**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Lucentis 10 mg/ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg ranibizumab*. Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab to adult patients and a single dose of 0.02 ml containing 0.2 mg ranibizumab to preterm infants.

*Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to pale brownish-yellow aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lucentis is indicated in adults for:
- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

Lucentis is indicated in preterm infants for:
- The 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

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

Posology

*Adults*
The recommended dose for Lucentis in adults 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 in adults 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, Lucentis 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 (see section 5.1).

*Lucentis and laser photocoagulation in DME and in macular oedema secondary to BRVO*
There is some experience of Lucentis administered concomitantly with laser photocoagulation (see section 5.1). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation.

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

*Preterm infants*
The recommended dose for Lucentis 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 24-week RAINBOW clinical study received one injection per eye. Patients who were treated with 0.2 mg in this clinical study did not require additional treatment in the subsequent long-term extension study which followed the patients up to five years of age (see section 5.1). 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.

*Special populations*
*Hepatic impairment*
Lucentis 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 (see section 5.2).

*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 Lucentis in children and adolescents below 18 years of age for indications other than retinopathy of prematurity have not been established. Available data in adolescent patients aged 12 to 17 years with visual impairment due to CNV are described in section 5.1 but no recommendation on a posology can be made.

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 for adults and 0.02 ml for preterm infants), a portion of the volume contained in the vial must be discarded prior to administration.

Lucentis should be inspected visually for particulate matter and discoloration prior to administration.

For information on preparation of Lucentis, see section 6.6.

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 (see section 4.4). 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*
In 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.

*Paediatric population*
For treatment of preterm infants the low volume high accuracy syringe provided together with an injection needle (30G x ½″) in the VISISURE kit should be used (see also section 6.6).

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

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 severe 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.

Intravitreal injection-related reactions

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

In adults transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis. Sustained IOP increases have also been identified (see section 4.8). 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 (see section 4.8).

Bilateral treatment

Limited data on bilateral use of Lucentis (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 Lucentis. 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-VEGF (vascular endothelial growth factor)

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

Withholding Lucentis 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 in the RAINBOW extension study up to the age of five years old. The safety profile of ranibizumab 0.2 mg during the extension study was consistent with that observed in the core study at 24 weeks (see section 4.8).

Populations with limited data

There is only limited experience in the treatment of subjects with DME due to type I diabetes. Lucentis has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is limited experience of treatment with Lucentis in diabetic patients with an HbA1c over 108 mmol/mol (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 Lucentis in patients with RVO presenting irreversible ischaemic visual function loss.

In patients with PM, there are limited data on the effect of Lucentis 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 Lucentis 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 (see section 4.8).

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

For the adjunctive use of verteporfin photodynamic therapy (PDT) and Lucentis in wet AMD and PM, see section 5.1.

For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see sections 4.2 and 5.1.

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 Lucentis was not affected by concomitant treatment with thiazolidinediones.

Paediatric population

No interaction studies have been performed.

## 4.6 Fertility, pregnancy and lactation

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 (see section 5.3). 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

Based on very limited data, ranibizumab may be excreted in human milk at low levels. The effect of ranibizumab on a breast-fed newborn/infant is unknown. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis.

Fertility

There are no data available on fertility.

## 4.7 Effects on ability to drive and use machines

The treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see section 4.8). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

## 4.8 Undesirable effects

Summary of the safety profile

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

The most frequently reported ocular adverse reactions following injection of Lucentis 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 (see section 4.4).

The adverse reactions experienced following administration of Lucentis in clinical studies are summarised in the table below.

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.

| | |
|---|---|
| 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 Lucentis 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 (vascular endothelial growth factor) 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 Lucentis clinical studies in patients with AMD, DME, PDR, RVO and CNV and there were no major differences between the groups treated with ranibizumab compared to control.

Paediatric population

The safety of Lucentis 0.2 mg was studied in a 6-month clinical study (RAINBOW), which included 73 preterm infants with ROP treated with ranibizumab 0.2 mg (see section 5.1). 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 RAINBOW study.

Long-term safety in preterm infants with ROP has been studied up to the age of five years old in the RAINBOW extension study and showed no new safety signals. The safety profile of ranibizumab 0.2 mg during the extension study was consistent with that observed in the core study at 24 weeks.

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 via the national reporting system listed in Appendix V.

## 4.9 Overdose

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 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antineovascularisation agents, ATC code: S01LA04

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 in adults and retinopathy of prematurity in preterm infants.

Clinical efficacy and safety

*Treatment of wet AMD*
In wet AMD, the clinical safety and efficacy of Lucentis have been assessed in three randomised, double-masked, sham- or active-controlled studies of 24 months duration in patients with neovascular AMD. A total of 1,323 patients (879 active and 444 control) were enrolled in these studies.

In study FVF2598g (MARINA), 716 patients with minimally classic or occult with no classic lesions were randomised in a 1:1:1 ratio to receive monthly injections of Lucentis 0.3 mg, Lucentis 0.5 mg or sham.

In study FVF2587g (ANCHOR), 423 patients with predominantly classic CNV lesions were randomised in a 1:1:1 ratio to receive Lucentis 0.3 mg monthly, Lucentis 0.5 mg monthly or verteporfin PDT (at baseline and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage).

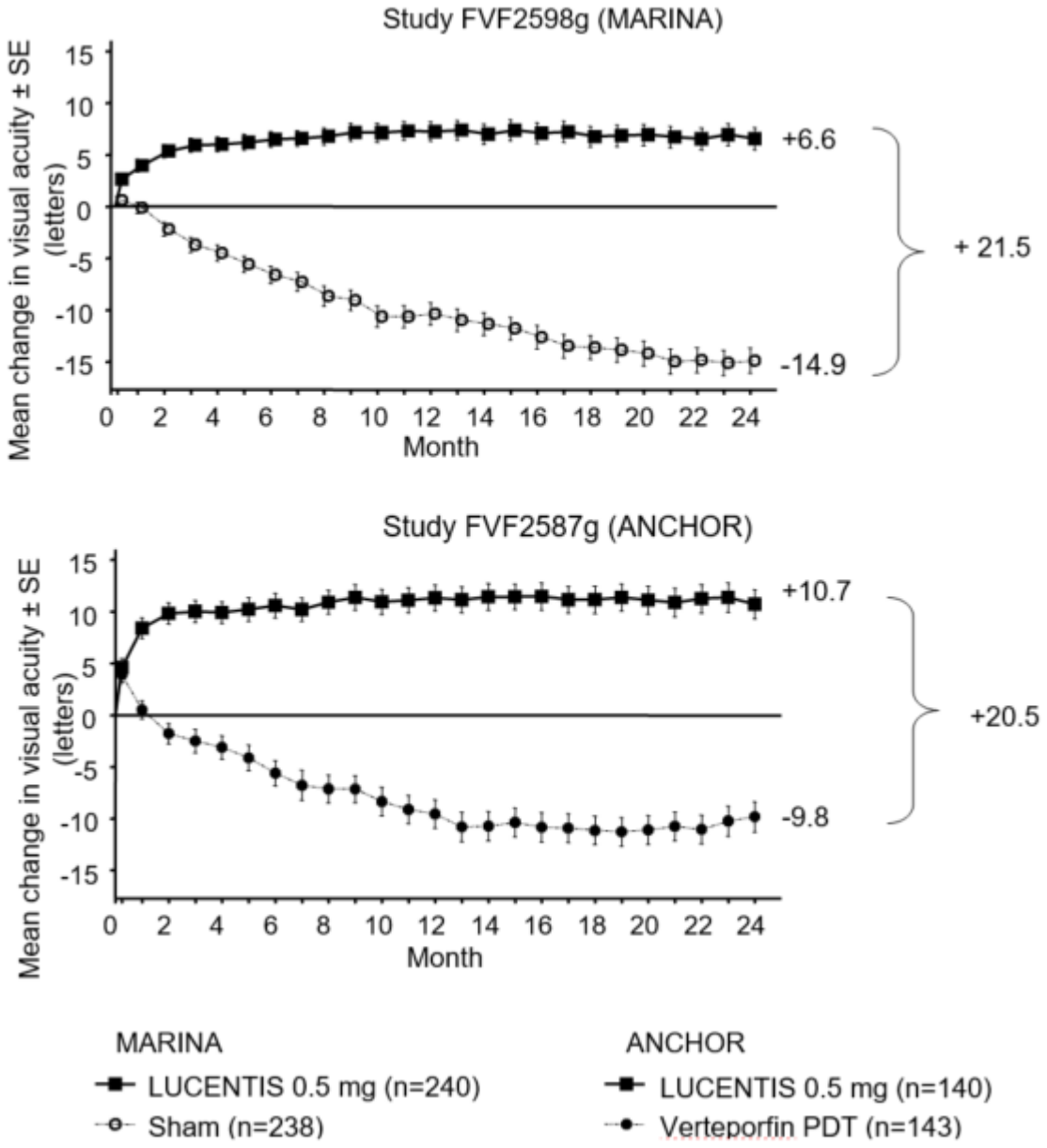
Key outcome measures are summarised in Table 1 and Figure 1.

**Table 1 Outcomes at Month 12 and Month 24 in study FVF2598g (MARINA) and FVF2587g (ANCHOR)**

| | | FVF2598g (MARINA) | | FVF2587g (ANCHOR) | |
|---|---|---|---|---|---|
| Outcome measure | Month | Sham (n=238) | Lucentis 0.5 mg (n=240) | Verteporfin PDT (n=143) | Lucentis 0.5 mg (n=140) |
| Loss of <15 letters in visual acuity (%)[a] (maintenance of vision, primary endpoint) | Month 12 | 62% | 95% | 64% | 96% |
| | Month 24 | 53% | 90% | 66% | 90% |
| Gain of ≥15 letters in visual acuity (%)[a] | Month 12 | 5% | 34% | 6% | 40% |
| | Month 24 | 4% | 33% | 6% | 41% |
| Mean change in visual acuity (letters) (SD)[a] | Month 12 | -10.5 (16.6) | +7.2 (14.4) | -9.5 (16.4) | +11.3 (14.6) |
| | Month 24 | -14.9 (18.7) | +6.6 (16.5) | -9.8 (17.6) | +10.7 (16.5) |

[a] $p<0.01$

**Figure 1 Mean change in visual acuity from baseline to Month 24 in study FVF2598g (MARINA) and study FVF2587g (ANCHOR)**




Results from both studies indicated that continued ranibizumab treatment may also be of benefit in patients who lost ≥15 letters of best-corrected visual acuity (BCVA) in the first year of treatment.

Statistically significant patient-reported visual functioning benefits were observed in both MARINA and ANCHOR with ranibizumab treatment over the control group as measured by the NEI VFQ-25.

In study FVF3192g (PIER), 184 patients with all forms of neovascular AMD were randomised in a 1:1:1 ratio to receive Lucentis 0.3 mg, Lucentis 0.5 mg or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months. From Month 14 of the study, sham-treated patients were allowed to receive ranibizumab and from Month 19, more frequent treatments were possible. Patients treated with Lucentis in PIER received a mean of 10 total treatments.

After an initial increase in visual acuity (following monthly dosing), on average, patients' visual acuity declined with quarterly dosing, returning to baseline at Month 12 and this effect was maintained in most ranibizumab-treated patients (82%) at Month 24. Limited data from sham subjects who later received ranibizumab suggested that early initiation of treatment may be associated with better preservation of visual acuity.

Data from two studies (MONT BLANC, BPD952A2308 and DENALI, BPD952A2309) conducted post approval confirmed the efficacy of Lucentis but did not demonstrate additional effect of the combined administration of verteporfin (Visudyne PDT) and Lucentis compared to Lucentis monotherapy.

*Treatment of visual impairment due to CNV secondary to PM*

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV in PM have been assessed based on the 12-month data of the double-masked, controlled pivotal study F2301 (RADIANCE). In this study 277 patients were randomised in a 2:2:1 ratio to the following arms:

- Group I (ranibizumab 0.5 mg, dosing regimen driven by "stability" criteria defined as no change in BCVA compared to two preceding monthly evaluations).
- Group II (ranibizumab 0.5 mg, dosing regimen driven by "disease activity" criteria defined as vision impairment attributable to intra- or subretinal fluid or active leakage due to the CNV lesion as assessed by optical coherence tomography and/or fluorescence angiography).
- Group III (vPDT - patients were allowed to receive ranibizumab treatment as of Month 3).

In Group II, which is the recommended posology (see section 4.2), 50.9% of patients required 1 or 2 injections, 34.5% required 3 to 5 injections and 14.7% required 6 to 12 injections over the 12-month study period. 62.9% of Group II patients did not require injections in the second 6 months of the study.

The key outcomes from RADIANCE are summarised in Table 2 and Figure 2.

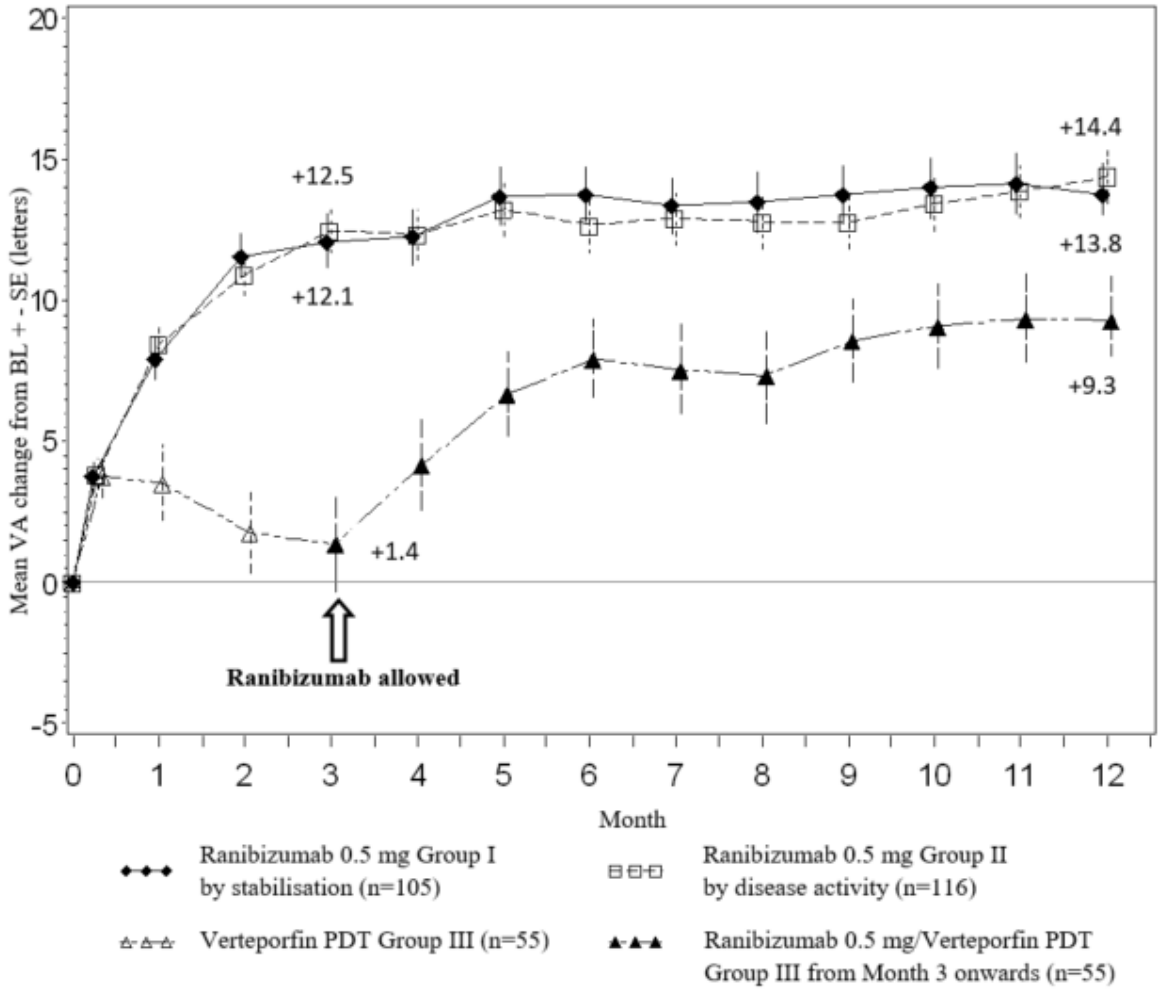
**Table 2 Outcomes at Month 3 and 12 (RADIANCE)**

| | **Group I Ranibizumab 0.5 mg "vision stability" (n=105)** | **Group II Ranibizumab 0.5 mg "disease activity" (n=116)** | **Group III vPDT[b] (n=55)** |
|---|---|---|---|
| **Month 3** | | | |
| Mean average BCVA change from Month 1 to Month 3 compared to baseline[a] (letters) | +10.5 | +10.6 | +2.2 |
| Proportion of patients who gained: ≥15 letters, or reached ≥84 letters in BCVA | 38.1% | 43.1% | 14.5% |
| **Month 12** | | | |
| Number of injections up to Month 12: | | | |
| Mean | 4.6 | 3.5 | N/A |
| Median | 4.0 | 2.5 | N/A |
| Mean average BCVA change from Month 1 to Month 12 compared to baseline (letters) | +12.8 | +12.5 | N/A |
| Proportion of patients who gained: ≥15 letters, or reached ≥84 letters in BCVA | 53.3% | 51.7% | N/A |

[a] $p<0.00001$ comparison with vPDT control

[b] Comparative control up to Month 3. Patients randomised to vPDT were allowed to receive ranibizumab treatment as of Month 3 (in Group III, 38 patients received ranibizumab as of Month 3)

**Figure 2 Mean change from baseline BCVA over time to Month 12 (RADIANCE)**




The improvement of vision was accompanied by a reduction in central retinal thickness.

Patient-reported benefits were observed with ranibizumab treatment arms over vPDT (p-value <0.05) in terms of improvement in the composite score and several subscales (general vision, near activities, mental health and dependency) of the NEI VFQ-25.

