NOVARTIS

פברואר 2016

רופא/ה / רוקח/ת נכבד/ה,

הנדון: Lucentis (ranibizumab), solution for injection
לוסנטיס, תמיסה להזרקה

אנו שמחים לעדכן כי בדצמבר 2014, משרד הבריאות הישראלי אישר פרזנטציה חדשה לתכשיר לוסנטיס:
מזרק מוכן לשימוש - Pre-filled syringe שיופץ בימים הקרובים לבתי המרקחת.
הפרזנטציה תצטרף לפרזנטציה הקיימת- בקבוקון (vial) ואביזרי הזרקה.

התכשיר שבנדון רשום בישראל להתוויות הבאות:
Treatment of patients with neovascular (wet) age-related macular degeneration (AMD).
Treatment of adult patients with visual impairment due to diabetic macular edema (DME).
Treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO).
The treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM).

המרכיב הפעיל: Ranibizumab 10mg/ml.

העלון אושר במרץ 2015 והודעה על כך הופצה באוגוסט 2015. העדכונים בעלון מופצים כעת בשנית לקראת הפצת הפרזנטציה החדשה.
עידכונים מהותיים בעלון הכוללים הוראות הזרקה באמצעות מזרק מוכן לשימוש סומנו בצורה הבאה: תוספת טקסט מסומן בכחול, ~~כיתוב עם קו חוצה~~ מציין ביטול טקסט מהותי.

העלון נשלח למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

רופא/ה / רוקח/ת נכבד/ה, אנא עדכנ/י את המטופל/ת במידע החדש הרלוונטי לו/ה.

בברכה,
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NOVARTIS

Prescribing Information

1. Trade name

Lucentis

2. Description and composition

Pharmaceutical form:
Solution for injection.

Lucentis is supplied in a vial or a pre-filled syringe.

Vial

Sterile, clear, colorless to pale yellow and preservative-free aqueous solution.

Pre-filled syringe

Sterile, clear, colorless to pale yellow and preservative-free aqueous solution.

Active substance:
One ml contains 10 mg ranibizumab.

Vial

Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution.

Pre-filled syringe

Each pre-filled syringe contains 1.65 mg of ranibizumab in 0.165 mL solution.

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

Active moiety:
Ranibizumab

Excipients:
α,α-trehalose dihydrate, L-histidine HCl monohydrate, L-histidine, polysorbate 20, water for injection

3. Indications

Lucentis is indicated for:

- The treatment of patients with neovascular (wet) age-related macular degeneration (AMD)
- The treatment of adult patients with visual impairment due to diabetic macular edema (DME)
- The treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO)
- The treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM).

4. Dosage and administration

Dosage

Single-use vial or single-use pre-filled syringe for intravitreal use only. Use of more than one injection from a vial can lead to product contamination and subsequent ocular infection.

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

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 not be shorter than one month.

~~Patients should be monitored monthly for visual acuity.~~

General target population

Treatment of wet AMD, visual impairment due to DME or due to macular edema secondary to RVO, visual impairment due to CNV secondary to PM

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. ~~confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis treatment.~~

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 anatomic parameters.

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, for example, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by two weeks at a time for wet AMD and central RVO (CRVO), or by one month at a time for DME and branch RVO (BRVO). If disease activity recurs, the treatment interval should be shortened accordingly.

In the treatment of visual impairment due to CNV secondary to PM, many patients may only need one or two injections during the first year, while some patients may need more frequent treatment (see section 12 Clinical studies).

Lucentis and laser photocoagulation in DME and branch RVO:

Lucentis has been used concomitantly with laser photocoagulation in clinical studies (see section 12 Clinical studies). 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 Visudyne photodynamic therapy in CNV secondary to PM

There is no experience of concomitant administration of Lucentis and Visudyne.

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 11 Clinical pharmacology-pharmacokinetic properties).

Paediatric patients
Lucentis is not recommended for use in children and adolescents due to a lack of data on safety and efficacy in these sub-populations.

Geriatric patients
No dose adjustment is required in the elderly.

Method of administration
As with all medicinal products for parenteral use, 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). Sterile paracentesis. equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 5 Contraindications). 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 14 Pharmaceutical information, Special precautions for disposal and other handling.

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

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with active or suspected ocular or periocular infections.

Patients with active severe intraocular inflammation.

6 Warnings and precautions

Treatment with Lucentis is for intravitreal injection only.

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 7 Adverse drug reactions). 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 (see section 7 Adverse drug reactions). Sustained IOP increases have also been reported. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.

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.
~~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).

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.

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 is a potential risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors. In the wet AMD Phase III studies, the overall frequency of arterial thromboembolic events was similar between ranibizumab and control. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control, however, the differences were not statistically significant.
The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack. Therefore, these patients should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and whether the benefit outweighs the potential risk.
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.

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 ischemic central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended.

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.

Driving and using machines

The Lucentis treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see section 7 Adverse drug reactions). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

7 Adverse drug reactions

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 6).
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.

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 trials in patients with AMD, DME, RVO

and PM and there were no major differences between the groups treated with ranibizumab compared to control.

Wet AMD population

A total of 1,315 patients constituted the safety population in the three controlled phase III studies for wet AMD [FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER)] with 24 months exposure to Lucentis and 440 patients were treated with the recommended dose of 0.5 mg.

Serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 6 Warnings and precautions).

Other serious ocular events observed among Lucentis-treated patients included intraocular inflammation and increased intraocular pressure (see section 6 Warnings and precautions).

The adverse events listed below in Table 7-1 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 injection, as defined in section 11 Clinical pharmacology or verteporfin PDT)) in the pooled data of the three controlled wet AMD studies. These were therefore considered potential adverse drug reactions. The safety data described below also include all adverse events suspected to be at least potentially related to the injection procedure or medicinal product in the 440 wAMD patients ~~of the combined~~ treated with 0.5 mg ~~treatment groups in wet AMD~~ Lucentis.

