrate, L-histidine, polysorbate 20, hydrochloric acid, sodium hydroxide and water for injection

## 3 DOSAGE FORM AND STRENGTH

Solution for injection in single use vial 2.3 mg per 0.23 mL.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Ranibizumab is indicated for the treatment in adult patients with:

- Neovascular (wet) age-related macular degeneration (AMD)
- Diabetic macular edema (DME)
- Macular edema following retinal vein occlusion (RVO)
- Visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM)
- Proliferative diabetic retinopathy (PDR)

Ranibizumab is indicated in preterm infants for treatment of:

- Retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease.

### 4.2 Posology and method of administration

During phase III and phase IV clinical studies in patients with wet AMD, Intas Ranibizumab was administered as 0.5 mg intravitreal injection every 4 weeks for 12 weeks and 24 weeks, respectively.

Information presented below is based on the innovator product.

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

Posology

*Adults*

The recommended dose for ranibizumab is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL. The interval between two doses injected into the same eye should be at least four weeks.

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, ranibizumab should be discontinued.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For PDR and RVO, treatment intervals may also be gradually extended, however, there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly.

The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months;

others may need more frequent treatment, including a monthly injection. For CNV secondary to pathologic myopia (PM), many patients may only need one or two injections during the first year.

*Ranibizumab and laser photocoagulation in DME and in macular oedema secondary to BRVO*
There is some experience of ranibizumab administered concomitantly with laser photocoagulation. When given on the same day, ranibizumab should be administered at least 30 minutes after laser photocoagulation. Ranibizumab can be administered in patients who have received previous laser photocoagulation.

*Ranibizumab and verteporfin photodynamic therapy in CNV secondary to PM*
There is no experience of concomitant administration of ranibizumab and verteporfin.

*Preterm infants*
The recommended dose for ranibizumab in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 ml. In preterm infants treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. Most patients (78%) in the clinical study received one injection per eye. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks.

Method of administration
Single-use vial for intravitreal use only.
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.
Ranibizumab should be inspected visually for particulate matter and discoloration prior to administration.
For information on preparation of ranibizumab, see “Storage and handing instructions”.
The 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) and the availability of sterile paracentesis (if required). The patient’s medical history

for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure. Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection, in accordance with local practice.

*Adults*

The injection needle should be inserted 3.5-4.0 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; a different scleral site should be used for subsequent injections.

*Pediatric population*

In preterm infants, the injection needle should be inserted into the eye 1.0 to 2.0 mm posterior to the limbus, with the needle pointing towards the optic nerve. The injection volume of 0.02 ml is then delivered.

**4.3 Contraindications**

Information presented in this section is based on the innovator product.

- Hypersensitivity to the active substance or to any of the excipients
- Patients with active or suspected ocular or periocular infections
- Patients with active severe intraocular inflammation

**4.4 Special warnings and precautions for use**

Information presented in this section is based on the innovator product.

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.

Intravitreal injection-related reactions

Intravitreous injections, including those with ranibizumab, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following

the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay.

Intraocular pressure increases

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.

Patients should be informed of the symptoms of these potential adverse reactions and instructed to inform their physician if they develop signs 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.

Bilateral treatment

Limited data on bilateral use of ranibizumab (including same-day administration) do not suggest an increased risk of systemic adverse events compared with unilateral treatment.

Immunogenicity

There is a potential for immunogenicity with ranibizumab. Since there is a potential for an increased systemic exposure in subjects with DME, an increased risk for developing hypersensitivity in this patient population cannot be excluded. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.

Concomitant use of other anti-vascular endothelial growth factor (VEGF)

Ranibizumab should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular).

Withholding ranibizumab in adults

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;
- an intraocular pressure of ≥30 mmHg;
- a retinal break;
- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥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 and potentially also other forms of CNV, include a large and/or high pigment epithelial retinal detachment. When initiating ranibizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Rhegmatogenous retinal detachment or macular holes in adults

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

Paediatric population

The warnings and precautions for adults also apply to preterm infants with ROP. Long-term safety in preterm infants with ROP has been studied for 2 years and showed no new safety signals. The safety profile in preterm infants has not been established beyond 2 years.