*Treatment of visual impairment due to CNV (other than secondary to PM and wet AMD)*
The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV have been assessed based on the 12-month data of the double-masked, sham-controlled pivotal study G2301 (MINERVA). In this study 178 adult patients were randomised in a 2:1 ratio to receive:

- ranibizumab 0.5 mg at baseline, followed by an individualised dosing regimen driven by disease activity as assessed by visual acuity and/or anatomical parameters (e.g. visual acuity impairment, intra/sub-retinal fluid, haemorrhage or leakage);
- sham injection at baseline, followed by an individualised treatment regimen driven by disease activity.

At Month 2, all patients received open-label treatment with ranibizumab as needed.

Key outcome measures from MINERVA are summarised in Table 3 and Figure 3. An improvement of vision was observed and was accompanied by a reduction in central subfield thickness over the 12-month period.

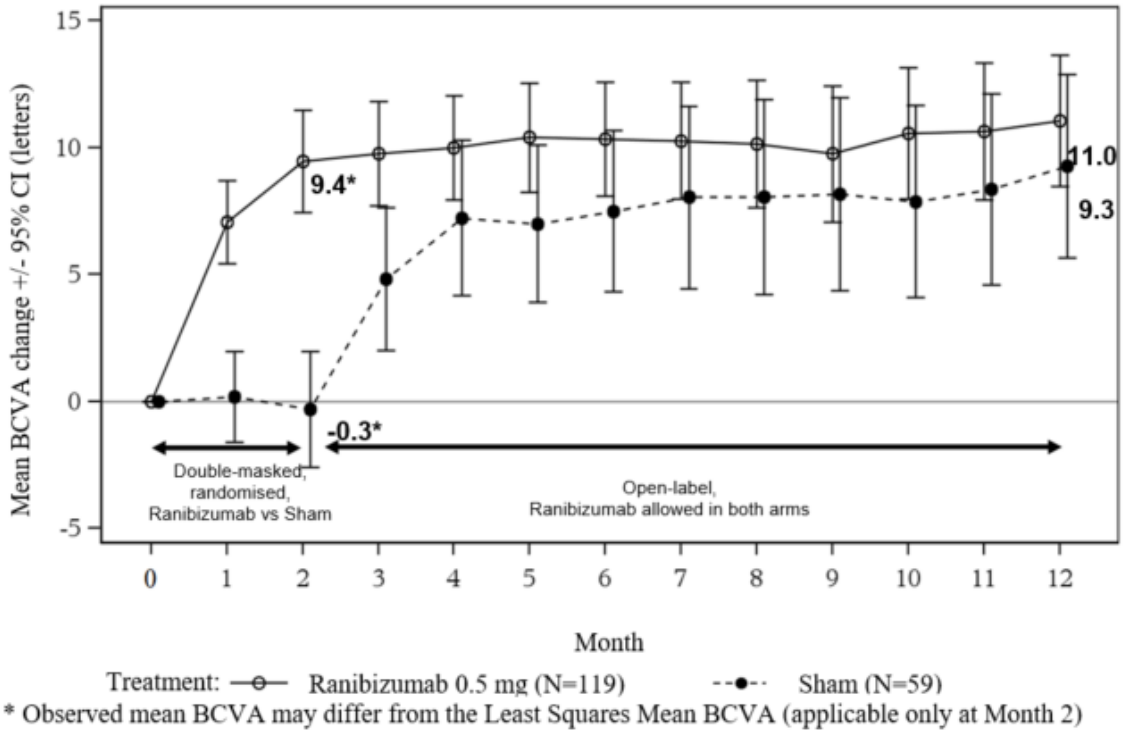
The mean number of injections given over 12 months was 5.8 in the ranibizumab arm versus 5.4 in those patients in the sham arm who were eligible to receive ranibizumab from Month 2 onwards. In the sham arm 7 out of 59 patients did not receive any treatment with ranibizumab in the study eye during the 12-month period.

**Table 3 Outcomes at Month 2 (MINERVA)**

| | **Ranibizumab 0.5 mg (n=119)** | **Sham (n=59)** |
|---|---|---|
| Mean BCVA change from baseline to Month 2 [a] | 9.5 letters | -0.4 letters |
| Patients gaining ≥15 letters from baseline or reaching 84 letters at Month 2 | 31.4% | 12.3% |
| Patients not losing >15 letters from baseline at Month 2 | 99.2% | 94.7% |
| Reduction in CSFT[b] from baseline to Month 2 [a] | 77 µm | -9.8 µm |

[a] One-sided p<0.001 comparison with sham control
[b] CSFT - central retinal subfield thickness

**Figure 3 Mean change from baseline BCVA over time to Month 12 (MINERVA)**



When comparing ranibizumab versus sham control at Month 2, a consistent treatment effect both overall and across baseline aetiology subgroups was observed:

**Table 4 Treatment effect overall and across baseline aetiology subgroups**

| **Overall and per baseline aetiology** | **Treatment effect over sham [letters]** | **Patient numbers [n] (treatment +sham)** |
|---|---|---|
| Overall | 9.9 | 178 |
| Angioid streaks | 14.6 | 27 |
| Post-inflammatory retinochoroidopathy | 6.5 | 28 |
| Central serous chorioretinopathy | 5.0 | 23 |
| Idiopathic chorioretinopathy | 11.4 | 63 |
| Miscellaneous aetiologies[a] | 10.6 | 37 |

[a] encompasses different aetiologies of low frequency of occurrence not included in the other subgroups

In the pivotal study G2301 (MINERVA), five adolescent patients aged 12 to 17 years with visual impairment secondary to CNV received open-label treatment with ranibizumab 0.5 mg at baseline followed by an individualised treatment regimen as for the adult population. BCVA improved from baseline to Month 12 in all five patients, ranging from 5 to 38 letters (mean of 16.6 letters). The improvement of vision was accompanied by a stabilisation or reduction in central subfield thickness over the 12-month period. The mean number of ranibizumab injections given in the study eye over 12 months was 3 (ranged from 2 to 5). Overall, ranibizumab treatment was well tolerated.

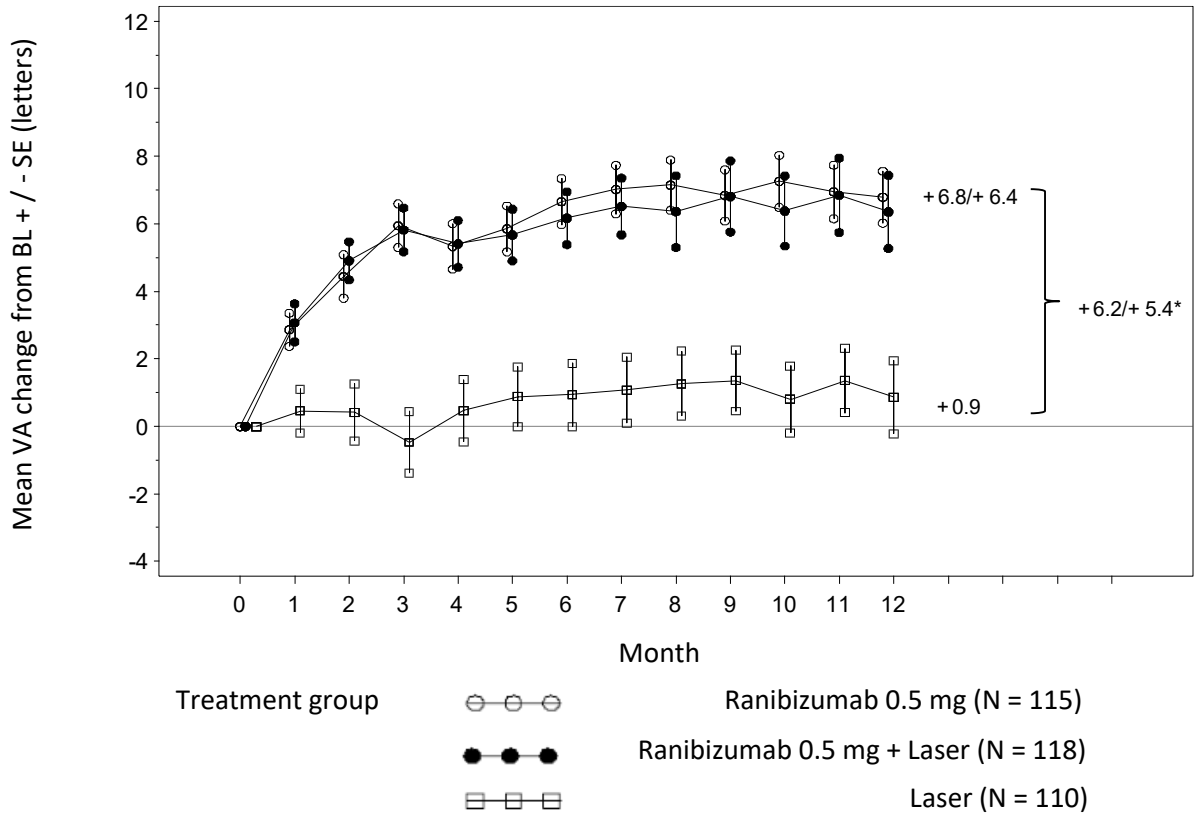
*Treatment of visual impairment due to DME*
The efficacy and safety of Lucentis have been assessed in three randomised, controlled studies of at least 12 months duration. A total of 868 patients (708 active and 160 control) were enrolled in these studies.

In the phase II study D2201 (RESOLVE), 151 patients were treated with ranibizumab (6 mg/ml, n=51, 10 mg/ml, n=51) or sham (n=49) by monthly intravitreal injections. The mean average change in BCVA from Month 1 to Month 12 compared to baseline was +7.8 (±7.72) letters in the pooled ranibizumab-treated patients (n=102), compared to -0.1 (±9.77) letters for sham-treated patients; and the mean change in BCVA at Month 12 from baseline was 10.3 (±9.1) letters compared to -1.4 (±14.2) letters, respectively ($p<0.0001$ for the treatment difference).

In the phase III study D2301 (RESTORE), 345 patients were randomised in a 1:1:1 ratio to receive ranibizumab 0.5 mg monotherapy and sham laser photocoagulation, combined ranibizumab 0.5 mg and laser photocoagulation or sham injection and laser photocoagulation. 240 patients, who had previously completed the 12-month RESTORE study, were enrolled in the open-label, multicentre 24-month extension (RESTORE Extension) study. Patients were treated with ranibizumab 0.5 mg *pro re nata* (PRN) in the same eye as the core study (D2301 RESTORE).

Key outcome measures are summarised in Table 5 (RESTORE and Extension) and Figure 4 (RESTORE).

**Figure 4 Mean change in visual acuity from baseline over time in study D2301 (RESTORE)**




BL=baseline; SE=standard error of mean
* Difference in least square means, p<0.0001/0.0004 based on two-sided stratified Cochran-Mantel-Haenszel test

The effect at 12 months was consistent in most subgroups. However, subjects with a baseline BCVA >73 letters and macular oedema with central retinal thickness <300 µm did not appear to benefit from treatment with ranibizumab compared to laser photocoagulation.

**Table 5 Outcomes at Month 12 in study D2301 (RESTORE) and at Month 36 in study D2301-E1 (RESTORE Extension)**

| Outcome measures at Month 12 compared to baseline in study D2301 (RESTORE) | Ranibizumab 0.5 mg n=115 | Ranibizumab 0.5 mg + Laser n=118 | Laser n=110 |
|---|---|---|---|
| Mean average change in BCVA from Month 1 to Month 12[a] (±SD) | 6.1 (6.4)[a] | 5.9 (7.9)[a] | 0.8 (8.6) |
| Mean change in BCVA at Month 12 (±SD) | 6.8 (8.3)[a] | 6.4 (11.8)[a] | 0.9 (11.4) |
| Gain of ≥15 letters or BCVA ≥84 letters at Month 12 (%) | 22.6 | 22.9 | 8.2 |
| Mean number of injections (Months 0-11) | 7.0 | 6.8 | 7.3 (sham) |
| | | | |
| Outcome measure at Month 36 compared to D2301 (RESTORE) baseline in study D2301-E1 (RESTORE Extension) | Prior ranibizumab 0.5 mg n=83 | Prior ranibizumab 0.5 mg + laser n=83 | Prior laser n=74 |
| Mean change in BCVA at Month 24 (SD) | 7.9 (9.0) | 6.7 (7.9) | 5.4 (9.0) |
| Mean change in BCVA at Month 36 (SD) | 8.0 (10.1) | 6.7 (9.6) | 6.0 (9.4) |
| Gain of ≥15 letters or BCVA ≥84 letters at Month 36 (%) | 27.7 | 30.1 | 21.6 |
| Mean number of injections (Months 12-35)* | 6.8 | 6.0 | 6.5 |

[a]$p<0.0001$ for comparisons of ranibizumab arms vs. laser arm.
n in D2301-E1 (RESTORE Extension) is the number of patients with a value at both D2301 (RESTORE) baseline (Month 0) and at the Month 36 visit.
* The proportion of patients who did not require any ranibizumab treatment during the extension phase was 19%, 25% and 20% in the prior ranibizumab, prior ranibizumab + laser and prior laser groups, respectively.

Statistically significant patient-reported benefits for most vision-related functions were observed with ranibizumab (with or without laser) treatment over the control group as measured by the NEI VFQ-25. For other subscales of this questionnaire no treatment differences could be established.

The long-term safety profile of ranibizumab observed in the 24-month extension study is consistent with the known Lucentis safety profile.

In the phase IIIb study D2304 (RETAIN), 372 patients were randomised in 1:1:1 ratio to receive:
- ranibizumab 0.5 mg with concomitant laser photocoagulation on a treat-and-extend (TE) regimen,
- ranibizumab 0.5 mg monotherapy on a TE regimen,
- ranibizumab 0.5 mg monotherapy on a PRN regimen.

In all groups, ranibizumab was administered monthly until BCVA was stable for at least three consecutive monthly assessments. On TE, ranibizumab was administered at treatment intervals of 2-3 months. In all groups, monthly treatment was re-initiated upon a decrease in BCVA due to DME progression and continued until stable BCVA was reached again.

The number of scheduled treatment visits after the initial 3 injections, was 13 and 20 for the TE and PRN regimens, respectively. With both TE regimens, more than 70% of patients maintained their BCVA with an average visit frequency of ≥2 months.

The key outcome measures are summarised in Table 6.

**Table 6 Outcomes in study D2304 (RETAIN)**

| Outcome measure compared to baseline | TE ranibizumab 0.5 mg + laser n=117 | TE ranibizumab 0.5 mg alone n=125 | PRN ranibizumab 0.5 mg n=117 |
|---|---|---|---|
| Mean average change in BCVA from Month 1 to Month 12 (SD) | 5.9 (5.5) [a] | 6.1 (5.7) [a] | 6.2 (6.0) |
| Mean average change in BCVA from Month 1 to Month 24 (SD) | 6.8 (6.0) | 6.6 (7.1) | 7.0 (6.4) |
| Mean change in BCVA at Month 24 (SD) | 8.3 (8.1) | 6.5 (10.9) | 8.1 (8.5) |
| Gain of ≥15 letters or BCVA ≥84 letters at Month 24(%) | 25.6 | 28.0 | 30.8 |
| Mean number of injections (months 0-23) | 12.4 | 12.8 | 10.7 |

[a] $p<0.0001$ for assessment of non-inferiority to PRN

In DME studies, the improvement in BCVA was accompanied by a reduction over time in mean CSFT in all the treatment groups.

*Treatment of PDR*

The clinical safety and efficacy of Lucentis in patients with PDR have been assessed in Protocol S which evaluated the treatment with ranibizumab 0.5 mg intravitreal injections compared with panretinal photocoagulation (PRP). The primary endpoint was the mean visual acuity change at year 2. Additionally, change in diabetic retinopathy (DR) severity was assessed based on fundus photographs using the DR severity score (DRSS).

Protocol S was a multicentre, randomised, active-controlled, parallel-assignment, non-inferiority phase III study in which 305 patients (394 study eyes) with PDR with or without DME at baseline were enrolled. The study compared ranibizumab 0.5 mg intravitreal injections to standard treatment with PRP. A total of 191 eyes (48.5%) were randomised to ranibizumab 0.5 mg and 203 eyes (51.5%) eyes were randomised to PRP. A total of 88 eyes (22.3%) had baseline DME: 42 (22.0%) and 46 (22.7%) eyes in the ranibizumab and PRP groups, respectively.

In this study, the mean visual acuity change at year 2 was +2.7 letters in the ranibizumab group compared to -0.7 letters in the PRP group. The difference in least square means was 3.5 letters (95% CI: [0.2 to 6.7]).

At year 1, 41.8% of eyes experienced a ≥2-step improvement in the DRSS when treated with ranibizumab (n=189) compared to 14.6% of eyes treated with PRP (n=199). The estimated difference between ranibizumab and laser was 27.4% (95% CI: [18.9, 35.9]).

**Table 7 DRSS improvement or worsening of ≥2 or ≥3 steps at year 1 in Protocol S (LOCF Method)**

| Categorised change from baseline | Protocol S | | |
|---|---|---|---|
| | Ranibizumab 0.5 mg (N=189) | PRP (N=199) | Difference in proportion (%), CI |
| ≥2-step improvement | | | |
| n (%) | 79 (41.8%) | 29 (14.6%) | 27.4 (18.9, 35.9) |
| ≥3-step improvement | | | |
| n (%) | 54 (28.6%) | 6 (3.0%) | 25.7 (18.9, 32.6) |
| ≥2-step worsening | | | |
| n (%) | 3 (1.6%) | 23 (11.6%) | -9.9 (-14.7, -5.2) |
| ≥3-step worsening | | | |
| n (%) | 1 (0.5%) | 8 (4.0%) | -3.4 (-6.3, -0.5) |
| DRSS = diabetic retinopathy severity score, n = number of patients who satisfied the condition at the visit, N = total number of study eyes. | | | |

At year 1 in the ranibizumab-treated group in Protocol S, ≥2-step improvement in DRSS was consistent in eyes without DME (39.9%) and with baseline DME (48.8%).

