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.

*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 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) (see section 5.1).
- the treatment of visual impairment due to diabetic macular oedema (DME) (see section 5.1).
- the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1).

4.2 Posology and method of administration

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

Posology

Treatment of wet AMD

The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml.

Treatment is given monthly and continued until maximum visual acuity is achieved i.e. the patient’s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment.

Thereafter patients should be monitored monthly for visual acuity.

Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

Treatment of visual impairment due to either DME or macular oedema secondary to RVO (see also section 5.1)

The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml.
Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient’s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended.

Thereafter patients should be monitored monthly for visual acuity.

Treatment is resumed when monitoring indicates loss of visual acuity due to DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

Lucentis and laser photocoagulation in DME and in macular oedema secondary to RVO

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.

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.

Ethnicity

Experience with treatment is limited in groups other than Caucasians.

Paediatric population

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

Method of administration

Single-use vial for intravitreal use only.

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

Before treatment, the patient should be instructed to self-administer antimicrobial drops (four times daily for 3 days before and following each injection).

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). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

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.

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

Intravitreal injection-related reactions
Intravitreal 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.

Bilateral treatment
The safety and efficacy of Lucentis therapy administered to both eyes concurrently have not been studied. If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.

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, include a large and/or high pigment epithelial retinal detachment. When initiating Lucentis 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, proliferative diabetic retinopathy, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Lucentis in diabetic patients with an HbA1c over 12% and uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

Prior history of stroke or transient ischaemic attacks
There are limited data on safety in the treatment of DME and macular oedema due to RVO patients with prior history of stroke or transient ischaemic attacks. Since there is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors caution should be exercised when treating such patients (see section 4.8).

Prior episodes of RVO, ischaemic branch RVO and central RVO
There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischaemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended.

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, see section 5.1.

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

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
It is unknown whether Lucentis is excreted in human milk. 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 Lucentis 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).

Patients should be informed of 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.

The adverse reactions experienced following administration of Lucentis in clinical trials 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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Common</td>
<td>Urinary tract infection*</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anaemia</td>
</tr>
</tbody>
</table>

Immune system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Hypersensitivity</td>
</tr>
</tbody>
</table>

Psychiatric disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>
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 following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the Lucentis clinical trials in patients with AMD, DME and RVO and there were no major differences between the groups treated with ranibizumab compared to control.
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: Ophthalmicals, antineovascularisation agents, ATC code: S01LA04

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<sub>110</sub>, VEGF<sub>121</sub> and VEGF<sub>165</sub>), 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 or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.

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 choroidal neovascularisation (CNV) received monthly intravitreal injections of Lucentis 0.3 mg (n=238) or 0.5 mg (n=240) or sham (n=238) injections.

In study FVF2587g (ANCHOR), 423 patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham PDT (n=140); 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT (n=140); or 3) sham intravitreal injections and active verteporfin PDT (n=143). Sham or active verteporfin PDT was given with the initial Lucentis injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage.

Key outcome measures are summarised in Tables 1, 2 and Figure 1.

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

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Month</th>
<th>Sham (n=238)</th>
<th>Lucentis 0.5 mg (n=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of &lt;15 letters in visual acuity (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Month 12</td>
<td>62%</td>
<td>95%</td>
</tr>
<tr>
<td>(maintenance of vision, primary endpoint)</td>
<td>Month 24</td>
<td>53%</td>
<td>90%</td>
</tr>
<tr>
<td>Gain of ≥15 letters in visual acuity (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Month 12</td>
<td>5%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>4%</td>
<td>33%</td>
</tr>
<tr>
<td>Mean change in visual acuity (letters) (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Month 12</td>
<td>-10.5 (16.6)</td>
<td>+7.2 (14.4)</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>-14.9 (18.7)</td>
<td>+6.6 (16.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> p<0.01
Table 2  Outcomes at Month 12 and Month 24 in study FVF2587g (ANCHOR)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Month</th>
<th>Verteporfin PDT (n=143)</th>
<th>Lucentis 0.5 mg (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of &lt;15 letters in visual acuity (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Month 12</td>
<td>64%</td>
<td>96%</td>
</tr>
<tr>
<td>(maintenance of vision, primary endpoint)</td>
<td>Month 24</td>
<td>66%</td>
<td>90%</td>
</tr>
<tr>
<td>Gain of ≥15 letters in visual acuity (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Month 12</td>
<td>6%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>6%</td>
<td>41%</td>
</tr>
<tr>
<td>Mean change in visual acuity (letters) (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Month 12</td>
<td>-9.5 (16.4)</td>
<td>+11.3 (14.6)</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>-9.8 (17.6)</td>
<td>+10.7 (16.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>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 trials 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.