Populations with limited data

There is only limited experience in the treatment of subjects with DME due to type 1 diabetes. Ranibizumab has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, proliferative diabetic retinopathy, or in patients with concurrent eye conditions, such as retinal detachment or macular hole. There is limited experience of treatment with ranibizumab in diabetic patients with glycosylated hemoglobin (HbA1c) over 12% and no experience in patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

There are insufficient data to conclude on the effect of ranibizumab in patients with RVO presenting irreversible ischaemic visual function loss.

In patients with PM, there are limited data on the effect of ranibizumab in patients who have previously undergone unsuccessful verteporfin photodynamic therapy (vPDT) treatment. Also, while a consistent effect was observed in subjects with subfoveal and juxtafoveal lesions, there are insufficient data to conclude on the effect of ranibizumab in PM subjects with extrafoveal lesions.

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.

There are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients.

**4.5 Drug interactions**

Information presented in this section is based on the innovator product.

No formal interaction studies have been performed.

For the adjunctive use of laser photocoagulation and ranibizumab in DME and BRVO, see "Posology and method of administration".

In clinical studies for the treatment of visual impairment due to DME, the outcome with regard to visual acuity or central retinal subfield thickness (CSFT) in patients treated with ranibizumab was not affected by concomitant treatment with thiazolidinediones.

Paediatric population

No interaction studies have been performed.

**4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)**

Information presented in this section is based on the innovator product.

Hepatic impairment

Ranibizumab has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population.

Renal impairment

Dose adjustment is not needed in patients with renal impairment.

Elderly

No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME.

Paediatric population

The safety and efficacy of ranibizumab in children and adolescents below 18 years of age for indications other than retinopathy of prematurity have not been established.

Women of childbearing potential/ contraception in females

Women of childbearing potential should use effective contraception during treatment.

Pregnancy

For ranibizumab, no clinical data on exposed pregnancies are available. Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/ foetal development. The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

Breast-feeding

It is unknown whether ranibizumab is excreted in human milk. Breast-feeding is not recommended during the use of ranibizumab.

Fertility

There are no data available on fertility.

## 4.7 Effects on ability to drive and use machines

Information presented in this section is based on the innovator product.

The treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines. Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

## 4.8 Undesirable effects

Information provided below is based on studies conducted with Intas Ranibizumab.

In prospective, comparative, assessor-blind, randomized (in 3:1 ratio to Intas Ranibizumab:Lucentis®), multicenter (21 centers across India), phase III study, 104 patients with wet AMD were administered with intravitreal injection of 0.5 mg Intas Ranibizumab (n=78) or Lucentis (n=26; manufactured by Novartis Pharma AG, Basel), every 4 weeks for 12 weeks. Total 13 adverse events (AEs) were reported during the study: 10 in patients treated with Intas Ranibizumab and 3 in patients treated with Lucentis (Table 1). All AEs were mild to moderate in severity. No serious AE (SAE) was reported during the study.

**Table 1: Adverse Events Reported During Phase III Clinical Study of Intas Ranibizumab**

| | **Incidence** | |
|---|---|---|
| **System organ class**<br>**Adverse event** | **Intas Ranibizumab**<br>**(n=78)** | **Lucentis**<br>**(n=26)** |
| Eye disorders | | |
| Increase intraocular pressure | 1 | - |
| Pain in eye | - | 1 |
| Hypopigmentation with scar at macula | 1 | - |
| Stromal infection (both eye) | 1 | - |
| Allergic conjunctivitis | - | 1 |
| Nervous system disorders | | |
| Paresthesia | 1 | - |
| Hallucinations | 1 | - |
| Gastrointestinal disorders | | |
| Diarrhea | 1 | - |
| Cardiac disorders | | |

| | Incidence | |
|---|---|---|
| **System organ class**<br>**Adverse event** | **Intas Ranibizumab**<br>**(n=78)** | **Lucentis**<br>**(n=26)** |
| Sick sinus syndrome | 1 | - |
| Respiratory, thoracic and mediastinal disorders | | |
| Common cold | 1 | - |
| Skin and subcutaneous tissue disorders | | |
| Itching | 1 | - |
| Folliculitis | 1 | - |
| Hypopigmented patch on hand | - | 1 |