An analysis of year 2 data from Protocol S demonstrated that 42.3% (n=80) of eyes in the ranibizumab-treated group had ≥2-step improvement in DRSS from baseline compared with 23.1% (n=46) of eyes in the PRP group. In the ranibizumab-treated group, ≥2-step improvement in DRSS from baseline was observed in 58.5% (n=24) of eyes with baseline DME and 37.8% (n=56) of eyes without DME.

DRSS was also assessed in three separate active-controlled phase III DME studies (ranibizumab 0.5 mg PRN vs laser) that included a total of 875 patients, of whom approximately 75% were of Asian origin. In a meta-analysis of these studies, 48.4% of the 315 patients with gradable DRSS scores in the subgroup of patients with moderately severe non-proliferative DR (NPDR) or worse at baseline experienced a ≥2-step improvement in the DRSS at Month 12 when treated with ranibizumab (n=192) vs 14.6% of patients treated with laser (n=123). The estimated difference between ranibizumab and laser was 29.9% (95% CI: [20.0, 39.7]). In the 405 DRSS gradable patients with moderate NPDR or better, a ≥2-step DRSS improvement was observed in 1.4% and 0.9% of the ranibizumab and laser groups, respectively.

*Treatment of visual impairment due to macular oedema secondary to RVO*
The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO have been assessed in the randomised, double-masked, controlled studies BRAVO and CRUISE that recruited subjects with BRVO (n=397) and CRVO (n=392), respectively. In both studies, subjects received either 0.3 mg or 0.5 mg ranibizumab or sham injections. After 6 months, patients in the sham-control arms switched to 0.5 mg ranibizumab.

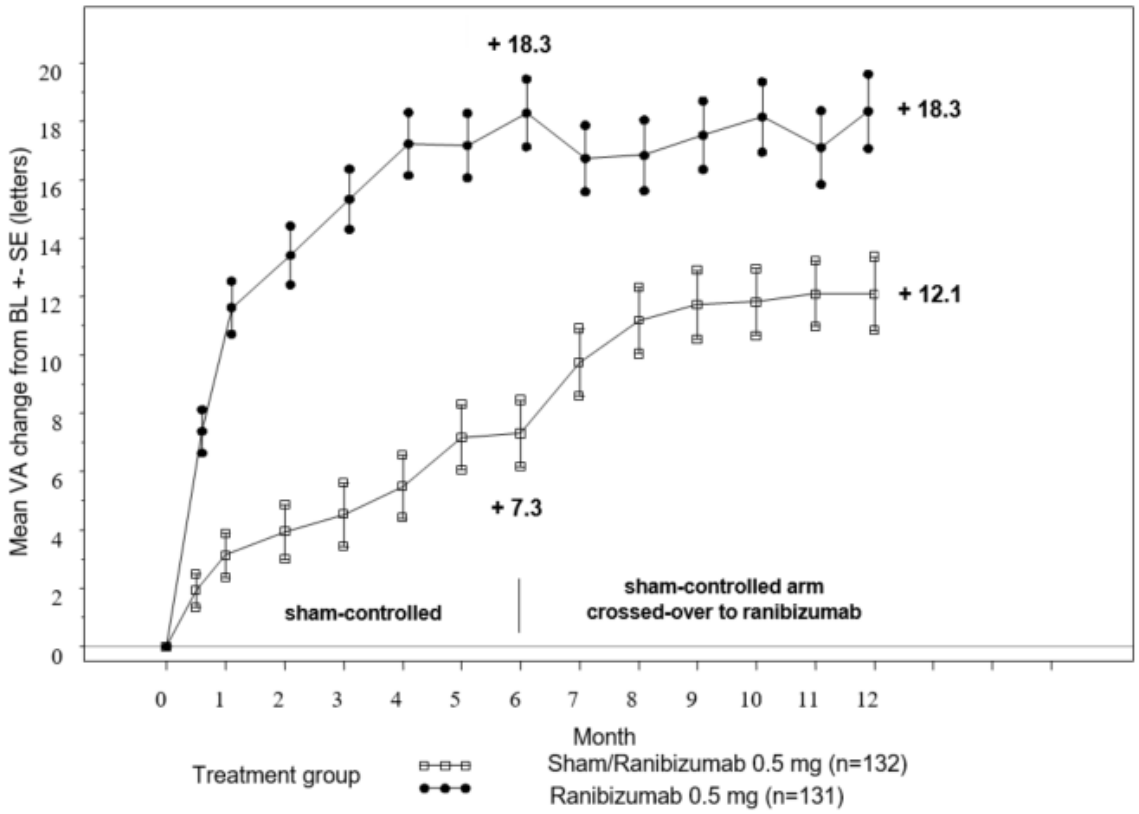
Key outcome measures from BRAVO and CRUISE are summarised in Table 8 and Figures 5 and 6.

**Table 8 Outcomes at Month 6 and 12 (BRAVO and CRUISE)**

| | BRAVO | | CRUISE | |
|---|---|---|---|---|
| | **Sham/Lucentis 0.5 mg (n=132)** | **Lucentis 0.5 mg (n=131)** | **Sham/Lucentis 0.5 mg (n=130)** | **Lucentis 0.5 mg (n=130)** |
| Mean change in visual acuity at Month 6[a] (letters) (SD) (primary endpoint) | 7.3 (13.0) | 18.3 (13.2) | 0.8 (16.2) | 14.9 (13.2) |
| Mean change in BCVA at Month 12 (letters) (SD) | 12.1 (14.4) | 18.3 (14.6) | 7.3 (15.9) | 13.9 (14.2) |
| Gain of ≥15 letters in visual acuity at Month 6[a] (%) | 28.8 | 61.1 | 16.9 | 47.7 |
| Gain of ≥15 letters in visual acuity at Month 12 (%) | 43.9 | 60.3 | 33.1 | 50.8 |
| Proportion (%) receiving laser rescue over 12 months | 61.4 | 34.4 | NA | NA |

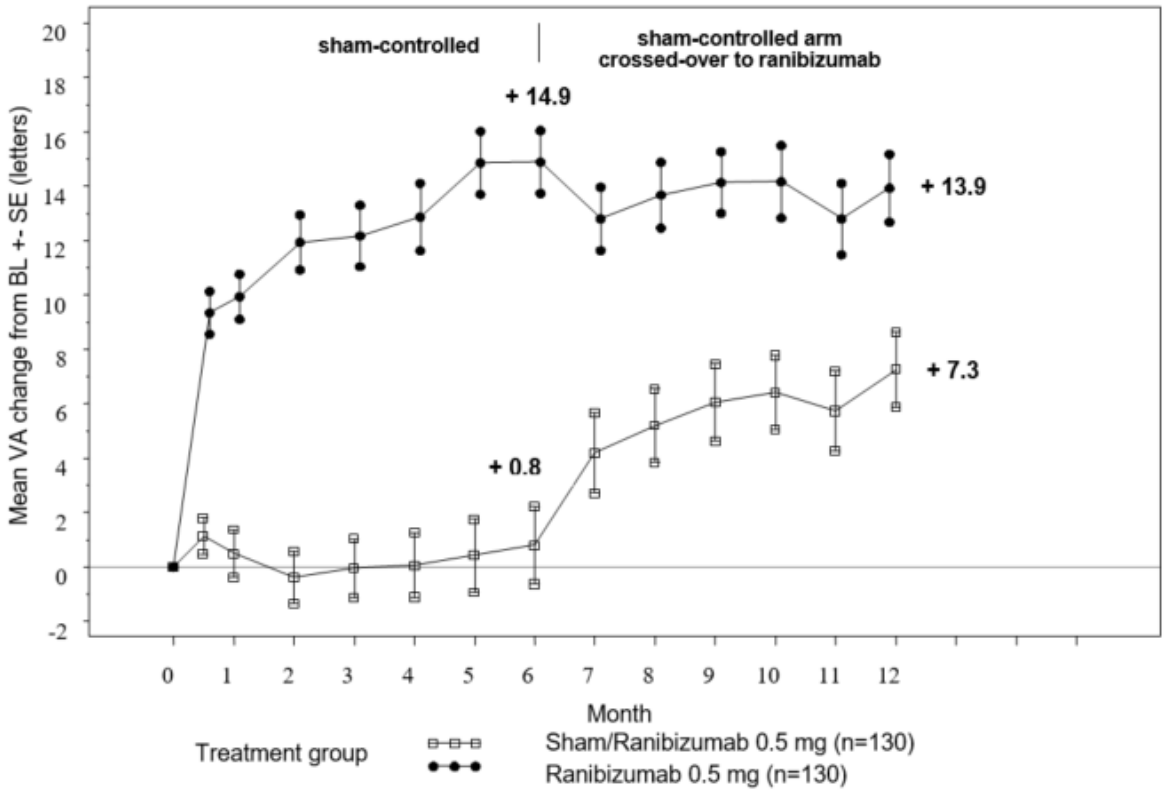
[a]p<0.0001for both studies

**Figure 5 Mean change from baseline BCVA over time to Month 6 and Month 12 (BRAVO)**




BL=baseline; SE=standard error of mean

**Figure 6 Mean change from baseline BCVA over time to Month 6 and Month 12 (CRUISE)**




BL=baseline; SE=standard error of mean

In both studies, the improvement of vision was accompanied by a continuous and significant reduction in the macular oedema as measured by central retinal thickness.

In patients with CRVO (CRUISE and extension study HORIZON): Subjects treated with sham in the first 6 months who subsequently received ranibizumab did not achieve comparable gains in visual acuity by Month 24 (~6 letters) compared to subjects treated with ranibizumab from study start (~12 letters).

Statistically significant patient-reported benefits in subscales related to near and distance activity were observed with ranibizumab treatment over the control group as measured by the NEI VFQ-25.

The long-term (24 months) clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO were assessed in the BRIGHTER (BRVO) and CRYSTAL (CRVO) studies. In both studies, subjects received a 0.5 mg ranibizumab PRN dosing regimen driven by individualised stabilisation criteria. BRIGHTER was a 3-arm randomised active-controlled study that compared 0.5 mg ranibizumab given as monotherapy or in combination with adjunctive laser photocoagulation to laser photocoagulation alone. After 6 months, subjects in the laser arm could receive 0.5 mg ranibizumab. CRYSTAL was a single-arm study with 0.5 mg ranibizumab monotherapy.

Key outcome measures from BRIGHTER and CRYSTAL are shown in Table 9.

**Table 9 Outcomes at Months 6 and 24 (BRIGHTER and CRYSTAL)**

| | BRIGHTER | | | CRYSTAL |
|---|---|---|---|---|
| | Lucentis 0.5 mg N=180 | Lucentis 0.5 mg + Laser N=178 | Laser* N=90 | Lucentis 0.5 mg N=356 |
| Mean change in BCVA at Month 6[a] (letters) (SD) | +14.8 (10.7) | +14.8 (11.13) | +6.0 (14.27) | +12.0 (13.95) |
| Mean change in BCVA at Month 24[b] (letters) (SD) | +15.5 (13.91) | +17.3 (12.61) | +11.6 (16.09) | +12.1 (18.60) |
| Gain of ≥15 letters in BCVA at Month 24 (%) | 52.8 | 59.6 | 43.3 | 49.2 |
| Mean number of injections (SD) (Months 0-23) | 11.4 (5.81) | 11.3 (6.02) | NA | 13.1 (6.39) |

[a] $p<0.0001$ for both comparisons in BRIGHTER at Month 6: Lucentis 0.5 mg vs Laser and Lucentis 0.5 mg + Laser vs Laser.

[b] $p<0.0001$ for null hypothesis in CRYSTAL that the mean change at Month 24 from baseline is zero.

* Starting at Month 6 ranibizumab 0.5 mg treatment was allowed (24 patients were treated with laser only).

In BRIGHTER, ranibizumab 0.5 mg with adjunctive laser therapy demonstrated non-inferiority versus ranibizumab monotherapy from baseline to Month 24 (95% CI -2.8, 1.4).

In both studies, a rapid and statistically significant decrease from baseline in central retinal subfield thickness was observed at Month 1. This effect was maintained up to Month 24.

The effect of ranibizumab treatment was similar irrespective of the presence of retinal ischaemia. In BRIGHTER, patients with ischaemia present (N=46) or absent (N=133) and treated with ranibizumab monotherapy had a mean change from baseline of +15.3 and +15.6 letters, respectively, at Month 24. In CRYSTAL, patients with ischaemia present (N=53) or absent (N=300) and treated with ranibizumab monotherapy had a mean change from baseline of +15.0 and +11.5 letters, respectively.

The effect in terms of visual improvement was observed in all patients treated with 0.5 mg ranibizumab monotherapy regardless of their disease duration in both BRIGHTER and CRYSTAL. In patients with <3 months disease duration an increase in visual acuity of 13.3 and 10.0 letters was seen at Month 1; and 17.7 and 13.2 letters at Month 24 in BRIGHTER and CRYSTAL, respectively. The corresponding visual acuity gain in patients with ≥12 months disease duration was 8.6 and 8.4 letters in the respective studies. Treatment initiation at the time of diagnosis should be considered.

The long-term safety profile of ranibizumab observed in the 24-month studies is consistent with the known Lucentis safety profile.

Paediatric population

*Treatment of ROP in preterm infants*
The clinical safety and efficacy of Lucentis 0.2 mg for the treatment of ROP in preterm infants have been assessed based on the 6-month data of the randomised, open-label, 3-arm, parallel-group superiority study H2301 (RAINBOW), which was designed to evaluate ranibizumab 0.2 mg and 0.1 mg given as intravitreal injections in comparison to laser therapy. Eligible patients had one of the following retinal findings in each eye:

- Zone I, stage 1+, 2+, 3 or 3+ disease, or
- Zone II, stage 3+ disease, or
- Aggressive posterior (AP)-ROP

In this study, 225 patients were randomised in a 1:1:1 ratio to receive intravitreal ranibizumab 0.2 mg (n=74), 0.1 mg (n=77), or laser therapy (n=74).

Treatment success, as measured by the absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after the first study treatment, was highest with ranibizumab 0.2 mg (80%) compared to laser therapy (66.2%) (see Table 10). The majority of patients treated with ranibizumab 0.2 mg (78.1%) received a single injection per eye.

**Table 10 Outcomes at Week 24 (RAINBOW)**

| | Treatment success | | | | | |
|---|---|---|---|---|---|---|
| Treatment | n/M (%) | 95% CI | Comparison | Odds ratio (OR)[a] | 95% CI | p-value[b] |
| Ranibizumab 0.2 mg (N=74) | 56/70 (80.0) | (0.6873, 0.8861) | Ranibizumab 0.2 mg vs laser | 2.19 | (0.9932, 4.8235) | 0.0254 |
| Laser therapy (N=74) | 45/68 (66.2) | (0.5368, 0.7721) | | | | |

CI = confidence interval, M = total number of patients with non-missing value on primary efficacy outcome (including imputed values), n = number of patients with absence of active ROP and absence of unfavourable structural outcome in both eyes 24 weeks after the first study treatment (including imputed values).
If a patient died or switched study treatment before or at week 24, then the patient was considered as having active ROP and unfavourable structural outcomes at week 24.

[a] Odds ratio is calculated by using Cochran-Mantel-Haenszel test with ROP zone at baseline (zone I and II; per CRF) as stratum factor.

[b] p-value for pairwise comparison is one-sided. For the primary endpoint the pre-specified significance level for the one-sided p-value was 0.025.

During the 24 weeks of the study, fewer patients in the ranibizumab 0.2 mg group switched to another treatment modality due to lack of response compared with the laser group (14.9% vs. 24.3%). Unfavourable structural outcomes were less frequently reported for ranibizumab 0.2 mg (1 patient, 1.4%) compared with laser therapy (7 patients, 10.1%).

The long-term efficacy and safety of ranibizumab 0.2 mg for the treatment of ROP in preterm infants have been assessed in study H2301E1 (RAINBOW extension), an extension study of study H2301 (RAINBOW), following patients to their 5$^{th}$ birthday.

The primary objective was to evaluate visual function at the patient's 5$^{th}$ birthday visit by assessing visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) with Lea symbols optotypes in the better-seeing eye (the eye with the higher ETDRS score).

An ETDRS score in patients who completed the 5th birthday visit was recorded for 83.3% (45/54) and 76.6% (36/47) of patients in the ranibizumab 0.2 mg arm and the laser arm, respectively. The least-squares (LS) mean (SE) was numerically higher in the ranibizumab 0.2 mg arm (66.8 [1.95]) compared to the laser arm (62.1 [2.18]) with a difference in LS mean ETDRS score of 4.7 (95% CI: -1.1, 10.5). The categorised visual acuity outcomes in the better-seeing eye at the patients' 5th birthday is presented in Table 11.

**Table 11 Visual acuity outcomes in the better-seeing eye[1] at the patients' 5th birthday visit**

| **Visual acuity category** | **Ranibizumab 0.2 mg N=61 n (%)** | **Laser N=54 n (%)** |
|---|---|---|
| ≥1 to ≤34 letters | 1 (1.6) | 2 (3.7) |
| ≥35 to ≤70 letters | 24 (39.3) | 23 (42.6) |
| ≥71 letters | 20 (32.8) | 11 (20.4) |

[1] The better-seeing eye is the eye with a higher ETDRS letter score at the 5th birthday visit. If both eyes have the same ETDRS letter score, then the right eye is assigned as the better-seeing eye.

The European Medicines Agency has waived the obligation to submit the results of studies with Lucentis in all subsets of the paediatric population in neovascular AMD, visual impairment due to DME, visual impairment due to macular oedema secondary to RVO, visual impairment due to CNV and diabetic retinopathy (see section 4.2 for information on paediatric use). In addition the European Medicines Agency has waived the obligation to submit the results of studies with Lucentis in the following subsets of the paediatric population for ROP: term newborn infants, infants, children and adolescents.

## 5.2 Pharmacokinetic properties

Following monthly intravitreal administration of Lucentis 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 Lucentis 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 Lucentis 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.

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

Paediatric population

Following intravitreal administration of Lucentis 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.