The use of Lucentis beyond 36 months has not been studied.

Study FVF3192g (PIER) was a randomised, double-masked, sham-controlled study designed to assess the safety and efficacy of Lucentis in 184 patients with all forms of neovascular AMD. Patients received Lucentis 0.3 mg (n=60) or 0.5 mg (n=61) intravitreal injections or sham (n=63) 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 cross over 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.

The primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline. 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. Data from a limited number of subjects that crossed over to receive ranibizumab after more than a year of sham-treatment suggested that early initiation of treatment may be associated with a better preservation of visual acuity.

In both the MARINA and ANCHOR studies, the improvement in visual acuity seen with Lucentis 0.5 mg at 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) scores. The differences between Lucentis 0.5 mg and the two control groups were assessed with p-values ranging from 0.009 to <0.0001.

The efficacy of Lucentis in the treatment of wet AMD has been further confirmed in AMD studies finalised since the marketing approval. Data from two studies (MONT BLANC, BPD952A2308 and DENALI, BPD952A2309) 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 DME
The efficacy and safety of Lucentis have been assessed in two randomised, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular oedema. A total of 496 patients (336 active and 160 control) were enrolled in these studies, the majority had type II diabetes, 28 ranibizumab-treated patients had type I diabetes.

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 until pre-defined treatment stopping criteria were met. The initial ranibizumab dose (0.3 mg or 0.5 mg) could be doubled at any time during the study after the first injection. Laser photocoagulation was allowed as rescue treatment from Month 3 in both treatment arms. The study had two parts: an exploratory part (the first 42 patients analysed at Month 6) and a confirmatory part (the remaining 109 patients analysed at Month 12).
Key outcome measures from the confirmatory part of the study (2/3 of patients) are summarised in Table 3.

Table 3  Outcomes at Month 12 in study D2201 (RESOLVE) (overall study population)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Ranibizumab pooled (n=102)</th>
<th>Sham (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean average change in BCVA from Month 1 to Month 12 compared to baseline(^a) (letters) (SD) (primary endpoint)</td>
<td>+7.8 (7.72)</td>
<td>-0.1 (9.77)</td>
</tr>
<tr>
<td>Mean change in BCVA at Month 12(^a) (letters) (SD)</td>
<td>+10.3 (9.14)</td>
<td>-1.4 (14.16)</td>
</tr>
<tr>
<td>Gain of ≥10 letters in BCVA (%) at Month 12(^a)</td>
<td>60.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Gain of ≥15 letters in BCVA (%) at Month 12</td>
<td>32.4</td>
<td>10.2</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0043</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)p<0.0001

In the phase III study D2301 (RESTORE), 345 patients with visual impairment due to macular oedema were randomised to receive either intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation (n=118), or sham injection and laser photocoagulation (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly assessments. The treatment was reinitiated when a reduction in BCVA due to DME progression was observed. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before injection of ranibizumab, and then as needed based on ETDRS criteria.

Key outcome measures are summarised in Table 4 and Figure 2.