In a prospective, multicenter, phase IV study, 126 patients with wet AMD were administered with intravitreal injection of 0.5 mg Intas Ranibizumab every 4 weeks for 24 weeks. Total 19 AEs were reported by 16 (12.70%) patients during the study. Of 19 AEs, 15 AEs were mild, 3 AEs were moderate and 1 AE was severe in nature. All AEs resolved except one AE of death. The causality assessment for death was judged as unlikely to the study drug. There were no other serious or significant AEs during the study. All the AEs are summarized by system organ class (SOC) and preferred term in the Table 2 below.

**Table 2: Adverse Events Reported During Phase IV Clinical Study of Intas Ranibizumab**

| **System organ class** | **MedDRA (PT) (Version 19.0)** | **n (%) e** |
|---|---|---|
| Eye disorders | Corneal oedema | 1 (0.79%) 1 |
| | Dry eye | 1 (0.79%) 1 |
| | Eye pruritus | 2 (1.59%) 2 |
| | Iridocyclitis | 1 (0.79%) 1 |
| | Ocular hyperaemia | 1 (0.79%) 1 |
| General disorders and administration site conditions | Death | 1 (0.79%) 1 |
| | Pyrexia | 5 (3.97%) 5 |
| Infections and infestations | Nasopharyngitis | 1 (0.79%) 1 |
| Investigations | Blood pressure increased | 1 (0.79%) 1 |
| | Intraocular pressure increased | 3 (2.38%) 4 |
| Nervous system disorders | Headache | 1 (0.79%) 1 |
| **Total** | | **16 (12.70%) 19** |

| System organ class | MedDRA (PT) (Version 19.0) | n (%) e |
|---|---|---|

n = Number of patient in respective categories;

e = Number of events

*Immunogenicity*

During the phase III clinical study of Intas Ranibizumab in patients with wet AMD, blood sample were collected for immunogenicity assessment at baseline visit and end of study visit. Out of 198 samples tested, no sample was positive for anti-drug antibody against ranibizumab.

During the phase IV clinical study of Intas Ranibizumab in patients with wet AMD, blood samples were collected for immunogenicity assessment at baseline visit, at week 2, week 4, week 6, week 8, week 12, week 16, week 20 and week 24 (or end of study visit). Of the 126 patients, 19 (15.1%) patients were confirmed positive for anti-ranibizumab antibodies for at least one time-point. Of these confirmed-positive patients, 10 (7.9%) patients were positive at pre-dose and 9 (7.1%) patients were positive at post-dose time-points.

Information presented below is based on the innovator product.

Summary of the safety profile

The majority of adverse reactions reported following administration of ranibizumab are related to the intravitreal injection procedure.

The most frequently reported ocular adverse reactions following injection of ranibizumab are: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus.

The most frequently reported non-ocular adverse reactions are headache, nasopharyngitis and arthralgia.

Less frequently reported, but more serious, adverse reactions include endophthalmitis, blindness, retinal detachment, retinal tear and iatrogenic traumatic cataract.

The adverse reactions experienced following administration of ranibizumab in clinical trials are summarised in Table 3.