## 5.3 Preclinical safety data

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

α,α-trehalose dihydrate
Histidine hydrochloride, monohydrate
Histidine
Polysorbate 20
Water for injections

### 6.2 Incompatibilities

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

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

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 (25°C) for up to 24 hours.

### 6.5 Nature and contents of container

Vial-only pack

One vial (type I glass) with a stopper (chlorobutyl rubber) containing 0.23 ml sterile solution.

Vial + filter needle pack

One vial (type I glass) with a stopper (chlorobutyl rubber) containing 0.23 ml sterile solution 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

Vial-only pack

The vial is for single use only. After injection any unused product must be discarded. Any vial showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the packaging seal remains intact.

For preparation and intravitreal injection the following medical devices for single use are needed:
- a 5 µm filter needle (18G)
- a 1 ml sterile syringe (including a 0.05 ml mark) and an injection needle (30G x ½″), for adult patients
- a low volume high accuracy sterile syringe, provided together with an injection needle (30G x ½″) in the VISISURE kit, for preterm infants

These medical devices are not included within this pack.

Vial + filter needle pack

The vial 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 x 1½″, 1.2 mm x 40 mm, provided)
- a 1 ml sterile syringe (including a 0.05 ml mark, not included within this pack) and an injection needle (30G x ½″, not included within this pack), for adult patients
- a low volume high accuracy sterile syringe, provided together with an injection needle (30G x ½″) in the VISISURE kit (not included within this pack), for preterm infants

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

1. Before withdrawal, remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).

2. Assemble a 5 µm filter needle (18G x 1½″, 1.2 mm x 40 mm) 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 x ½″, 0.3 mm x 13 mm) 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 the paediatric population

To prepare Lucentis for intravitreal administration to **preterm infants**, please adhere to the instructions for use included in the VISISURE kit.

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/374/002
EU/1/06/374/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 2007
Date of latest renewal: 11 November 2016

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

## 1. NAME OF THE MEDICINAL PRODUCT

Lucentis 10 mg/ml solution for injection in pre-filled syringe

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg ranibizumab*. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. The extractable volume of one pre-filled syringe is 0.1 ml. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
*Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to pale brownish-yellow aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lucentis is indicated in adults for:
- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

### 4.2 Posology and method of administration

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

Posology

The recommended dose for Lucentis 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, Lucentis 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 ~~i~~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 (see section 5.1).

*Lucentis and laser photocoagulation in DME and in macular oedema secondary to BRVO*
There is some experience of Lucentis administered concomitantly with laser photocoagulation (see section 5.1). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation.

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

Special populations

*Hepatic impairment*
Lucentis 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 (see section 5.2).

*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 Lucentis in children and adolescents below 18 years of age have not been established. Available data in adolescent patients aged 12 to 17 years with visual impairment due to CNV are described in section 5.1.

Method of administration

Single-use pre-filled syringe for intravitreal use only. The pre-filled syringe contains more than the recommended dose of 0.5 mg. The extractable volume of the pre-filled syringe (0.1 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., 0.5 mg ranibizumab).

Lucentis should be inspected visually for particulate matter and discoloration prior to administration.

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 (see section 4.4). 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.

For information on preparation of Lucentis, see section 6.6.

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

## 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 severe 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.

Intravitreal injection-related reactions

Intravitreous injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Lucentis. 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 Lucentis. Sustained IOP increases have also been identified (see section 4.8). 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 (see section 4.8).

Bilateral treatment

Limited data on bilateral use of Lucentis (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 Lucentis. 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-VEGF (vascular endothelial growth factor)

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

Withholding Lucentis

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

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

Populations with limited data

There is only limited experience in the treatment of subjects with DME due to type I diabetes. Lucentis has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is limited experience of treatment with Lucentis in diabetic patients with an HbA1c over 108 mmol/mol (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 Lucentis in patients with RVO presenting irreversible ischaemic visual function loss.

In patients with PM, there are limited data on the effect of Lucentis 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 Lucentis 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 (see section 4.8).

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

For the adjunctive use of verteporfin photodynamic therapy (PDT) and Lucentis in wet AMD and PM, see section 5.1.

For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see sections 4.2 and 5.1.

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 Lucentis was not affected by concomitant treatment with thiazolidinediones.

## 4.6 Fertility, pregnancy and lactation

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 (see section 5.3). 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

Based on very limited data, ranibizumab may be excreted in human milk at low levels. The effect of ranibizumab on a breast-fed newborn/infant is unknown. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis.

Fertility

There are no data available on fertility.

## 4.7 Effects on ability to drive and use machines

The treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see section 4.8). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

## 4.8 Undesirable effects

Summary of the safety profile

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

The most frequently reported ocular adverse reactions following injection of Lucentis 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 (see section 4.4).

The adverse reactions experienced following administration of Lucentis in clinical studies are summarised in the table below.

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.

| | |
|---|---|
| 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 Lucentis 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 (vascular endothelial growth factor) 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 Lucentis clinical studies in patients with AMD, DME, PDR, RVO and CNV and there were no major differences between the groups treated with ranibizumab compared to control.

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 via the national reporting system listed in Appendix V.

## 4.9 Overdose

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 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antineovascularisation agents, ATC code: S01LA04

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.

Clinical efficacy and safety

*Treatment of wet AMD*
In wet AMD, the clinical safety and efficacy of Lucentis have been assessed in three randomised, double-masked, sham- or active-controlled studies of 24 months duration in patients with neovascular AMD. A total of 1,323 patients (879 active and 444 control) were enrolled in these studies.

In study FVF2598g (MARINA), 716 patients with minimally classic or occult with no classic lesions were randomised in a 1:1:1 ratio to receive monthly injections of Lucentis 0.3 mg, Lucentis 0.5 mg or sham.

In study FVF2587g (ANCHOR), 423 patients with predominantly classic CNV lesions were randomised in a 1:1:1 ratio to receive Lucentis 0.3 mg monthly, Lucentis 0.5 mg monthly or verteporfin PDT (at baseline and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage).

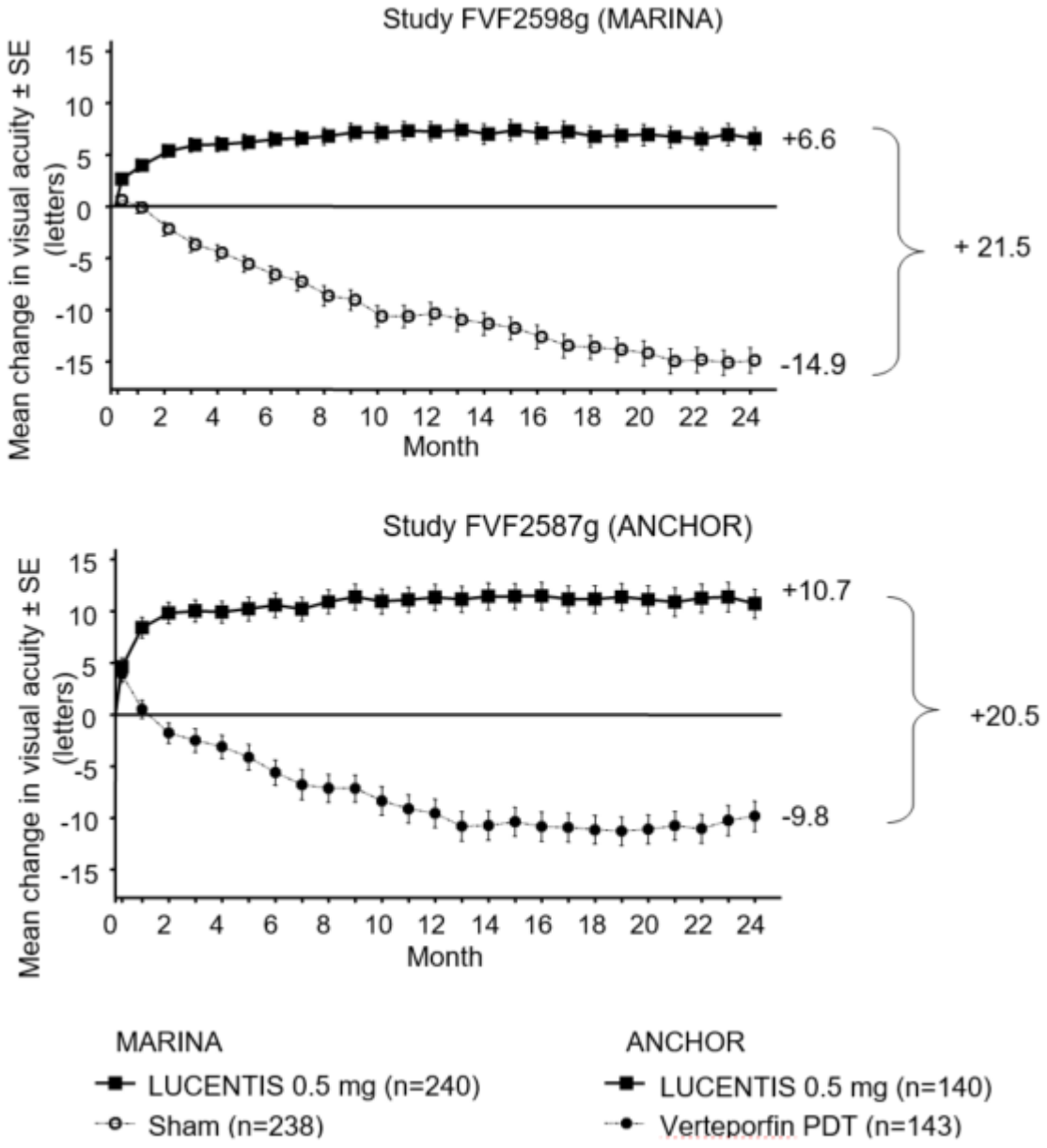
Key outcome measures are summarised in Table 1 and Figure 1.

**Table 1 Outcomes at Month 12 and Month 24 in study FVF2598g (MARINA) and FVF2587g (ANCHOR)**

| | | FVF2598g (MARINA) | | FVF2587g (ANCHOR) | |
|---|---|---|---|---|---|
| Outcome measure | Month | Sham (n=238) | Lucentis 0.5 mg (n=240) | Verteporfin PDT (n=143) | Lucentis 0.5 mg (n=140) |
| Loss of <15 letters in visual acuity (%)[a] (maintenance of vision, primary endpoint) | Month 12 | 62% | 95% | 64% | 96% |
| | Month 24 | 53% | 90% | 66% | 90% |
| Gain of ≥15 letters in visual acuity (%)[a] | Month 12 | 5% | 34% | 6% | 40% |
| | Month 24 | 4% | 33% | 6% | 41% |
| Mean change in visual acuity (letters) (SD)[a] | Month 12 | -10.5 (16.6) | +7.2 (14.4) | -9.5 (16.4) | +11.3 (14.6) |
| | Month 24 | -14.9 (18.7) | +6.6 (16.5) | -9.8 (17.6) | +10.7 (16.5) |

[a] $p<0.01$

**Figure 1 Mean change in visual acuity from baseline to Month 24 in study FVF2598g (MARINA) and study FVF2587g (ANCHOR)**




Results from both studies indicated that continued ranibizumab treatment may also be of benefit in patients who lost ≥15 letters of best-corrected visual acuity (BCVA) in the first year of treatment.

Statistically significant patient-reported visual functioning benefits were observed in both MARINA and ANCHOR with ranibizumab treatment over the control group as measured by the NEI VFQ-25.

In study FVF3192g (PIER), 184 patients with all forms of neovascular AMD were randomised in a 1:1:1 ratio to receive Lucentis 0.3 mg, Lucentis 0.5 mg or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months. From Month 14 of the study, sham-treated patients were allowed to receive ranibizumab and from Month 19, more frequent treatments were possible. Patients treated with Lucentis in PIER received a mean of 10 total treatments.

After an initial increase in visual acuity (following monthly dosing), on average, patients' visual acuity declined with quarterly dosing, returning to baseline at Month 12 and this effect was maintained in most ranibizumab-treated patients (82%) at Month 24. Limited data from sham subjects who later received ranibizumab suggested that early initiation of treatment may be associated with better preservation of visual acuity.

Data from two studies (MONT BLANC, BPD952A2308 and DENALI, BPD952A2309) conducted post approval confirmed the efficacy of Lucentis but did not demonstrate additional effect of the combined administration of verteporfin (Visudyne PDT) and Lucentis compared to Lucentis monotherapy.

Treatment of visual impairment due to CNV secondary to PM

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV in PM have been assessed based on the 12-month data of the double-masked, controlled pivotal study F2301 (RADIANCE). In this study 277 patients were randomised in a 2:2:1 ratio to the following arms:

- Group I (ranibizumab 0.5 mg, dosing regimen driven by "stability" criteria defined as no change in BCVA compared to two preceding monthly evaluations).
- Group II (ranibizumab 0.5 mg, dosing regimen driven by "disease activity" criteria defined as vision impairment attributable to intra- or subretinal fluid or active leakage due to the CNV lesion as assessed by optical coherence tomography and/or fluorescence angiography).
- Group III (vPDT - patients were allowed to receive ranibizumab treatment as of Month 3).

In Group II, which is the recommended posology (see section 4.2), 50.9% of patients required 1 or 2 injections, 34.5% required 3 to 5 injections and 14.7% required 6 to 12 injections over the 12-month study period. 62.9% of Group II patients did not require injections in the second 6 months of the study.

The key outcomes from RADIANCE are summarised in Table 2 and Figure 2.

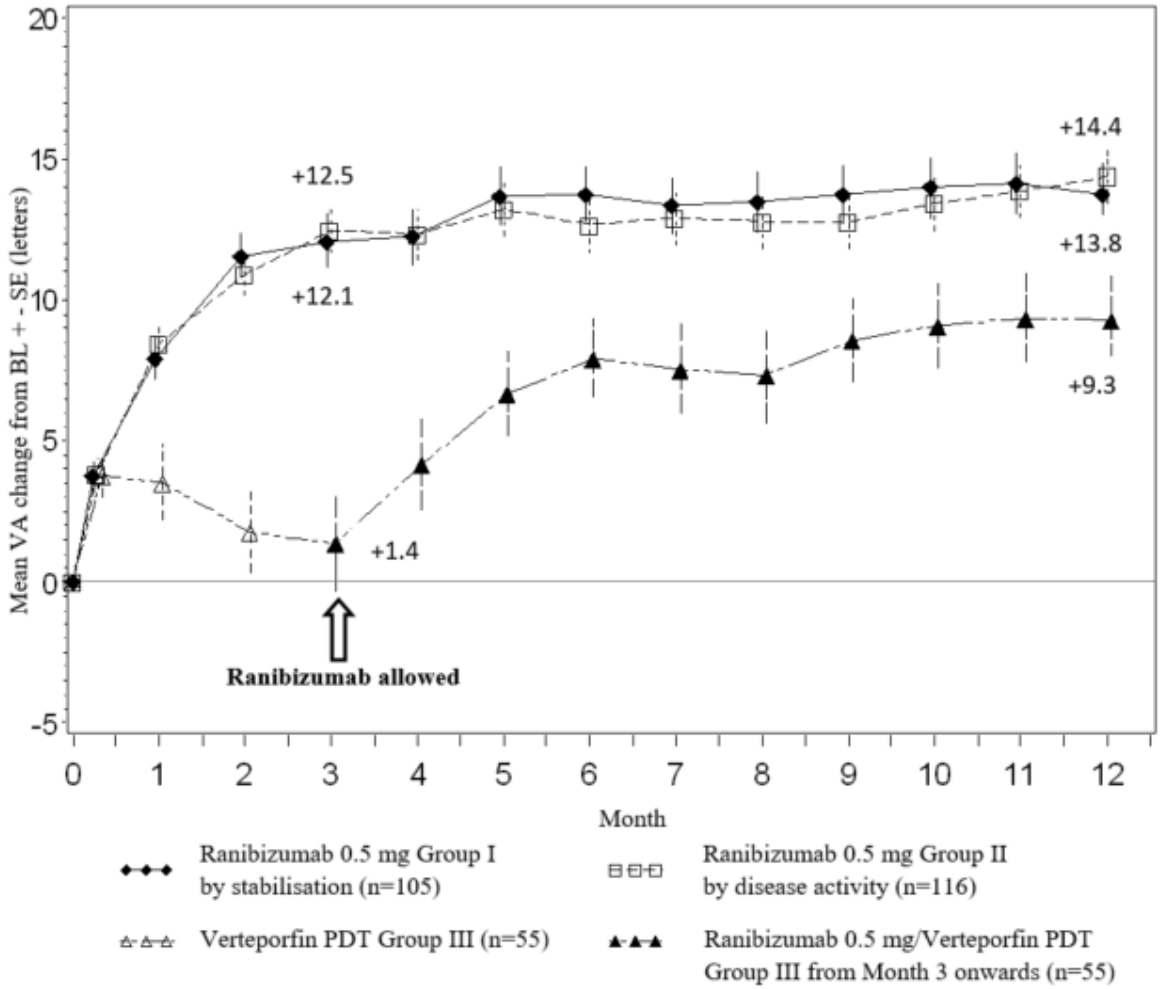
**Table 2 Outcomes at Month 3 and 12 (RADIANCE)**

| | **Group I Ranibizumab 0.5 mg "vision stability" (n=105)** | **Group II Ranibizumab 0.5 mg "disease activity" (n=116)** | **Group III vPDT[b] (n=55)** |
|---|---|---|---|
| **Month 3** | | | |
| Mean average BCVA change from Month 1 to Month 3 compared to baseline[a] (letters) | +10.5 | +10.6 | +2.2 |
| Proportion of patients who gained: ≥15 letters, or reached ≥84 letters in BCVA | 38.1% | 43.1% | 14.5% |
| **Month 12** | | | |
| Number of injections up to Month 12: | | | |
| Mean | 4.6 | 3.5 | N/A |
| Median | 4.0 | 2.5 | N/A |
| Mean average BCVA change from Month 1 to Month 12 compared to baseline (letters) | +12.8 | +12.5 | N/A |
| Proportion of patients who gained: ≥15 letters, or reached ≥84 letters in BCVA | 53.3% | 51.7% | N/A |

[a] $p<0.00001$ comparison with vPDT control

[b] Comparative control up to Month 3. Patients randomised to vPDT were allowed to receive ranibizumab treatment as of Month 3 (in Group III, 38 patients received ranibizumab as of Month 3)

**Figure 2 Mean change from baseline BCVA over time to Month 12 (RADIANCE)**




The improvement of vision was accompanied by a reduction in central retinal thickness.