Table 4  Outcomes at Month 12 in study D2301 (RESTORE)

<table>
<thead>
<tr>
<th>Outcome measure compared to baseline</th>
<th>Ranibizumab 0.5 mg n=115</th>
<th>Ranibizumab 0.5 mg + Laser n=118</th>
<th>Laser n=110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean average change in BCVA from Month 1 to Month 12(^a) (±SD)</td>
<td>6.1 (6.4)</td>
<td>5.9 (7.9)</td>
<td>0.8 (8.6)</td>
</tr>
<tr>
<td>Gain of ≥10 letters or BCVA ≥84(^a) (%)</td>
<td>37.4</td>
<td>43.2</td>
<td>15.5</td>
</tr>
<tr>
<td>Gain of ≥15 letters or BCVA ≥84 (%)</td>
<td>22.6</td>
<td>22.9</td>
<td>8.2</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0032</td>
<td>0.0021</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)p<0.0001
**Figure 2** Mean change in visual acuity from baseline over time in study D2301 (RESTORE)

<table>
<thead>
<tr>
<th>Month</th>
<th>Treatment group</th>
<th>Ranibizumab 0.5 mg (N = 115)</th>
<th>Ranibizumab 0.5 mg + Laser (N = 118)</th>
<th>Laser (N = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ranibizumab 0.5 mg (N = 115)</td>
<td>+6.8/+ 6.4</td>
<td>+6.2/+ 5.4*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ranibizumab 0.5 mg + Laser (N = 118)</td>
<td>+0.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 was consistent in most subgroups. However, subjects with a fairly good baseline BCVA (>73 letters) together with macular oedema with central retinal thickness of <300 μm did not appear to benefit from treatment with ranibizumab compared to laser photocoagulation.

The improvement in visual acuity seen with Lucentis 0.5 mg at 12 months was accompanied by patient-reported benefits with regards to most vision-related functions as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) scores. For other subscales of this questionnaire no treatment differences could be established. The difference between Lucentis 0.5 mg and the control group was assessed with p-values of 0.0137 (ranibizumab mono) and 0.0041 (ranibizumab+laser) for the VFQ-25 composite score.

In both studies, the improvement of vision was accompanied by a continuous decrease in the macular oedema as measured by central retinal thickness (CRT).

**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 intravitreal ranibizumab or sham injections. After 6 months, patients in the sham-control arms were crossed over to 0.5 mg ranibizumab. In BRAVO, laser photocoagulation as rescue was allowed in all arms from Month 3.
Key outcome measures from BRAVO and CRUISE are summarised in Tables 5 and 6 and Figures 3 and 4.

**Table 5**  Outcomes at Month 6 and 12 (BRAVO)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sham/Lucentis 0.5 mg (n=132)</th>
<th>Lucentis 0.5 mg (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in visual acuity at Month 6a (letters) (SD) (primary endpoint)</td>
<td>7.3 (13.0)</td>
<td>18.3 (13.2)</td>
</tr>
<tr>
<td>Mean change in BCVA at Month 12 (letters) (SD)</td>
<td>12.1 (14.4)</td>
<td>18.3 (14.6)</td>
</tr>
<tr>
<td>Gain of ≥15 letters in visual acuity at Month 6a (%)</td>
<td>28.8</td>
<td>61.1</td>
</tr>
<tr>
<td>Gain of ≥15 letters in visual acuity at Month 12 (%)</td>
<td>43.9</td>
<td>60.3</td>
</tr>
<tr>
<td>Proportion (%) receiving laser rescue over 12 months</td>
<td>61.4</td>
<td>34.4</td>
</tr>
</tbody>
</table>

*p<0.0001

**Figure 3**  Mean change from baseline BCVA over time to Month 6 and Month 12 (BRAVO)

BL=baseline; SE=standard error of mean
Table 6   Outcomes at Month 6 and 12 (CRUISE)