Tabulated list of adverse reactions[#]

The adverse reactions are listed by system organ class and frequency using the following convention: 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) not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 3: Adverse Reactions Reported During Clinical Studies of Ranibizumab**

| | |
|---|---|
| Infections and infestations | |
| *Very common* | Nasopharyngitis |
| *Common* | Urinary tract infection* |
| Blood and lymphatic system disorders | |
| *Common* | Anaemia |
| Immune system disorders | |
| *Common* | Hypersensitivity |
| Psychiatric disorders | |
| *Common* | Anxiety |
| Nervous system disorders | |
| *Very common* | Headache |
| Eye disorders | |
| *Very common* | Vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus. |
| *Common* | Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia. |
| *Uncommon* | Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. |

| | |
|---|---|
| Respiratory, thoracic and mediastinal disorders | |
| *Common* | Cough |
| Gastrointestinal disorders | |
| *Common* | Nausea |
| Skin and subcutaneous tissue disorders | |
| *Common* | Allergic reactions (rash, urticaria, pruritus, erythema) |
| Musculoskeletal and connective tissue disorders | |
| *Very common* | Arthralgia |
| Investigations | |
| *Very common* | Intraocular pressure increased |

# Adverse reactions were defined as adverse events (in at least 0.5 percentage points of patients) which occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with ranibizumab 0.5 mg than in those receiving control treatment (sham or verteporfin PDT).

* observed only in DME population

Product-class-related adverse reactions

In the wet AMD phase III studies, the overall frequency of non-ocular haemorrhages, an adverse event potentially related to systemic VEGF inhibition, was slightly increased in ranibizumab-treated patients. However, there was no consistent pattern among the different haemorrhages. 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 ranibizumab clinical trials in patients with AMD, CNV, DME, PDR and RVO, and there were no major differences between the groups treated with ranibizumab compared to control.

Paediatric population

The safety of ranibizumab 0.2 mg was studied in a 6-month clinical trial, which included 73 preterm infants with ROP treated with ranibizumab 0.2 mg. Ocular adverse reactions reported in more than one patient treated with ranibizumab 0.2 mg were retinal haemorrhage and conjunctival haemorrhage. Non-ocular adverse reactions reported in more than one patient treated with ranibizumab 0.2 mg were nasopharyngitis, anaemia, cough, urinary tract infection and allergic

reactions. Adverse reactions established for adult indications are considered applicable to preterm infants with ROP, though not all were observed in the clinical trial. Long-term safety in preterm infants with ROP has been studied for 2 years in the clinical trial extension trial and showed no new safety signals. The safety profile in preterm infants has not been established beyond 2 years.

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. Healthcare professionals are asked to report any suspected adverse reactions.

### 4.9 Overdose

Information presented in this section is based on the innovator product.

Cases of accidental overdose have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions associated with these reported cases were intraocular pressure increased, transient blindness, reduced visual acuity, corneal oedema, corneal pain, and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Mechanism of action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the 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. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.

### 5.2 Pharmacodynamic properties

**Pharmacotherapeutic group**

Ophthalmologicals, antineovascularisation agents

**ATC code**

S01LA04

**Clinical efficacy**

Information presented below is based on the study conducted with Intas Ranibizumab.

Efficacy and safety profile of Intas Ranibizumab and Lucentis (manufactured by Novartis Pharma AG, Basel) was evaluated during the prospective, comparative, assessor-blind, randomized, multicentre phase 3 study in patients with wet AMD. Total 104 patients were administered with intravitreal injection of 0.5 mg Intas Ranibizumab (n=78) or Lucentis (n=26), every 4 weeks for 12 weeks. The primary efficacy endpoint was proportion of patients who loses fewer than15 letters (approximately 3 lines) from baseline visual acuity. Secondary efficacy endpoints were: mean increase in best corrected visual acuity (BCVA) from baseline in the study eye at end study visit, and change in central retinal thickness in the study eye compared to baseline, measured by optical coherence tomography (OCT).