Patient-reported benefits were observed with ranibizumab treatment arms over vPDT (p-value <0.05) in terms of improvement in the composite score and several subscales (general vision, near activities, mental health and dependency) of the NEI VFQ-25.

Treatment of visual impairment due to CNV (other than secondary to PM and wet AMD)
The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV have been assessed based on the 12-month data of the double-masked, sham-controlled pivotal study G2301 (MINERVA). In this study 178 adult patients were randomised in a 2:1 ratio to receive:

- ranibizumab 0.5 mg at baseline, followed by an individualised dosing regimen driven by disease activity as assessed by visual acuity and/or anatomical parameters (e.g. visual acuity impairment, intra/sub-retinal fluid, haemorrhage or leakage);
- sham injection at baseline, followed by an individualised treatment regimen driven by disease activity.

At Month 2, all patients received open-label treatment with ranibizumab as needed.

Key outcome measures from MINERVA are summarised in Table 3 and Figure 3. An improvement of vision was observed and was accompanied by a reduction in central subfield thickness over the 12-month period.

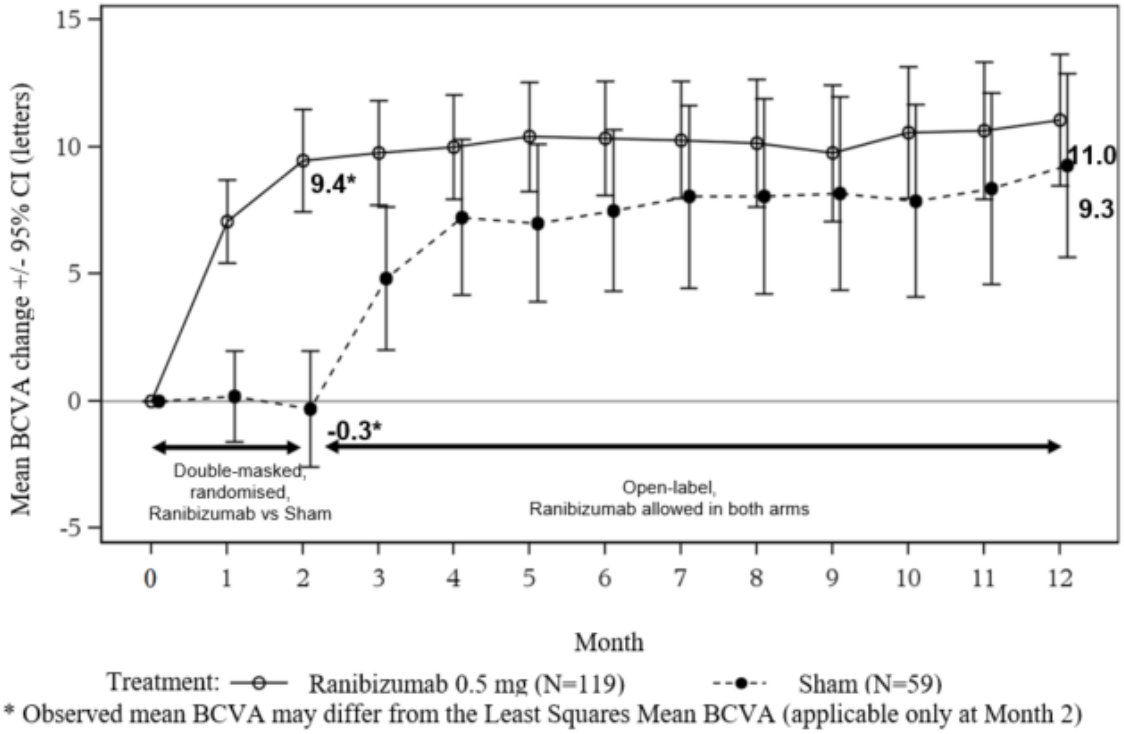
The mean number of injections given over 12 months was 5.8 in the ranibizumab arm versus 5.4 in those patients in the sham arm who were eligible to receive ranibizumab from Month 2 onwards. In the sham arm 7 out of 59 patients did not receive any treatment with ranibizumab in the study eye during the 12-month period.

**Table 3 Outcomes at Month 2 (MINERVA)**

| | **Ranibizumab 0.5 mg (n=119)** | **Sham (n=59)** |
|---|---|---|
| Mean BCVA change from baseline to Month 2 [a] | 9.5 letters | -0.4 letters |
| Patients gaining ≥15 letters from baseline or reaching 84 letters at Month 2 | 31.4% | 12.3% |
| Patients not losing >15 letters from baseline at Month 2 | 99.2% | 94.7% |
| Reduction in CSFT[b] from baseline to Month 2 [a] | 77 µm | -9.8 µm |

[a] One-sided p<0.001 comparison with sham control
[b] CSFT - central retinal subfield thickness

**Figure 3 Mean change from baseline BCVA over time to Month 12 (MINERVA)**



When comparing ranibizumab versus sham control at Month 2, a consistent treatment effect both overall and across baseline aetiology subgroups was observed:

**Table 4 Treatment effect overall and across baseline aetiology subgroups**

| **Overall and per baseline aetiology** | **Treatment effect over sham [letters]** | **Patient numbers [n] (treatment +sham)** |
|---|---|---|
| Overall | 9.9 | 178 |
| Angioid streaks | 14.6 | 27 |
| Post-inflammatory retinochoroidopathy | 6.5 | 28 |
| Central serous chorioretinopathy | 5.0 | 23 |
| Idiopathic chorioretinopathy | 11.4 | 63 |
| Miscellaneous aetiologies[a] | 10.6 | 37 |

[a] encompasses different aetiologies of low frequency of occurrence not included in the other subgroups

In the pivotal study G2301 (MINERVA), five adolescent patients aged 12 to 17 years with visual impairment secondary to CNV received open-label treatment with ranibizumab 0.5 mg at baseline followed by an individualised treatment regimen as for the adult population. BCVA improved from baseline to Month 12 in all five patients, ranging from 5 to 38 letters (mean of 16.6 letters). The improvement of vision was accompanied by a stabilisation or reduction in central subfield thickness over the 12-month period. The mean number of ranibizumab injections given in the study eye over 12 months was 3 (ranged from 2 to 5). Overall, ranibizumab treatment was well tolerated.

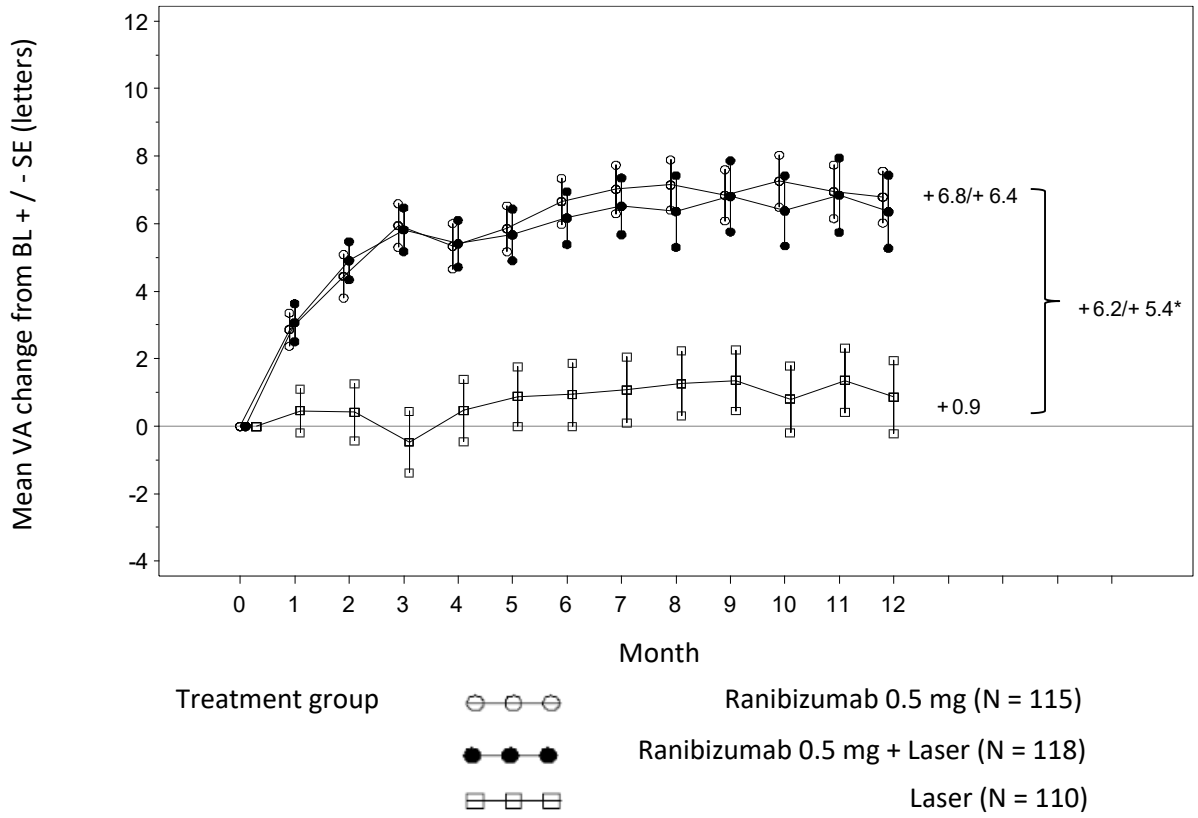
*Treatment of visual impairment due to DME*
The efficacy and safety of Lucentis have been assessed in three randomised, controlled studies of at least 12 months duration. A total of 868 patients (708 active and 160 control) were enrolled in these studies.

In the phase II study D2201 (RESOLVE), 151 patients were treated with ranibizumab (6 mg/ml, n=51, 10 mg/ml, n=51) or sham (n=49) by monthly intravitreal injections. The mean average change in BCVA from Month 1 to Month 12 compared to baseline was +7.8 (±7.72) letters in the pooled ranibizumab-treated patients (n=102), compared to -0.1 (±9.77) letters for sham-treated patients; and the mean change in BCVA at Month 12 from baseline was 10.3 (±9.1) letters compared to -1.4 (±14.2) letters, respectively ($p<0.0001$ for the treatment difference).

In the phase III study D2301 (RESTORE), 345 patients were randomised in a 1:1:1 ratio to receive ranibizumab 0.5 mg monotherapy and sham laser photocoagulation, combined ranibizumab 0.5 mg and laser photocoagulation or sham injection and laser photocoagulation. 240 patients, who had previously completed the 12-month RESTORE study, were enrolled in the open-label, multicentre 24-month extension (RESTORE Extension) study. Patients were treated with ranibizumab 0.5 mg *pro re nata* (PRN) in the same eye as the core study (D2301 RESTORE).

Key outcome measures are summarised in Table 5 (RESTORE and Extension) and Figure 4 (RESTORE).

**Figure 4 Mean change in visual acuity from baseline over time in study D2301 (RESTORE)**




BL=baseline; SE=standard error of mean
* Difference in least square means, p<0.0001/0.0004 based on two-sided stratified Cochran-Mantel-Haenszel test

The effect at 12 months was consistent in most subgroups. However, subjects with a baseline BCVA >73 letters and macular oedema with central retinal thickness <300 µm did not appear to benefit from treatment with ranibizumab compared to laser photocoagulation.

**Table 5 Outcomes at Month 12 in study D2301 (RESTORE) and at Month 36 in study D2301-E1 (RESTORE Extension)**

| Outcome measures at Month 12 compared to baseline in study D2301 (RESTORE) | Ranibizumab 0.5 mg n=115 | Ranibizumab 0.5 mg + Laser n=118 | Laser n=110 |
|---|---|---|---|
| Mean average change in BCVA from Month 1 to Month 12[a] (±SD) | 6.1 (6.4)[a] | 5.9 (7.9)[a] | 0.8 (8.6) |
| Mean change in BCVA at Month 12 (±SD) | 6.8 (8.3)[a] | 6.4 (11.8)[a] | 0.9 (11.4) |
| Gain of ≥15 letters or BCVA ≥84 letters at Month 12 (%) | 22.6 | 22.9 | 8.2 |
| Mean number of injections (Months 0-11) | 7.0 | 6.8 | 7.3 (sham) |
| | | | |
| Outcome measure at Month 36 compared to D2301 (RESTORE) baseline in study D2301-E1 (RESTORE Extension) | Prior ranibizumab 0.5 mg n=83 | Prior ranibizumab 0.5 mg + laser n=83 | Prior laser n=74 |
| Mean change in BCVA at Month 24 (SD) | 7.9 (9.0) | 6.7 (7.9) | 5.4 (9.0) |
| Mean change in BCVA at Month 36 (SD) | 8.0 (10.1) | 6.7 (9.6) | 6.0 (9.4) |
| Gain of ≥15 letters or BCVA ≥84 letters at Month 36 (%) | 27.7 | 30.1 | 21.6 |
| Mean number of injections (Months 12-35)* | 6.8 | 6.0 | 6.5 |

[a]$p<0.0001$ for comparisons of ranibizumab arms vs. laser arm.
n in D2301-E1 (RESTORE Extension) is the number of patients with a value at both D2301 (RESTORE) baseline (Month 0) and at the Month 36 visit.
* The proportion of patients who did not require any ranibizumab treatment during the extension phase was 19%, 25% and 20% in the prior ranibizumab, prior ranibizumab + laser and prior laser groups, respectively.

Statistically significant patient-reported benefits for most vision-related functions were observed with ranibizumab (with or without laser) treatment over the control group as measured by the NEI VFQ-25. For other subscales of this questionnaire no treatment differences could be established.

The long-term safety profile of ranibizumab observed in the 24-month extension study is consistent with the known Lucentis safety profile.

In the phase IIIb study D2304 (RETAIN), 372 patients were randomised in 1:1:1 ratio to receive:
- ranibizumab 0.5 mg with concomitant laser photocoagulation on a treat-and-extend (TE) regimen,
- ranibizumab 0.5 mg monotherapy on a TE regimen,
- ranibizumab 0.5 mg monotherapy on a PRN regimen.

In all groups, ranibizumab was administered monthly until BCVA was stable for at least three consecutive monthly assessments. On TE, ranibizumab was administered at treatment intervals of 2-3 months. In all groups, monthly treatment was re-initiated upon a decrease in BCVA due to DME progression and continued until stable BCVA was reached again.

The number of scheduled treatment visits after the initial 3 injections, was 13 and 20 for the TE and PRN regimens, respectively. With both TE regimens, more than 70% of patients maintained their BCVA with an average visit frequency of ≥2 months.

The key outcome measures are summarised in Table 6.

**Table 6 Outcomes in study D2304 (RETAIN)**

| Outcome measure compared to baseline | TE ranibizumab 0.5 mg + laser n=117 | TE ranibizumab 0.5 mg alone n=125 | PRN ranibizumab 0.5 mg n=117 |
|---|---|---|---|
| Mean average change in BCVA from Month 1 to Month 12 (SD) | 5.9 (5.5) [a] | 6.1 (5.7) [a] | 6.2 (6.0) |
| Mean average change in BCVA from Month 1 to Month 24 (SD) | 6.8 (6.0) | 6.6 (7.1) | 7.0 (6.4) |
| Mean change in BCVA at Month 24 (SD) | 8.3 (8.1) | 6.5 (10.9) | 8.1 (8.5) |
| Gain of ≥15 letters or BCVA ≥84 letters at Month 24(%) | 25.6 | 28.0 | 30.8 |
| Mean number of injections (months 0-23) | 12.4 | 12.8 | 10.7 |

[a] $p<0.0001$ for assessment of non-inferiority to PRN

In DME studies, the improvement in BCVA was accompanied by a reduction over time in mean CSFT in all the treatment groups.

*Treatment of PDR*

The clinical safety and efficacy of Lucentis in patients with PDR have been assessed in Protocol S which evaluated the treatment with ranibizumab 0.5 mg intravitreal injections compared with panretinal photocoagulation (PRP). The primary endpoint was the mean visual acuity change at year 2. Additionally, change in diabetic retinopathy (DR) severity was assessed based on fundus photographs using the DR severity score (DRSS).

Protocol S was a multicentre, randomised, active-controlled, parallel-assignment, non-inferiority phase III study in which 305 patients (394 study eyes) with PDR with or without DME at baseline were enrolled. The study compared ranibizumab 0.5 mg intravitreal injections to standard treatment with PRP. A total of 191 eyes (48.5%) were randomised to ranibizumab 0.5 mg and 203 eyes (51.5%) eyes were randomised to PRP. A total of 88 eyes (22.3%) had baseline DME: 42 (22.0%) and 46 (22.7%) eyes in the ranibizumab and PRP groups, respectively.

In this study, the mean visual acuity change at year 2 was +2.7 letters in the ranibizumab group compared to -0.7 letters in the PRP group. The difference in least square means was 3.5 letters (95% CI: [0.2 to 6.7]).

At year 1, 41.8% of eyes experienced a ≥2-step improvement in the DRSS when treated with ranibizumab (n=189) compared to 14.6% of eyes treated with PRP (n=199). The estimated difference between ranibizumab and laser was 27.4% (95% CI: [18.9, 35.9]).