<table>
<thead>
<tr>
<th></th>
<th>Sham/Lucentis 0.5 mg (n=130)</th>
<th>Lucentis 0.5 mg (n=130)</th>
</tr>
</thead>
</table>
| Mean change in visual acuity at Month 6
d (letters) (SD) (primary endpoint) | 0.8 (16.2)                    | 14.9 (13.2)             |
| Mean change in BCVA at Month 12
d (letters) (SD)                  | 7.3 (15.9)                    | 13.9 (14.2)             |
| Gain of ≥15 letters in visual acuity at Month 6 (%) | 16.9                        | 47.7                    |
| Gain of ≥15 letters in visual acuity at Month 12 (%) | 33.1                        | 50.8                    |

*p<0.0001

Figure 4   Mean change from baseline BCVA over time to Month 6 and Month 12 (CRUISE)

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 BRVO (BRAVO and extension study HORIZON): After 2 years, subjects that were treated with sham in the first 6 months and subsequently crossed over to ranibizumab treatment had achieved comparable gains in VA (~15 letters) compared to subjects that were treated with ranibizumab from study start (~16 letters). However the number of patients completing 2 years was limited and in HORIZON only quarterly monitoring visits were scheduled. Therefore there is currently insufficient evidence to conclude on recommendations as to when ranibizumab treatment should be initiated in patients with BRVO.
In patients with CRVO (CRUISE and extension study HORIZON): After 2 years, subjects that were treated with sham in the first 6 months and subsequently crossed over to ranibizumab treatment did not achieve comparable gains in VA (~6 letters) compared to subjects that were treated with ranibizumab from study start (~12 letters).

The improvement in visual acuity observed with ranibizumab treatment at 6 and 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) sub-scales related to near and distance activity. The difference between Lucentis 0.5 mg and the control group was assessed at Month 6 with p-values of 0.02 to 0.0002.

**Paediatric population**
Safety and efficacy of ranibizumab have not yet been studied in paediatric patients.

The European Medicine 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 diabetic macular oedema and visual impairment due to macular oedema secondary to retinal vein occlusion (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 ($C_{\text{max}}$) 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). $C_{\text{max}}$ 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 $C_{\text{max}}$, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/ml, and $C_{\text{min}}$ 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 vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.23 ml sterile solution in a vial (type I glass) with a stopper (chlorobutyl rubber), with 1 filter needle, 1 injection needle and 1 syringe (polypropylene). Pack containing 1 vial.

6.6 Special precautions for disposal and other handling

Vials are for single use only.

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

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.

2. Assemble the 5 µm filter needle (provided) onto the 1 ml syringe (provided) 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 the injection needle (provided) onto the syringe.

7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

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

8. Carefully expel the air 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/374/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 22 January 2007
Date of latest renewal: 22 January 2012

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
USA

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

Name and address of the manufacturer responsible for batch release

Novartis Pharma S.A.S.
Centre de Biotechnologie
8, rue de l'Industrie
F-68330 Huningue
France

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

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs
The PSUR submission schedule follows a 1-year cycle.
• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The Marketing Authorisation Holder (MAH) shall ensure that updated physician information packs are provided to all ophthalmology clinics where Lucentis is expected to be used. The physician information pack should contain the following:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Sterile techniques, including periocular and ocular disinfection, to minimise risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- Key signs and symptoms of IVT injection related adverse events
- Management of IVT injection related adverse events

The patient information pack should be provided in the form of both patient information booklets and 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
- When to seek urgent attention from the health care provider

The MAH must implement this educational plan nationally, prior to marketing, and as agreed with the competent authorities in the Member States.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

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

1 vial of 0.23 ml solution for injection

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.
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 AUTHORIZATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORIZATION NUMBER(S)

EU/1/06/374/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.
## MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

### VIAL LABEL

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lucentis 10 mg/ml solution for injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ranibizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravitreal use</td>
<td></td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP</td>
<td></td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td>Lot</td>
<td></td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 vial = 2.3 mg ranibizumab.</td>
<td></td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
Package leaflet: Information for the patient
Lucentis 10 mg/ml solution for injection
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.