The primary efficacy endpoint was achieved in 98.7% patients treated with Intas Ranibizumab and in 100% patients treated with Lucentis at the end of 12-week study period (estimated difference: -1.3%; 95% CI: -3.83, 1.23; *p*=0.5593). Mean increase in BCVA from baseline to 12 weeks was 7.99 in Intas Ranibizumab group versus 8.65 in Lucentis group (estimated difference: -0.67; 95% CI: -4.76, 3.42; *p*=0.7470). Mean (SD) BCVA improved from 42.74 (15.68) at baseline to 50.72 (18.4) at week 12 in Intas Ranibizumab group and from 45.57 (16.14) at baseline to 54.23 (18.16) at week 12 in Lucentis group. Similarly, mean decrease in central retinal thickness from baseline to 12 weeks was 124.43 μm in Intas Ranibizumab group versus 89.88 μm in Lucentis group (estimated difference: 34.54; 95% CI: -22.07, 91.15; *p*=0.2289). Mean (SD) central retinal thickness improved from 374.40 (137.19) at baseline to 249.97 (84.05) at week 12 in Intas Ranibizumab group and from 358.88 (154.77) at baseline to 269 (113.37) at week 12 in Lucentis group.

Safety and efficacy of Intas Ranibizumab was evaluated during the prospective, multicentre phase IV study in patients with wet AMD. Total 126 patients were administered with intravitreal

injection of 0.5 mg Intas Ranibizumab every 4 weeks for 24 weeks. Safety and immunogenicity evaluations were primary objectives and efficacy evaluation was a secondary objective of this study. Following Intas Ranibizumab injection, 97% patients lost <15 letters from baseline to month 12. There was statistically significant improvement in best-corrected visual acuity, central retinal thickness and visual functional questionnaire-25 score from baseline to month 24.

Pediatric population

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

**5.3 Pharmacokinetic properties**

Information presented in this section is based on the innovator product.

Following monthly intravitreal administration of ranibizumab to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels ($C_{max}$) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/mL, as assessed in an *in vitro* cellular proliferation assay). $C_{max}$ was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Serum concentrations in a limited number of DME patients indicate that a slightly higher systemic exposure cannot be excluded compared to those observed in neovascular AMD patients. Serum ranibizumab concentrations in RVO patients were similar or slightly higher compared to those observed in neovascular AMD patients.

Based on analysis of population pharmacokinetics and disappearance of ranibizumab from serum for patients with neovascular AMD treated with the 0.5 mg dose, the average vitreous elimination half-life of ranibizumab is approximately 9 days. Upon monthly intravitreal administration of ranibizumab 0.5 mg/eye, serum ranibizumab $C_{max}$, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/mL, and $C_{min}$ is predicted to generally range between 0.07 and 0.49 ng/mL. Serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal ranibizumab concentrations.

*Patients with renal impairment*

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (136 of 200) of patients had renal impairment (46.5% mild [50-80 mL/min], 20%

moderate [30-50 mL/min], and 1.5% severe [<30 mL/min]). In RVO patients, 48.2% (253 of 525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). Systemic clearance was slightly lower, but this was not clinically significant.

*Patients with hepatic impairment*

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with hepatic impairment.

Paediatric population

Following intravitreal administration of ranibizumab to preterm infants with ROP at a dose of 0.2 mg (per eye), serum ranibizumab concentrations were higher than those observed in neovascular AMD adult patients receiving 0.5 mg in one eye. Based on a population pharmacokinetic analysis, the differences in $C_{max}$ and $AUC_{inf}$ were approximately 16-fold and 12-fold higher, respectively. The apparent systemic half-life was approximately 6 days. A PK/PD analysis showed no clear relationship between systemic ranibizumab concentrations and systemic VEGF concentrations.

## 6 NONCLINICAL PROPERTIES

### 6.1 Animal toxicology or pharmacology

Information presented below is based on studies conducted with Intas Ranibizumab.

In acute toxicity studies, maximum tolerated dose (MTD) of Intas Ranibizumab was more than 3 mg/kg body weight in mice and more than 1.5 mg/kg body weight in rats when administered by intramuscular and subcutaneous routes. In a 28-day repeat-dose toxicity study in rats, no observed effect level (NOAEL) of Intas Ranibizumab was 250 mcg/kg body weight when administered as once weekly injection by subcutaneous route. In a comparative 28-day repeat-dose toxicity study in rabbits, NOAEL of Intas Ranibizumab was 125 mcg/kg body weight when administered as once weekly injection by intravitreous route. In local tolerance studies, Intas Ranibizumab was non-sensitizer in guinea pigs and non-irritant in rabbits.