**Table 7 DRSS improvement or worsening of ≥2 or ≥3 steps at year 1 in Protocol S (LOCF Method)**

| Categorised change from baseline | Protocol S | | |
|---|---|---|---|
| | Ranibizumab 0.5 mg (N=189) | PRP (N=199) | Difference in proportion (%), CI |
| ≥2-step improvement | | | |
| n (%) | 79 (41.8%) | 29 (14.6%) | 27.4 (18.9, 35.9) |
| ≥3-step improvement | | | |
| n (%) | 54 (28.6%) | 6 (3.0%) | 25.7 (18.9, 32.6) |
| ≥2-step worsening | | | |
| n (%) | 3 (1.6%) | 23 (11.6%) | -9.9 (-14.7, -5.2) |
| ≥3-step worsening | | | |
| n (%) | 1 (0.5%) | 8 (4.0%) | -3.4 (-6.3, -0.5) |
| DRSS = diabetic retinopathy severity score, n = number of patients who satisfied the condition at the visit, N = total number of study eyes. | | | |

At year 1 in the ranibizumab-treated group in Protocol S, ≥2-step improvement in DRSS was consistent in eyes without DME (39.9%) and with baseline DME (48.8%).

An analysis of year 2 data from Protocol S demonstrated that 42.3% (n=80) of eyes in the ranibizumab-treated group had ≥2-step improvement in DRSS from baseline compared with 23.1% (n=46) of eyes in the PRP group. In the ranibizumab-treated group, ≥2-step improvement in DRSS from baseline was observed in 58.5% (n=24) of eyes with baseline DME and 37.8% (n=56) of eyes without DME.

DRSS was also assessed in three separate active-controlled phase III DME studies (ranibizumab 0.5 mg PRN vs laser) that included a total of 875 patients, of whom approximately 75% were of Asian origin. In a meta-analysis of these studies, 48.4% of the 315 patients with gradable DRSS scores in the subgroup of patients with moderately severe non-proliferative DR (NPDR) or worse at baseline experienced a ≥2-step improvement in the DRSS at Month 12 when treated with ranibizumab (n=192) vs 14.6% of patients treated with laser (n=123). The estimated difference between ranibizumab and laser was 29.9% (95% CI: [20.0, 39.7]). In the 405 DRSS gradable patients with moderate NPDR or better, a ≥2-step DRSS improvement was observed in 1.4% and 0.9% of the ranibizumab and laser groups, respectively.

*Treatment of visual impairment due to macular oedema secondary to RVO*
The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO have been assessed in the randomised, double-masked, controlled studies BRAVO and CRUISE that recruited subjects with BRVO (n=397) and CRVO (n=392), respectively. In both studies, subjects received either 0.3 mg or 0.5 mg ranibizumab or sham injections. After 6 months, patients in the sham-control arms switched to 0.5 mg ranibizumab.

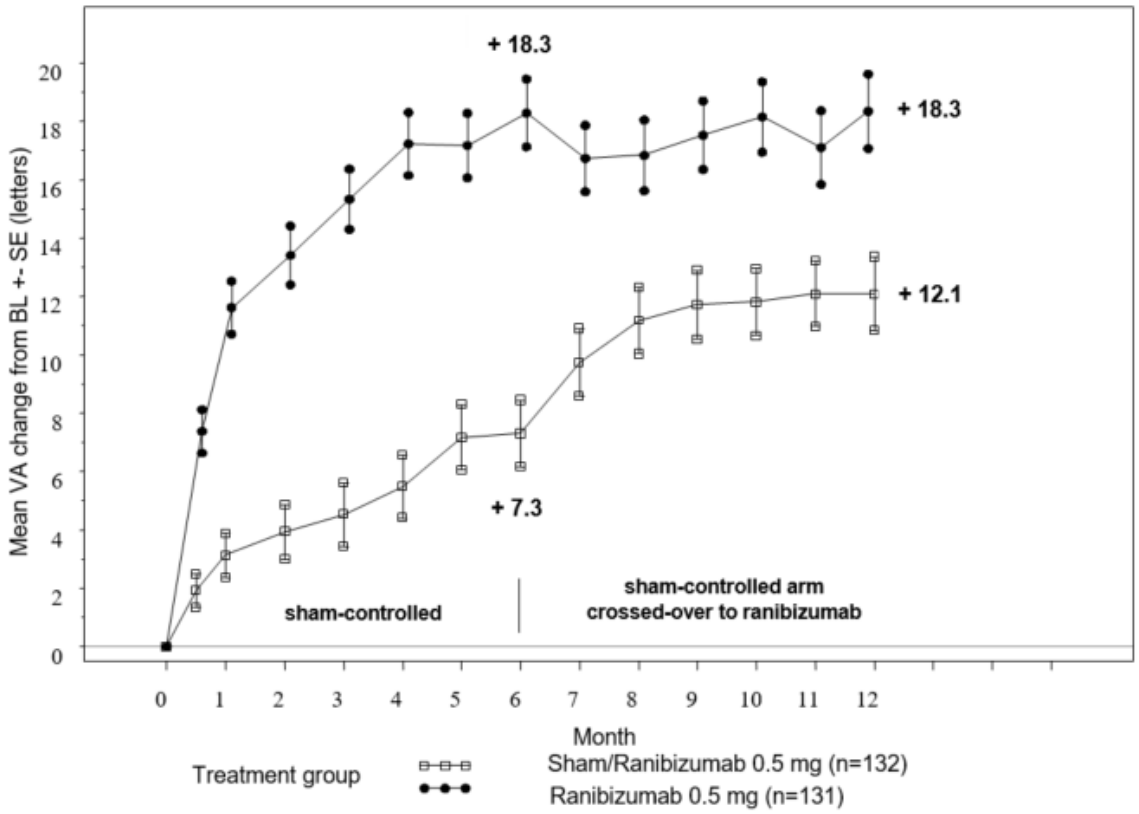
Key outcome measures from BRAVO and CRUISE are summarised in Table 8 and Figures 5 and 6.

**Table 8 Outcomes at Month 6 and 12 (BRAVO and CRUISE)**

| | BRAVO | | CRUISE | |
|---|---|---|---|---|
| | **Sham/Lucentis 0.5 mg (n=132)** | **Lucentis 0.5 mg (n=131)** | **Sham/Lucentis 0.5 mg (n=130)** | **Lucentis 0.5 mg (n=130)** |
| Mean change in visual acuity at Month 6[a] (letters) (SD) (primary endpoint) | 7.3 (13.0) | 18.3 (13.2) | 0.8 (16.2) | 14.9 (13.2) |
| Mean change in BCVA at Month 12 (letters) (SD) | 12.1 (14.4) | 18.3 (14.6) | 7.3 (15.9) | 13.9 (14.2) |
| Gain of ≥15 letters in visual acuity at Month 6[a] (%) | 28.8 | 61.1 | 16.9 | 47.7 |
| Gain of ≥15 letters in visual acuity at Month 12 (%) | 43.9 | 60.3 | 33.1 | 50.8 |
| Proportion (%) receiving laser rescue over 12 months | 61.4 | 34.4 | NA | NA |

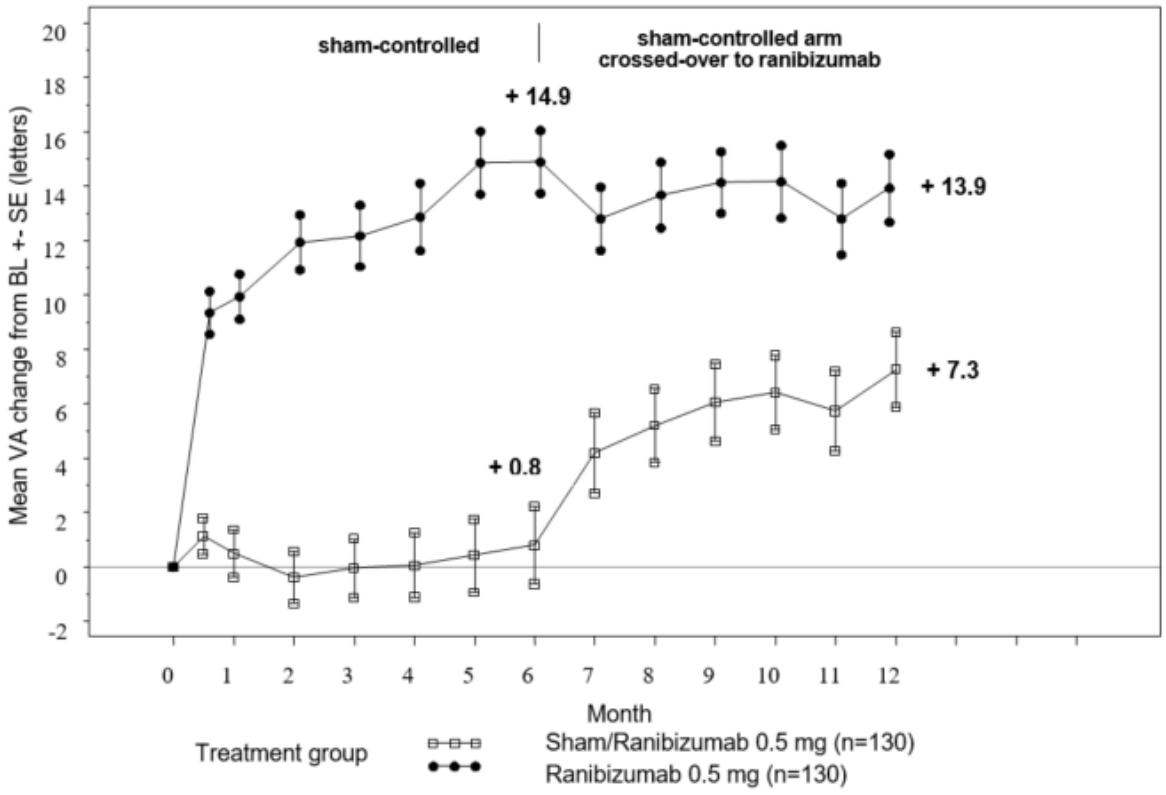
[a]p<0.0001for both studies

**Figure 5 Mean change from baseline BCVA over time to Month 6 and Month 12 (BRAVO)**




BL=baseline; SE=standard error of mean

**Figure 6 Mean change from baseline BCVA over time to Month 6 and Month 12 (CRUISE)**




BL=baseline; SE=standard error of mean

In both studies, the improvement of vision was accompanied by a continuous and significant reduction in the macular oedema as measured by central retinal thickness.

In patients with CRVO (CRUISE and extension study HORIZON): Subjects treated with sham in the first 6 months who subsequently received ranibizumab did not achieve comparable gains in visual acuity by Month 24 (~6 letters) compared to subjects treated with ranibizumab from study start (~12 letters).

Statistically significant patient-reported benefits in subscales related to near and distance activity were observed with ranibizumab treatment over the control group as measured by the NEI VFQ-25.

The long-term (24 months) clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO were assessed in the BRIGHTER (BRVO) and CRYSTAL (CRVO) studies. In both studies, subjects received a 0.5 mg ranibizumab PRN dosing regimen driven by individualised stabilisation criteria. BRIGHTER was a 3-arm randomised active-controlled study that compared 0.5 mg ranibizumab given as monotherapy or in combination with adjunctive laser photocoagulation to laser photocoagulation alone. After 6 months, subjects in the laser arm could receive 0.5 mg ranibizumab. CRYSTAL was a single-arm study with 0.5 mg ranibizumab monotherapy.

Key outcome measures from BRIGHTER and CRYSTAL are shown in Table 9.

**Table 9 Outcomes at Months 6 and 24 (BRIGHTER and CRYSTAL)**

| | BRIGHTER | | | CRYSTAL |
|---|---|---|---|---|
| | Lucentis 0.5 mg N=180 | Lucentis 0.5 mg + Laser N=178 | Laser* N=90 | Lucentis 0.5 mg N=356 |
| Mean change in BCVA at Month 6[a] (letters) (SD) | +14.8 (10.7) | +14.8 (11.13) | +6.0 (14.27) | +12.0 (13.95) |
| Mean change in BCVA at Month 24[b] (letters) (SD) | +15.5 (13.91) | +17.3 (12.61) | +11.6 (16.09) | +12.1 (18.60) |
| Gain of ≥15 letters in BCVA at Month 24 (%) | 52.8 | 59.6 | 43.3 | 49.2 |
| Mean number of injections (SD) (months 0-23) | 11.4 (5.81) | 11.3 (6.02) | NA | 13.1 (6.39) |

[a] $p<0.0001$ for both comparisons in BRIGHTER at Month 6: Lucentis 0.5 mg vs Laser and Lucentis 0.5 mg + Laser vs Laser.

[b] $p<0.0001$ for null hypothesis in CRYSTAL that the mean change at Month 24 from baseline is zero.

* Starting at Month 6 ranibizumab 0.5 mg treatment was allowed (24 patients were treated with laser only).

In BRIGHTER, ranibizumab 0.5 mg with adjunctive laser therapy demonstrated non-inferiority versus ranibizumab monotherapy from baseline to Month 24 (95% CI -2.8, 1.4).

In both studies, a rapid and statistically significant decrease from baseline in central retinal subfield thickness was observed at Month 1. This effect was maintained up to Month 24.

The effect of ranibizumab treatment was similar irrespective of the presence of retinal ischaemia. In BRIGHTER, patients with ischaemia present (N=46) or absent (N=133) and treated with ranibizumab monotherapy had a mean change from baseline of +15.3 and +15.6 letters, respectively, at Month 24. In CRYSTAL, patients with ischaemia present (N=53) or absent (N=300) and treated with ranibizumab monotherapy had a mean change from baseline of +15.0 and +11.5 letters, respectively.

The effect in terms of visual improvement was observed in all patients treated with 0.5 mg ranibizumab monotherapy regardless of their disease duration in both BRIGHTER and CRYSTAL. In patients with <3 months disease duration an increase in visual acuity of 13.3 and 10.0 letters was seen at Month 1; and 17.7 and 13.2 letters at Month 24 in BRIGHTER and CRYSTAL, respectively. The corresponding visual acuity gain in patients with ≥12 months disease duration was 8.6 and 8.4 letters in the respective studies. Treatment initiation at the time of diagnosis should be considered.

The long-term safety profile of ranibizumab observed in the 24-month studies is consistent with the known Lucentis safety profile.

Paediatric population

The safety and efficacy of ranibizumab 0.5 mg in pre-filled syringe have not been studied in paediatric patients.

The European Medicines Agency has waived the obligation to submit the results of studies with Lucentis in all subsets of the paediatric population in neovascular AMD, visual impairment due to DME, visual impairment due to macular oedema secondary to RVO and visual impairment due to CNV and diabetic retinopathy (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Following monthly intravitreal administration of Lucentis 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 Lucentis 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 Lucentis 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.

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

## 5.3 Preclinical safety data

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

α,α-trehalose dihydrate
Histidine hydrochloride, monohydrate
Histidine
Polysorbate 20
Water for injections

### 6.2 Incompatibilities

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

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

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

## 6.5 Nature and contents of container

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 finger grip, and is packed in a sealed tray.

Pack size of one pre-filled syringe.

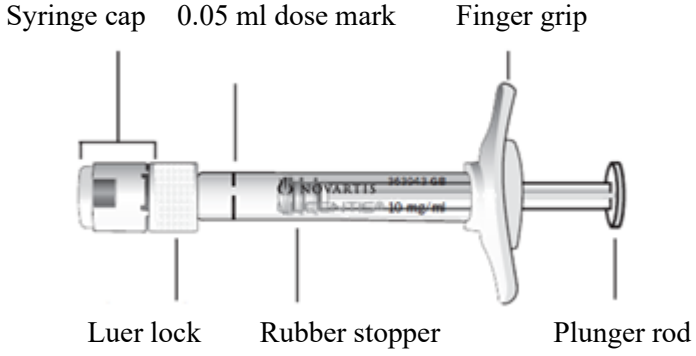
## 6.6 Special precautions for disposal and other handling

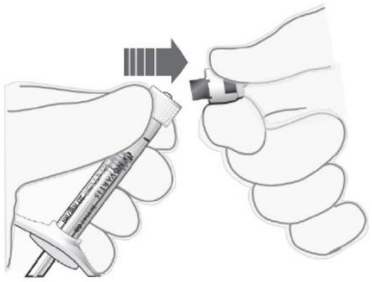
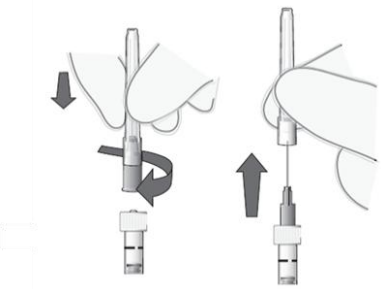
The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discoloured, cloudy or contains particles.

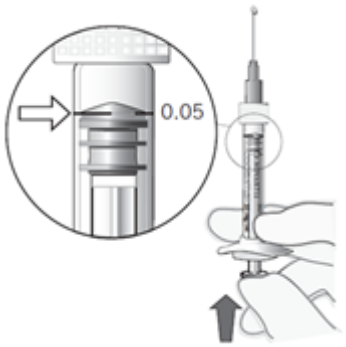
The pre-filled syringe contains more than the recommended dose of 0.5 mg. The extractable volume of the pre-filled syringe (0.1 ml) is not to be used in total. The excess volume should be expelled prior to injection. Injecting the entire volume of the pre-filled syringe could result in overdose. To expel 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., 0.5 mg ranibizumab).

For the intravitreal injection, a 30G x ½″ sterile injection needle should be used.