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

Lucentis belongs to a group of medicines called antineovascularisation agents. It contains the active substance ranibizumab, which is a part of an antibody. Antibodies are proteins which specifically recognise and bind to other unique proteins in the body. Ranibizumab binds selectively to a protein called human vascular endothelial growth factor A (VEGF-A). VEGF-A causes abnormal blood vessel growth and swelling in the macula which damage the macula and can impair vision. The macula is the central part of the light-sensitive back part of the eye called the retina that is responsible for sharp, central vision and is important for activities such as reading or recognising faces. By binding to VEGF-A, Lucentis can block its actions and prevent this abnormal growth and swelling.

Lucentis is used in adults to treat damage to the macula caused by growth of leaky, abnormal blood vessels in diseases such as wet age-related macular degeneration (wet AMD). It is also used to treat diseases such as macular oedema (swelling) caused by diabetes (called diabetic macular oedema, DME) or macular oedema due to a blockage of the veins behind the retina (retinal vein occlusion, RVO) where fluid accumulates into the back of the eye. Lucentis reduces leaking of the blood vessels, swelling in the macula and damage to your retina which, on average, results in improved vision, as measured on an eye chart.

These diseases affect the central part of the retina (called the macula) at the back of the eye. The macula provides central vision and damage to the macula causes loss of “straight-ahead” 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.

Children and adolescents (below 18 years of age)
The use of Lucentis in children and adolescents has not been studied 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 might become pregnant are advised to use effective contraception during treatment.
- There is no experience of using Lucentis in pregnant women; therefore the potential risks are unknown. If you are pregnant, think you may be pregnant or are planning to become pregnant, please discuss this with your doctor before Lucentis treatment.
- Lucentis is not recommended during breast-feeding because it is not known whether Lucentis passes into human milk. 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 should not be shorter than 1 month. All Lucentis injections will be administered by your eye doctor.

Before the injection, your doctor will use antibiotic eye drops and 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.

If you are being treated for wet age-related macular degeneration (wet AMD)
The injection is given once a month in the first 3 months. Afterwards, your doctor will monitor your vision on a monthly basis. If your condition is found to be worsening, your doctor will administer Lucentis to your affected eye again.

If you are being treated for visual impairment due to diabetic macular oedema (DME) or macular oedema secondary to retinal vein occlusion (RVO)
The injection is given once a month. Your doctor will monitor your vision monthly. If your vision remains the same while you are being given Lucentis treatment, your doctor may decide to stop the
treatment with Lucentis. Your doctor will continue to monitor your vision monthly and will decide if treatment with Lucentis should be resumed or not. Your doctor may decide that you also need to be treated with laser for this condition. If so, laser can be administered together with Lucentis.

Your doctor will ask you to use antimicrobial eye drops four times daily for 3 days before and after each injection in order to prevent any possible eye infection.

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

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

If a dose of Lucentis is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

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 described in section 2 of this leaflet (please read section 2 “What you need to know before you are given Lucentis”). 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.

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

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.
- 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 (10 mg/ml). Each ml contains 10 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 yellow and aqueous.

Lucentis is supplied as a pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper, one filter needle for withdrawal of the vial contents, one injection needle and one syringe for withdrawal of the vial contents and for intravitreal injection.

**Marketing Authorisation Holder**
Novartis Europharm Limited
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United Kingdom

**Manufacturer**
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France
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Luxembourg/Luxemburg**
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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**

Single-use vial for intravitreal use only

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

In wet AMD, visual impairment due to DME and macular oedema secondary to RVO, the recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml.

**Treatment of wet AMD**

Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient’s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment.

Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

**Treatment of visual impairment due to DME and macular oedema secondary to RVO**

Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient’s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended.

Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

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

Before treatment, the patient should be instructed to self-administer antimicrobial drops (four times daily for 3 days before and following each injection).

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. The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.
To prepare Lucentis for intravitreal administration, please adhere to the following instructions:

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.

2. Assemble the 5 µm filter needle (provided) onto the 1 ml syringe (provided) 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 the injection needle (provided) onto the syringe.

7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

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

8. Carefully expel the air 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.

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