Information presented below is based on the innovator product.

Bilateral intravitreal administration of ranibizumab to cynomolgus monkeys at doses between 0.25 mg/eye and 2.0 mg/eye once every 2 weeks for up to 26 weeks resulted in dose-dependent ocular effects.

Intraocularly, there were dose-dependent increases in anterior chamber flare and cells with a peak 2 days after injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery. In the posterior segment, there were vitreal cell infiltration and floaters, which also tended to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study, the severity of the vitreous inflammation increased with the number of injections. However, evidence of reversibility was observed after recovery. The nature and timing of the posterior segment inflammation is suggestive of an immune-mediated antibody response, which may be clinically irrelevant. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were secondary to severe inflammation. A transient increase in post-dose intraocular pressure was observed following intravitreal injections, irrespective of dose.

Microscopic ocular changes were related to inflammation and did not indicate degenerative processes. Granulomatous inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished, and in some instances resolved, during the recovery period. Following intravitreal administration, no signs of systemic toxicity were detected. Serum and vitreous antibodies to ranibizumab were found in a subset of treated animals.

No carcinogenicity or mutagenicity data are available.

In pregnant monkeys, intravitreal ranibizumab treatment resulting in maximal systemic exposures 0.9-7-fold a worst case clinical exposure did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, although, based on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and embryo-/foetotoxic.

The absence of ranibizumab-mediated effects on embryo-foetal development is plausibly related mainly to the inability of the Fab fragment to cross the placenta. Nevertheless, a case was described with high maternal ranibizumab serum levels and presence of ranibizumab in foetal serum, suggesting that the anti-ranibizumab antibody acted as (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer. As the embryo-foetal development investigations were performed in healthy pregnant animals and

disease (such as diabetes) may modify the permeability of the placenta towards a Fab fragment, the study should be interpreted with caution.

## 7 DESCRIPTION

Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kilodaltons and is produced by an *Escherichia coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product. Ranibizumab is a sterile, clear and colorless to pale yellow solution in a single use glass vial.

## 8 PHARMACEUTICAL PARTICULARS

### 8.1 Incompatibilities

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

### 8.2 Shelf-life

36 months

### 8.3 Packaging information

Single Vial Pack

Ranibizumab is supplied in a 0.23 mL vial containing 2.3 mg ranibizumab solution for intravitreal injection (10 mg/mL). In addition, each carton contains one filter needle (18G × 1½", 5 µm) for withdrawal of vial contents, one injection needle (30G × ½") for intravitreal injection, one syringe (1 mL) for withdrawal of vial content and a package insert.

Multiple Vial Pack

Ranibizumab is supplied in a 0.23 mL vial containing 2.3 mg ranibizumab solu tion for intravitreal injection (10 mg/mL). In addition, each carton contains one filter needle (18G × 1½", 5 µm) for

withdrawal of vial contents, one injection needle (30G × ½") for intravitreal injection and a package insert.

**8.4 Storage and handing instructions**

Store in a refrigerator (2°C - 8°C) in carton to protect from light.

Do not freeze.

Keep out of the reach and sight of children.

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

**Special precautions for disposal and other handling**

Vial + injection kit

The vial, injection needle, filter needle and syringe are for single use only. Re-use may lead to infection or other illness/ injury. All components are sterile. Any component with packaging showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the component packaging seal remains intact.

Multiple Vial Pack

The vial, injection needle, and filter needle are for single use only. Re-use may lead to infection or other illness/ injury. All components are sterile. Any component with packaging showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the component packaging seal remains intact.