To prepare Lucentis for intravitreal administration, please adhere to the instructions for use:

| | |
|---|---|
| **Introduction** | Read all the instructions carefully before using the pre-filled syringe.<br>The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.<br>**Note: The dose must be set to 0.05 ml.** |
| **Pre-filled syringe description** | <br>**Figure 1** |

| | | |
|---|---|---|
| **Prepare** | 1. Make sure that the pack contains:<br>• a sterile pre-filled syringe in a sealed tray.<br>2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe. | |
| **Check syringe** | 3. Check that:<br>• the syringe cap is not detached from the Luer lock.<br>• the syringe is not damaged.<br>• the solution looks clear, colourless to pale brownish-yellow and does not contain any particles.<br>4. If any of the above is not true, discard the pre-filled syringe and use a new one. | |
| **Remove syringe cap** | 5. Snap off (do not turn or twist) the syringe cap (see Figure 2).<br>6. Dispose of the syringe cap (see Figure 3). | <br>**Figure 2**<br><br>**Figure 3** |
| **Attach needle** | 7. Attach a 30G x ½″ sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock (see Figure 4).<br>8. Carefully remove the needle cap by pulling it straight off (see Figure 5).<br>**Note: Do not wipe the needle at any time.** | <br>**Figure 4** **Figure 5** |

<table>
<tr><td>Dislodge air bubbles</td><td>9. Hold the syringe upright.<br>10. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).</td><td><br>Figure 6</td></tr>
<tr><td>Set dose</td><td>11. Hold the syringe at eye level and carefully push the plunger until the edge below the dome of the rubber stopper is aligned with the dose mark (see Figure 7). This will expel the air and the excess solution and set the dose to 0.05 ml.<br>Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.</td><td>
<br>Figure 7</td></tr>
<tr><td>Inject</td><td colspan="2">The injection procedure should be carried out under aseptic conditions.<br>12. 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.<br>13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 ml.<br>14. A different scleral site should be used for subsequent injections.<br>15. 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.</td></tr>
</table>

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/374/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 2007
Date of latest renewal: 11 November 2016

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Roche Singapore Technical Operations Pte. Ltd.
10 Tuas Bay Link
Singapore 637394
Singapore

Name and address of the manufacturers responsible for batch release

**Solution for injection**
Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000 Ljubljana
Slovenia

Lek Pharmaceuticals d.d.
Verovškova ulica 57
Ljubljana, 1526
Slovenia

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

**Solution for injection in pre-filled syringe**
Novartis Manufacturing NV
Rijksweg 14
2870 Puurs-Sint-Amands
Belgium

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Lucentis is marketed, at launch and after launch all ophthalmological clinics where Lucentis is expected to be used are provided with an up-to-date patient information pack.

The patient information pack should be provided in both the form of patient information booklets and an audio-CD that contain following key elements:
- Patient information leaflet
- How to prepare for Lucentis treatment
- What are the steps following treatment with Lucentis
- Key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment & retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT

Lucentis 10 mg/ml solution for injection
ranibizumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 10 mg of ranibizumab. Vial containing 2.3 mg of ranibizumab.

## 3. LIST OF EXCIPIENTS

Also contains: α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1x 0.23 ml vial
Single dose for adults: 0.5 mg/0.05 ml. Excess volume to be expelled.
Single dose for babies born prematurely: 0.2 mg/0.02 ml. Excess volume to be expelled.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravitreal use.
Vial for single use only.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/374/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lucentis 10 mg/ml solution for injection
ranibizumab
Intravitreal use

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.3 mg/0.23 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT

Lucentis 10 mg/ml solution for injection in pre-filled syringe
ranibizumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe of 0.165 ml solution contains 1.65 mg of ranibizumab (10 mg/ml).

## 3. LIST OF EXCIPIENTS

Also contains: α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe of 0.165 ml.
Single dose of 0.5 mg/0.05 ml.
Excess volume should be expelled prior to injection.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only. Upon opening of the sealed tray, proceed under aseptic conditions.
Set dose to 0.05 ml dose mark.
Read the package leaflet before use.
Intravitreal use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the pre-filled syringe in its sealed tray in the carton to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/374/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**BLISTER FOIL**

**PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lucentis 10 mg/ml solution for injection in pre-filled syringe
ranibizumab
Intravitreal use

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

0.165 ml

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL**

**PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lucentis 10 mg/ml solution for injection
ranibizumab
Intravitreal use

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.165 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**VIAL + FILTER NEEDLE**

## 1. NAME OF THE MEDICINAL PRODUCT

Lucentis 10 mg/ml solution for injection
ranibizumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 10 mg of ranibizumab. Vial containing 2.3 mg of ranibizumab.

## 3. LIST OF EXCIPIENTS

Also contains: α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1x 0.23 ml vial, 1 filter needle.
Single dose for adults: 0.5 mg/0.05 ml. Excess volume to be expelled.
Single dose for babies born prematurely: 0.2 mg/0.02 ml. Excess volume to be expelled.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravitreal use.
Vial and filter needle for single use only.
Read the package leaflet before use.
The filter needle is not for injection.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/374/004

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lucentis 10 mg/ml solution for injection
ranibizumab
Intravitreal use

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.3 mg/0.23 ml

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the adult patient**

**Lucentis 10 mg/ml solution for injection**
ranibizumab

**ADULTS**

Please find information for babies born prematurely on the other side of this leaflet.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Lucentis is and what it is used for
2. What you need to know before you are given Lucentis
3. How Lucentis is given
4. Possible side effects
5. How to store Lucentis
6. Contents of the pack and other information


## 1. What Lucentis is and what it is used for

**What Lucentis is**
Lucentis is a solution which is injected into the eye. Lucentis belongs to a group of medicines called antineovascularisation agents. It contains the active substance called ranibizumab.

**What Lucentis is used for**
Lucentis is used in adults to treat several eye diseases causing vision impairment.

These diseases result from damage to the retina (light-sensitive layer at the back of the eye) caused by:
- Growth of leaky, abnormal blood vessels. This is observed in diseases such as age-related macular degeneration (AMD) and proliferative diabetic retinopathy (PDR, a disease caused by diabetes). It may also be associated with choroidal neovascularisation (CNV) due to pathologic myopia (PM), angioid streaks, central serous chorioretinopathy or inflammatory CNV.
- Macular oedema (swelling of the centre of the retina). This swelling can be caused by diabetes (a disease called diabetic macular oedema (DME)) or by the blockage of retinal veins of the retina (a disease called retinal vein occlusion (RVO)).

**How Lucentis works**
Lucentis specifically recognises and binds to a protein called human vascular endothelial growth factor A (VEGF-A) present in the eye. In excess, VEGF-A causes abnormal blood vessel growth and swelling in the eye which can lead to impairment of vision in diseases like AMD, DME, PDR, RVO, PM and CNV. By binding to VEGF-A, Lucentis can block its actions and prevent this abnormal growth and swelling.

In these diseases, Lucentis can help to stabilise and in many cases improve your vision.

## 2. What you need to know before you are given Lucentis

**You must not receive Lucentis**
- If you are allergic to ranibizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have an infection in or around your eye.
- If you have pain or redness (severe intraocular inflammation) in your eye.

**Warnings and precautions**
Talk to your doctor before you are given Lucentis.
- Lucentis is given as an injection into the eye. Occasionally, an infection in the internal portion of the eye, pain or redness (inflammation), detachment or tear of one of the layers in the back of the eye (retinal detachment or tear and retinal pigment epithelial detachment or tear), or clouding of the lens (cataract) may occur after Lucentis treatment. It is important to identify and treat such an infection or retinal detachment as soon as possible. Please tell your doctor immediately if you develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light.
- In some patients the eye pressure may increase for a short period directly after the injection. This is something you may not notice, therefore your doctor may monitor this after each injection.
- Inform your doctor if you have a prior history of eye conditions or eye treatments, or if you have had a stroke or experienced transient signs of stroke (weakness or paralysis of limbs or face, difficulty speaking or understanding). This information will be taken into account to evaluate if Lucentis is the appropriate treatment for you.

Please see section 4 (“Possible side effects”) for more detailed information on side effects that could occur during Lucentis therapy.

**Children and adolescents (below 18 years of age)**
Except for retinopathy of prematurity, the use of Lucentis in children and adolescents has not been established and is therefore not recommended. For the treatment of babies born prematurely with retinopathy of prematurity (ROP) please see the other side of this leaflet.

**Other medicines and Lucentis**
Tell your doctor if you are using, have recently used or might use any other medicines.

**Pregnancy and breast-feeding**
- Women who could become pregnant must use effective contraception during treatment and for at least three further months after the last injection of Lucentis.
- There is no experience of using Lucentis in pregnant women. Lucentis should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant, think you may be pregnant or planning to become pregnant, discuss this with your doctor before treatment with Lucentis.
- Small amounts of Lucentis may pass into breast milk, therefore Lucentis is not recommended during breast-feeding. Ask your doctor or pharmacist for advice before Lucentis treatment.

**Driving and using machines**
After Lucentis treatment you may experience some temporary vision blurring. If this happens, do not drive or use machines until this resolves.

## 3. How Lucentis is given

Lucentis is administered as a single injection into your eye by your eye doctor under a local anaesthetic. The usual dose of an injection is 0.05 ml (which contains 0.5 mg of active substance). The interval between two doses injected into the same eye should be at least four weeks. All injections will be administered by your eye doctor.

Before the injection, your doctor will wash your eye carefully to prevent infection. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection.

The treatment is started with one injection of Lucentis per month. Your doctor will monitor the condition of your eye and, depending on how you respond to the treatment, will decide if and when you need to receive further treatment.

Detailed instructions for use are given at the end of the leaflet under "How to prepare and administer Lucentis to adults".

**Elderly (age 65 years and over)**
Lucentis can be used for people of 65 years of age and over without dose adjustment.

**Before stopping Lucentis treatment**
If you are considering stopping Lucentis treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Lucentis.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects associated with the administration of Lucentis are either due to the medicine itself or the injection procedure and mostly affect the eye.

The most serious side effects are described below:
**Common serious side effects** (may affect up to 1 in 10 people): Detachment or tear of the layer in the back of the eye (retinal detachment or tear), resulting in flashes of light with floaters progressing to a temporary loss of sight, or a clouding of the lens (cataract).
**Uncommon serious side effects** (may affect up to 1 in 100 people): Blindness, infection of the eyeball (endophthalmitis) with inflammation of the inside of the eye.

The symptoms you might experience are pain or increased discomfort in your eye, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light. **Please tell your doctor immediately if you develop any of these side effects**.

The most frequently reported side effects are described below:
**Very common side effects** (may affect more than 1 in 10 people)
Visual side effects include: Inflammation of the eye, bleeding in the back of the eye (retinal bleeding), visual disturbances, eye pain, small particles or spots in your vision (floaters), bloodshot eye, eye irritation, a feeling of having something in the eye, increased tear production, inflammation or infection of the eyelid margins, dry eye, redness or itching of the eye and increased eye pressure.
Non-visual side effects include: Sore throat, nasal congestion, runny nose, headache and joint pain.

Other side effects which may occur following Lucentis treatment are described below:
**Common side effects**
Visual side effects include: Decreased sharpness of vision, swelling of a section of the eye (uvea, cornea), inflammation of the cornea (front part of eye), small marks on the surface of the eye, blurred vision, bleeding at the site of injection, bleeding in the eye, discharge from the eye with itching, redness and swelling (conjunctivitis), light sensitivity, eye discomfort, swelling of the eyelid, eyelid pain.
Non-visual side effects include: Urinary tract infection, low red blood cells count (with symptoms such as tiredness, breathlessness, dizziness, pale skin), anxiety, cough, nausea, allergic reactions like rash, hives, itching and skin reddening.

**Uncommon side effects**
Visual side effects include: Inflammation and bleeding in the front part of the eye, sac of pus on the eye, changes of the central part of the eye surface, pain or irritation at the site of injection, abnormal sensation in the eye, irritation of the eyelid.

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lucentis

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hours.
- Keep the vial in the outer carton in order to protect from light.
- Do not use any pack that is damaged.

## 6. Contents of the pack and other information

**What Lucentis contains**
- The active substance is ranibizumab. Each ml contains 10 mg ranibizumab. Each vial contains 2.3 mg ranibizumab in 0.23 ml solution. This provides a suitable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
- The other ingredients are α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.

**What Lucentis looks like and contents of the pack**
Lucentis is a solution for injection in a vial (0.23 ml). The solution is clear, colourless to pale brownish-yellow and aqueous.

Two different pack types are available:

Vial-only pack
Pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper. The vial is for single use only.

Vial + filter needle pack
Pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper and one blunt filter needle (18G x 1½″, 1.2 mm x 40 mm, 5 micrometres) for withdrawal of the vial contents. All components are for single use only.

**Marketing Authorisation Holder**
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Slovenia

Lek Pharmaceuticals d.d.
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Ljubljana, 1526
Slovenia

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Slovenská republika**
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

**Suomi/Finland**
Novartis Finland Oy
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**Sverige**
Novartis Sverige AB
Tel: +46 8 732 32 00

**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

**THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:**

Please also refer to section 3 “How Lucentis is given”.

## How to prepare and administer Lucentis to adults

Single-use vial for intravitreal use only

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

In wet AMD, in CNV, in PDR and in visual impairment due to DME or to macular oedema secondary to RVO the recommended dose for Lucentis 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 anatomical parameters indicate that the patient is not benefiting from continued treatment, Lucentis 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.

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

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

Lucentis should be inspected visually for particulate matter and discoloration prior to administration.

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.

Vial-only pack

The vial is for single use only. After injection any unused product must be discarded. Any vial showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the packaging seal remains intact.

For preparation and intravitreal injection the following medical devices for single use are needed:
- a 5 µm filter needle (18G)
- a 1 ml sterile syringe (including a 0.05 ml mark)
- an injection needle (30G x ½″).

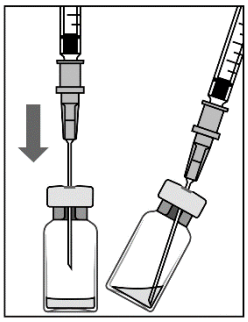
These medical devices are not included within the Lucentis pack.

Vial + filter needle pack

All components are sterile and for single use only. 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. Re-use may lead to infection or other illness/injury.

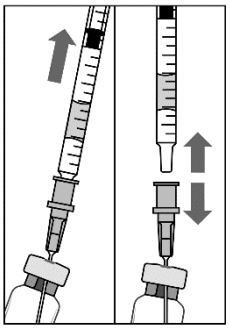
For preparation and intravitreal injection the following medical devices for single use are needed:
- a 5 µm filter needle (18G x 1½″, 1.2 mm x 40 mm, provided)
- a 1 ml sterile syringe (including a 0.05 ml mark, not included within the Lucentis pack)
- an injection needle (30G x ½″; not included within the Lucentis pack)

To prepare Lucentis for intravitreal administration to adult patients, please adhere to the following instructions:



1. Before withdrawal, remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).

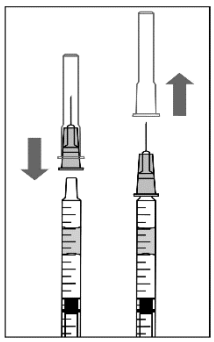
2. Assemble a 5 µm filter needle (18G x 1½″, 1.2 mm x 40 mm, 5 µm) onto a 1 ml syringe using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.



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.

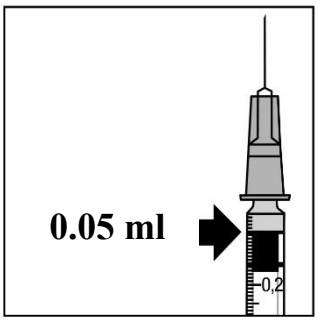
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.



6. Aseptically and firmly assemble an injection needle (30G x ½″, 0.3 mm x 13 mm) 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 from the syringe 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.

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.

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.

**Package leaflet: Information for the patient**

**Lucentis 10 mg/ml solution for injection in pre-filled syringe**
ranibizumab

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Lucentis is and what it is used for
2. What you need to know before you are given Lucentis
3. How Lucentis is given
4. Possible side effects
5. How to store Lucentis
6. Contents of the pack and other information


## 1. What Lucentis is and what it is used for

**What Lucentis is**
Lucentis is a solution which is injected into the eye. Lucentis belongs to a group of medicines called antineovascularisation agents. It contains the active substance called ranibizumab.

**What Lucentis is used for**
Lucentis is used in adults to treat several eye diseases causing vision impairment.

These diseases result from damage to the retina (light-sensitive layer at the back of the eye) caused by:
- Growth of leaky, abnormal blood vessels. This is observed in diseases such as age-related macular degeneration (AMD) and proliferative diabetic retinopathy (PDR, a disease caused by diabetes). It may also be associated with choroidal neovascularisation (CNV) due to pathologic myopia (PM), angioid streaks, central serous chorioretinopathy or inflammatory CNV.
- Macular oedema (swelling of the centre of the retina). This swelling can be caused by diabetes (a disease called diabetic macular oedema (DME)) or by the blockage of retinal veins of the retina (a disease called retinal vein occlusion (RVO)).

**How Lucentis works**
Lucentis specifically recognises and binds to a protein called human vascular endothelial growth factor A (VEGF-A) present in the eye. In excess, VEGF-A causes abnormal blood vessel growth and swelling in the eye which can lead to impairment of vision in diseases like AMD, DME, PDR, RVO, PM and CNV. By binding to VEGF-A, Lucentis can block its actions and prevent this abnormal growth and swelling.

In these diseases, Lucentis can help to stabilise and in many cases improve your vision.

## 2. What you need to know before you are given Lucentis

**You must not receive Lucentis**
- If you are allergic to ranibizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have an infection in or around your eye.
- If you have pain or redness (severe intraocular inflammation) in your eye.

**Warnings and precautions**
Talk to your doctor before you are given Lucentis.
- Lucentis is given as an injection into the eye. Occasionally, an infection in the internal portion of the eye, pain or redness (inflammation), detachment or tear of one of the layers in the back of the eye (retinal detachment or tear and retinal pigment epithelial detachment or tear), or clouding of the lens (cataract) may occur after Lucentis treatment. It is important to identify and treat such an infection or retinal detachment as soon as possible. Please tell your doctor immediately if you develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light.
- In some patients the eye pressure may increase for a short period directly after the injection. This is something you may not notice, therefore your doctor may monitor this after each injection.
- Inform your doctor if you have a prior history of eye conditions or eye treatments, or if you have had a stroke or experienced transient signs of stroke (weakness or paralysis of limbs or face, difficulty speaking or understanding). This information will be taken into account to evaluate if Lucentis is the appropriate treatment for you.

Please see section 4 ("Possible side effects") for more detailed information on side effects that could occur during Lucentis therapy.

**Children and adolescents (below 18 years of age)**
The use of Lucentis in children and adolescents has not been established and is therefore not recommended.

**Other medicines and Lucentis**
Tell your doctor if you are using, have recently used or might use any other medicines.

**Pregnancy and breast-feeding**
- Women who could become pregnant must use effective contraception during treatment and for at least three further months after the last injection of Lucentis.
- There is no experience of using Lucentis in pregnant women. Lucentis should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant, think you may be pregnant or planning to become pregnant, discuss this with your doctor before treatment with Lucentis.
- Small amounts of Lucentis may pass into breast milk, therefore Lucentis is not recommended during breast-feeding. Ask your doctor or pharmacist for advice before Lucentis treatment.

**Driving and using machines**
After Lucentis treatment you may experience some temporary vision blurring. If this happens, do not drive or use machines until this resolves.

## 3. How Lucentis is given

Lucentis is administered as a single injection into your eye by your eye doctor under a local anaesthetic. The usual dose of an injection is 0.05 ml (which contains 0.5 mg of active substance). The pre-filled syringe contains more than the recommended dose of 0.5 mg. The extractable volume 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.

The interval between two doses injected into the same eye should be at least four weeks. All injections will be administered by your eye doctor.

Before the injection, your doctor will wash your eye carefully to prevent infection. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection.

The treatment is started with one injection of Lucentis per month. Your doctor will monitor the condition of your eye and, depending on how you respond to the treatment, will decide if and when you need to receive further treatment.

Detailed instructions for use are given at the end of the leaflet under “How to prepare and administer Lucentis”.

**Elderly (age 65 years and over)**
Lucentis can be used for people of 65 years of age and over without dose adjustment.

**Before stopping Lucentis treatment**
If you are considering stopping Lucentis treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Lucentis.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects associated with the administration of Lucentis are either due to the medicine itself or the injection procedure and mostly affect the eye.

The most serious side effects are described below:
**Common serious side effects** (may affect up to 1 in 10 people): Detachment or tear of the layer in the back of the eye (retinal detachment or tear), resulting in flashes of light with floaters progressing to a temporary loss of sight, or a clouding of the lens (cataract).
**Uncommon serious side effects** (may affect up to 1 in 100 people): Blindness, infection of the eyeball (endophthalmitis) with inflammation of the inside of the eye.

The symptoms you might experience are pain or increased discomfort in your eye, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light. **Please tell your doctor immediately if you develop any of these side effects**.

The most frequently reported side effects are described below:
**Very common side effects** (may affect more than 1 in 10 people)
Visual side effects include: Inflammation of the eye, bleeding in the back of the eye (retinal bleeding), visual disturbances, eye pain, small particles or spots in your vision (floaters), bloodshot eye, eye irritation, a feeling of having something in the eye, increased tear production, inflammation or infection of the eyelid margins, dry eye, redness or itching of the eye and increased eye pressure.
Non-visual side effects include: Sore throat, nasal congestion, runny nose, headache and joint pain.

Other side effects which may occur following Lucentis treatment are described below:
**Common side effects**
Visual side effects include: Decreased sharpness of vision, swelling of a section of the eye (uvea, cornea), inflammation of the cornea (front part of eye), small marks on the surface of the eye, blurred vision, bleeding at the site of injection, bleeding in the eye, discharge from the eye with itching, redness and swelling (conjunctivitis), light sensitivity, eye discomfort, swelling of the eyelid, eyelid pain.
Non-visual side effects include: Urinary tract infection, low red blood cells count (with symptoms such as tiredness, breathlessness, dizziness, pale skin), anxiety, cough, nausea, allergic reactions like rash, hives, itching and skin reddening.

**Uncommon side effects**
Visual side effects include: Inflammation and bleeding in the front part of the eye, sac of pus on the eye, changes of the central part of the eye surface, pain or irritation at the site of injection, abnormal sensation in the eye, irritation of the eyelid.

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lucentis

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and pre-filled syringe label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Prior to use, the sealed tray may be kept at room temperature (25°C) for up to 24 hours.
- Keep the pre-filled syringe in its unopened tray in the carton in order to protect from light.
- Do not use any pack that is damaged.

## 6. Contents of the pack and other information

**What Lucentis contains**
- The active substance is ranibizumab. Each ml contains 10 mg ranibizumab. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
- The other ingredients are α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.

**What Lucentis looks like and contents of the pack**
Lucentis is a solution for injection in a pre-filled syringe. The pre-filled syringe contains 0.165 ml of a sterile, clear, colourless to pale brownish-yellow aqueous solution. The pre-filled syringe contains more than the recommended dose of 0.5 mg. The extractable volume 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.

Pack size of one pre-filled syringe, packed in a sealed tray. The pre-filled syringe is for single use only.

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2870 Puurs-Sint-Amands
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**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

The following information is intended for healthcare professionals only:

Please also refer to section 3 “How Lucentis is given”.

**How to prepare and administer Lucentis**

Single-use pre-filled syringe for intravitreal use only

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

In wet AMD, in CNV, in PDR and in visual impairment due to DME or to macular oedema secondary to RVO the recommended dose for Lucentis 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 anatomical parameters indicate that the patient is not benefiting from continued treatment, Lucentis 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.

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

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

Lucentis should be inspected visually for particulate matter and discoloration prior to administration.

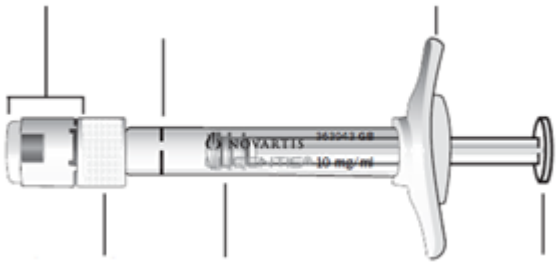
The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The patient's medical history for hypersensitivity 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.

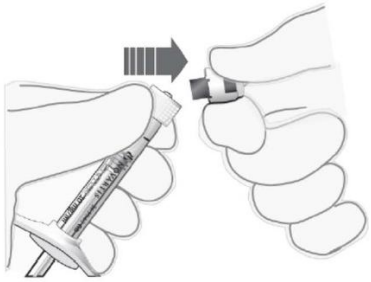
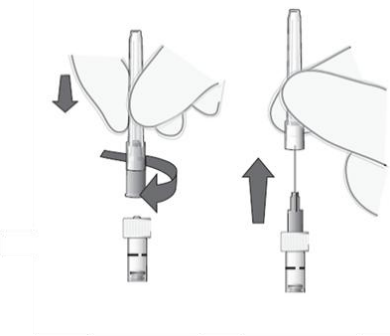
The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discoloured, cloudy or contains particles.

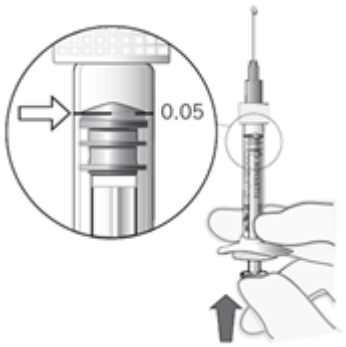
The pre-filled syringe contains more than the recommended dose of 0.5 mg. The extractable volume of the pre-filled syringe (0.1 ml) is not to be used in total. The excess volume should be expelled prior to injection. Injecting the entire volume of the pre-filled syringe could result in overdose. To expel 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., 0.5 mg ranibizumab).

For the intravitreal injection, a 30G x ½″ sterile injection needle should be used.

To prepare Lucentis for intravitreal administration, please adhere to the instructions for use:

<table>
<tr><td>Introduction</td><td colspan="2">Read all the instructions carefully before using the pre-filled syringe.<br>The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.<br>Note: The dose must be set to 0.05 ml.</td></tr>
<tr><td>Pre-filled syringe description</td><td colspan="2">Syringe cap 0.05 ml dose mark Finger grip<br><br>Luer lock Rubber stopper Plunger rod<br>Figure 1</td></tr>
<tr><td>Prepare</td><td colspan="2">1. Make sure that the pack contains:<br>• a sterile pre-filled syringe in a sealed tray.<br>2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe.</td></tr>
<tr><td>Check syringe</td><td>3. Check that:<br>• the syringe cap is not detached from the Luer lock.<br>• the syringe is not damaged.<br>• the solution looks clear, colourless to pale brownish-yellow and does not contain any particles.<br>4. If any of the above is not true, discard the pre-filled syringe and use a new one.</td><td></td></tr>
</table>

| | | |
|---|---|---|
| **Remove syringe cap** | 5. Snap off (do not turn or twist) the syringe cap (see Figure 2).<br>6. Dispose of the syringe cap (see Figure 3). | <br>**Figure 2**<br><br>**Figure 3** |
| **Attach needle** | 7. Attach a 30G x ½″ sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock (see Figure 4).<br>8. Carefully remove the needle cap by pulling it straight off (see Figure 5).<br>**Note: Do not wipe the needle at any time.** | <br>**Figure 4** **Figure 5** |

<table>
<tr><td>Dislodge air bubbles</td><td>9. Hold the syringe upright.<br>10. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).</td><td><br>Figure 6</td></tr>
<tr><td>Set dose</td><td>11. Hold the syringe at eye level and carefully push the plunger until the edge below the dome of the rubber stopper is aligned with the dose mark (see Figure 7). This will expel the air and the excess solution and set the dose to 0.05 ml.<br>Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.</td><td>
<br>Figure 7</td></tr>
<tr><td>Inject</td><td colspan="2">The injection procedure should be carried out under aseptic conditions.<br>12. 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.<br>13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 ml.<br>14. A different scleral site should be used for subsequent injections.<br>15. 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.</td></tr>
</table>

**Package leaflet: Information for guardians of babies born prematurely**

**Lucentis 10 mg/ml solution for injection**
ranibizumab

## BABIES BORN PREMATURELY

Please find information for adults on the other side of this leaflet.

**Read all of this leaflet carefully before your baby is given this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your baby's doctor.
- If your baby gets any side effects, talk to your baby's doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Lucentis is and what it is used for
2. What you need to know before your baby is given Lucentis
3. How Lucentis is given
4. Possible side effects
5. How to store Lucentis
6. Contents of the pack and other information


### 1. What Lucentis is and what it is used for

**What Lucentis is**
Lucentis is a solution which is injected into the eye. Lucentis belongs to a group of medicines called antineovascularisation agents. It contains the active substance called ranibizumab.

**What Lucentis is used for**
Lucentis is used in babies born prematurely to treat retinopathy of prematurity (ROP), a disease causing vision impairment due to damage to the back of the eye (the retina) caused by abnormal growth of blood vessels.

**How Lucentis works**
Lucentis specifically recognises and binds to a protein called human vascular endothelial growth factor A (VEGF-A) present in the eye. In excess, VEGF-A causes abnormal blood vessel growth in the eye. Lucentis can block its actions and prevent this abnormal growth.

### 2. What you need to know before your baby is given Lucentis

**Your baby must not receive Lucentis**
- If your baby is allergic to ranibizumab or any of the other ingredients of this medicine (listed in section 6).
- If your baby has an infection in or around the eye.
- If your baby has pain or redness (severe intraocular inflammation) in the eye.

**Warnings and precautions**
Talk to your baby's doctor before your baby is given Lucentis.
- Lucentis is given as an injection into the eye. Occasionally, an infection in the internal portion of the eye, pain or redness (inflammation), detachment or tear of one of the layers in the back of the eye (retinal detachment or tear and retinal pigment epithelial detachment or tear), or clouding of the lens (cataract) may occur after Lucentis treatment. It is important to identify and

treat such an infection or retinal detachment as soon as possible. **Please tell the doctor immediately if your baby develops signs such as eye pain or worsening eye redness.**
- In some patients the eye pressure may increase for a short period directly after the injection. Your baby's doctor may monitor this after each injection.

Please see section 4 ("Possible side effects") for more detailed information on side effects that could occur during Lucentis therapy.

**Other medicines and Lucentis**
Tell your baby's doctor if your baby is receiving, has recently received or might receive any other medicines.

## 3. How Lucentis is given

Lucentis will be administered by an eye doctor as a single injection into your baby's eyes, usually under local anaesthetic. The usual dose of an injection is 0.02 ml (which contains 0.2 mg of active substance). The interval between two doses injected into the same eye should be at least four weeks. All injections will be administered by the eye doctor.

Before the injection, your baby's doctor will wash your baby's eyes carefully to prevent infection. The doctor will also give your baby a local anaesthetic to reduce or prevent any pain.

The treatment is started with one injection of Lucentis in each eye (some babies may only need treatment in one eye). The doctor will monitor the condition of your baby's eye(s) and, depending on how your baby responds to the treatment, will decide if and when further treatment is needed.

Detailed instructions for use are given at the end of the leaflet under "How to prepare and administer Lucentis to preterm infants".

**Before stopping Lucentis treatment**
If you are considering stopping Lucentis treatment for your baby, please go to your next appointment and discuss this with your baby's doctor. Your baby's doctor will advise you and decide how long your baby should be treated with Lucentis.

If you have any further questions on the use of this medicine, ask your baby's doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects associated with the administration of Lucentis are due either to the medicine itself or to the injection procedure and mostly affect the eye.

**The most common side effects in babies born prematurely are described below:**

Visual side effects include: Bleeding in the back of the eye (retinal bleeding), bleeding in the eye or at the site of injection, and bloodshot eye (conjunctival bleeding).

Non-visual side effects include: Sore throat, nasal congestion and runny nose, low red blood cell counts (with symptoms such as tiredness, breathlessness, pale skin), cough, urinary tract infection, allergic reactions like rash and skin reddening.

**Additional side effects that have been observed with Lucentis in adults are listed below. These side effects may also occur in babies born prematurely**.

The most serious side effects in adults are described below:
Common serious side effects (may affect up to 1 in 10 people): Detachment or tear of the layer in the back of the eye (retinal detachment or tear) progressing to a temporary loss of sight, or a clouding of the lens (cataract).
Uncommon serious side effects (may affect up to 1 in 100 people): Blindness, infection of the eyeball (endophthalmitis) with inflammation of the inside of the eye.

It is important to identify and treat serious side effects such as infection of the eyeball or retinal detachment as soon as possible. **Please tell the doctor immediately if your baby develops signs such as eye pain or worsening eye redness.**

Other side effects in adults are described below:
Very common side effects (may affect more than 1 in 10 people)
Visual side effects include: Inflammation of the eye, visual disturbances, eye pain, small particles or spots in your vision (floaters), eye irritation, a feeling of having something in the eye, increased tear production, inflammation or infection of the eyelid margins, dry eye, redness or itching of the eye and increased eye pressure.
Non-visual side effects include: Headache and joint pain.

Common side effects
Visual side effects include: Decreased sharpness of vision, swelling of a section of the eye (uvea, cornea), inflammation of the cornea (front part of eye), small marks on the surface of the eye, blurred vision, discharge from the eye with itching, redness and swelling (conjunctivitis), light sensitivity, eye discomfort, swelling of the eyelid, eyelid pain.
Non-visual side effects include: Anxiety, nausea.

Uncommon side effects
Visual side effects include: Inflammation and bleeding in the front part of the eye, sac of pus on the eye, changes of the central part of the eye surface, pain or irritation at the site of injection, abnormal sensation in the eye, irritation of the eyelid.

If you have any questions about any side effects, ask your baby's doctor.

**Reporting of side effects**
If you observe any side effects in your baby, talk to your baby`s doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lucentis

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hours.
- Keep the vial in the outer carton in order to protect from light.
- Do not use any pack that is damaged.

## 6. Contents of the pack and other information

**What Lucentis contains**
- The active substance is ranibizumab. Each ml contains 10 mg ranibizumab. Each vial contains 2.3 mg ranibizumab in 0.23 ml solution. This provides a suitable amount to deliver a single dose of 0.02 ml containing 0.2 mg ranibizumab.
- The other ingredients are α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.

**What Lucentis looks like and contents of the pack**
Lucentis is a solution for injection in a vial (0.23 ml). The solution is clear, colourless to pale brownish-yellow and aqueous.

Two different pack types are available:

Vial-only pack
Pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper. The vial is for single use only.

Vial + filter needle pack
Pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper and one blunt filter needle (18G x 1½″, 1.2 mm x 40 mm, 5 micrometres) for withdrawal of the vial contents. All components are for single use only.

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**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

**THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:**

Please also refer to section 3 “How Lucentis is given”.

**How to prepare and administer Lucentis to preterm infants**

Single-use vial for intravitreal use only.

Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections in preterm infants.

**For treatment of preterm infants use the low volume high accuracy syringe provided together with an injection needle (30G x ½″) in the VISISURE kit.**

**For preterm infants the recommended dose for Lucentis is 0.2 mg given as a single intravitreal injection.** This corresponds to an injection volume of 0.02 ml. In preterm infants treatment of retinopathy of prematurity (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 24-week RAINBOW clinical study received one injection per eye. Patients who were treated with 0.2 mg in this clinical study did not require additional treatment in the subsequent long-term extension study which followed the patients up to five years of age. 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.

Lucentis should be inspected visually for particulate matter and discoloration prior to administration.

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.

Vial-only pack
The vial is for single use only. After injection any unused product must be discarded. Any vial showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the packaging seal remains intact.

For preparation and intravitreal injection the following medical devices for single use are needed:
- a 5 µm filter needle (18G); not included within the Lucentis pack
- a low volume high accuracy sterile syringe (supplied separately inside the VISISURE kit)
- an injection needle (30G x ½″); (supplied separately inside the VISISURE kit)

Vial + filter needle pack
All components are sterile and for single use only. 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. Re-use may lead to infection or other illness/injury.

For preparation and intravitreal injection the following medical devices for single use are needed:
- a 5 µm filter needle (18G x 1½″, 1.2 mm x 40 mm, provided)
- a low volume high accuracy sterile syringe (supplied separately inside the VISISURE kit)
- an injection needle (30G x ½″) (supplied separately inside the VISISURE kit)

To prepare Lucentis for intravitreal administration to preterm infants please adhere to the instructions for use in the VISISURE kit.

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.