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

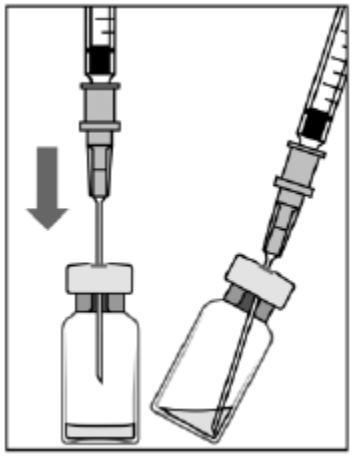
- a 5 µm filter needle (18G × 1½″)
- a 1 mL sterile syringe (including a 0.05 mL mark)
- an injection needle (30G × ½″)

Use in adult population:

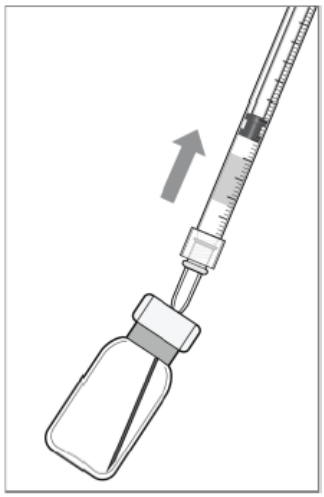
To prepare Intas Ranibizumab for intravitreal administration **to adults**, please adhere to the following instructions:

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.
2. Assemble a 5 µm filter needle (18G × 1½″) onto a 1 mL syringe using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.

3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

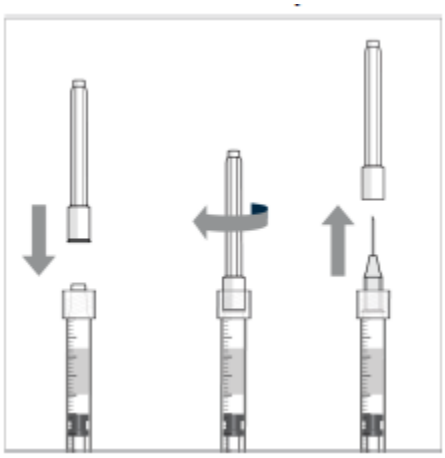


4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

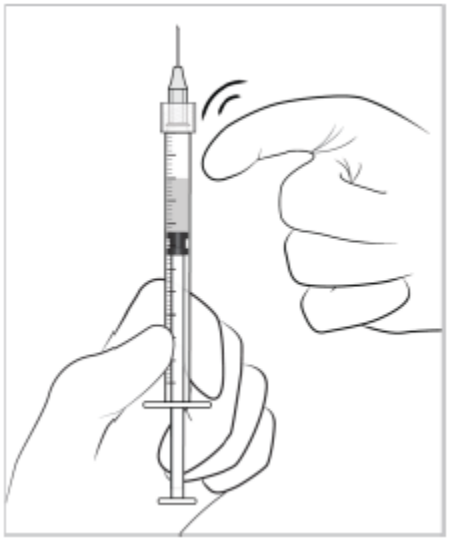


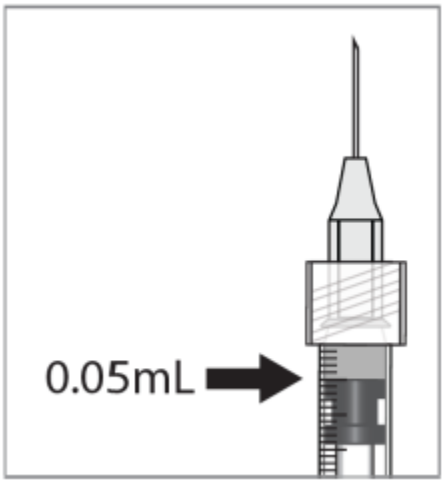
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.
6. Aseptically and firmly assemble an injection needle (30G × ½″) onto the syringe.
7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

   Note: Grip at the hub of the injection needle while removing the cap.



8. Carefully expel the air along with the excess solution and adjust the dose to the 0.05 mL mark on the syringe. The syringe is ready for injection.
   Note: Do not wipe the injection needle. Do not pull back on the plunger.



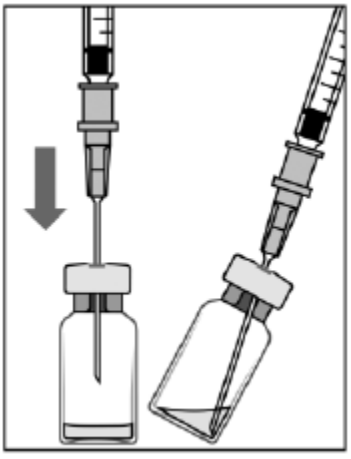



After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

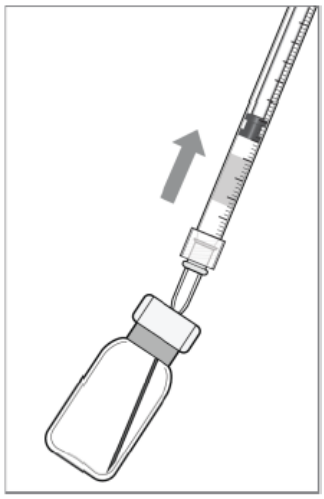
Use in pediatric population:

To prepare Intas Ranibizumab for intravitreal administration **to preterm infants**, please adhere to the following instructions:

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.
2. Assemble a 5 µm filter needle (18G × 1½″) onto a 1 mL syringe using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.
3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

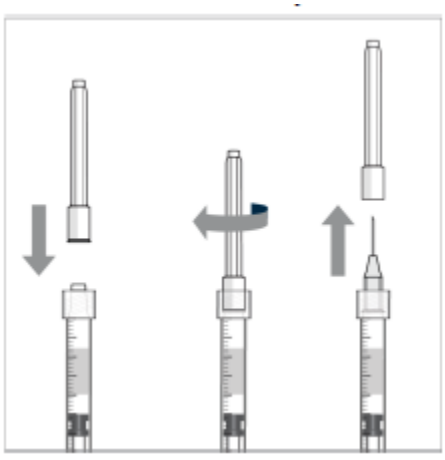


4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.



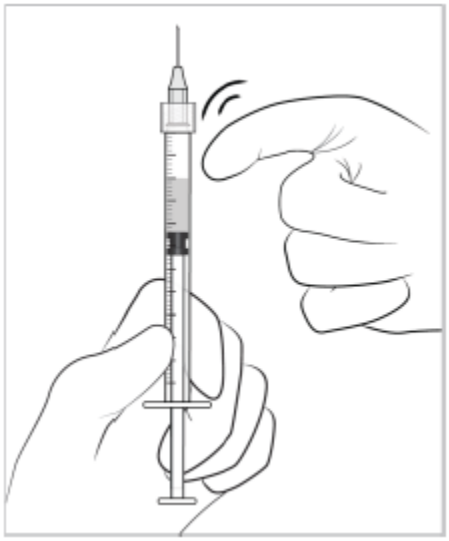
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.
6. Aseptically and firmly assemble an injection needle (30G × ½″) onto the syringe.
7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

   Note: Grip at the hub of the injection needle while removing the cap.



8. Carefully expel the air along with the excess solution and adjust the dose to the 0.02 mL mark on the syringe. The syringe is ready for injection.

Note: Do not wipe the injection needle. Do not pull back on the plunger.



After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

## 9 PATIENT COUNSELLING INFORMATION

Advise patients that in the days following ranibizumab administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist.

## 10 DETAILS OF MANUFACTURER

Intas Pharmaceuticals Limited
Plot no. 423/P/A, Sarkhej – Bavla Highway,
Village – Moraiya, Taluka – Sanand,
District – Ahmedabad, Gujarat – 382213, India.

## 11 DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Permission number: MF-35/2015;
Date of approval: 20-Feb-2015

## 12 VERSION NUMBER & DATE OF REVISION

Version 03

Revised in Aug 2022