DME population

The safety of Lucentis was studied in a one-year sham-controlled trial (RESOLVE) and in a one-year laser-controlled trial (RESTORE) conducted respectively in 102 and 235 ranibizumab-treated patients with visual impairment due to DME (see section 12 Clinical studies). The event of urinary tract infection, in the common frequency category, met the adverse reaction criteria for the Table 7-1 below; otherwise ocular and non-ocular events in the RESOLVE and RESTORE trials were reported with a frequency and severity similar to those seen in the wet AMD trials.

RVO population

The safety of Lucentis was studied in two 12-month trials (BRAVO and CRUISE) conducted respectively in 264 and 261 ranibizumab-treated patients with visual impairment due to macular edema secondary to BRVO and CRVO, respectively (see section 12 Clinical Studies). Ocular and non-ocular events in the BRAVO and CRUISE trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

PM population

The safety of Lucentis was studied in the 12-month clinical trial (RADIANCE), which included 224 ranibizumab-treated patients with visual impairment due to CNV secondary to PM (see section 12 Clinical studies). Ocular and non-ocular events in this trial were reported with a frequency and severity similar to those seen in the wet AMD trials.

Tabulated summary of adverse drug reactions from clinical trials[#]

The adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 7-1 Adverse drug reactions from clinical trials

Blood and lymphatic system disorders	
Common	Anaemia
Immune system disorders	
Common	Hypersensitivity
Psychiatric disorders	
Common	Anxiety
Nervous system disorders	
Very common	Headache
Common	Stroke
Eye disorders	
Very common	Intraocular inflammation, vitritis, vitreous detachment, retinal hemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperemia, 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 hemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site hemorrhage, eye hemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperemia
Uncommon	Blindness, endophthalmitis, hypopyon, hyphema, keratopathy, iris adhesions, corneal deposits, corneal edema, 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
Infections and infestations	

Very common	Nasopharyngitis
Common	Influenza, urinary tract infection*
Investigations	
Very common	Intraocular pressure increased

*Observed only in the DME population

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).

8 Interactions

No formal interaction studies have been performed.
In clinical trials for treatment of visual impairment due to DME, the outcome with regards to visual acuity or central retinal thickness in patients treated with Lucentis was not affected by concomitant treatment with thiazolidinediones (see section 12 Clinical studies)
~~For the adjunctive use of verteporfin photodynamic therapy (PDT) and Lucentis in wet AMD and PM, see section 12 Clinical studies.~~
For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see section 12 Clinical studies and 4 Dosage and administration.

9 Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

Women of child-bearing 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 13 Non-clinical safety data). 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-/fetotoxic. 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 not known whether Lucentis is excreted in human milk. Breast-feeding is not recommended during the use of Lucentis.

Fertility

There is no fertility data available.

10 Overdosage

Cases of accidental overdose (injection of volumes greater than the recommended 0.05ml Lucetis) have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions most frequently 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.

In clinical trials doses up to 2 mg of ranibizumab in an injection volume of 0.05 mL to 0.10 mL have been administered to patients with wet AMD and DME. The type and frequency of ocular and systemic adverse events were consistent with those reported for the 0.5 mg (in 0.05 mL) Lucentis dose.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineovascularization agents, ATC code: S01LA04.

Mechanism of action (MOA)

Ranibizumab is a humanized 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.

Pharmacodynamics (PD)

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularization, as well as vascular leakage, which are thought to contribute to the progression of the neovascular form of age-related macular degeneration ~~or~~, to the development of CNV secondary to pathologic myopia, ~~and~~ or to the macular edema causing visual impairment in diabetes and retinal vein occlusion.

Pharmacokinetics

Absorption

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. 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 in DME and RVO patients were similar to those observed in neovascular AMD patients.

Distribution and elimination

Based on analysis of population pharmacokinetics and the 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. Serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal ranibizumab concentrations.

Special populations

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 in a population pharmacokinetic analysis 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.

12 Clinical studies

Treatment of wet AMD

In wet AMD the clinical safety and efficacy of Lucentis have been assessed in three randomized, double-masked, sham**- or active-controlled studies in patients with neovascular AMD [FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER)]. A total of 1,323 patients (879 active and 444 control) were enrolled in these studies.

Study FVF2598g (MARINA) and study FVF2587g (ANCHOR)

In the 24-month study FVF2598g (MARINA), patients with minimally classic or occult (with no classic) choroidal neovascularisation (CNV) received monthly intravitreal injections of Lucentis 0.3 mg or 0.5 mg or sham injections. A total of 716 patients were enrolled in this study (sham, 238; Lucentis 0.3 mg, 238; Lucentis 0.5 mg, 240).

In the 24-month study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham PDT; 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Verteporfin (or sham) PDT was given with the initial Lucentis (or sham) injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage. A total of 423 patients were enrolled in this study (; Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140, verteporfin PDT, 143).

** *The sham Lucentis injection control procedure involved anesthetizing the eye in a manner identical to a Lucentis intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.*

Key outcomes are summarized in Tables 12-1, 12-2 and Figure 12-1.

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

Outcome measure	Month	Sham (n=238)	Lucentis 0.5 mg (n=240)
Loss of <15 letters in visual acuity (%)[a] (maintenance of vision)	Month 12	62%	95%
	Month 24	53%	90%
Gain of ≥15 letters in visual acuity (%)[a]	Month 12	5%	34%
	Month 24	4%	33%
Mean change in visual acuity (letters) (SD)[a]	Month 12	-10.5 (16.6)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+6.6 (16.5)

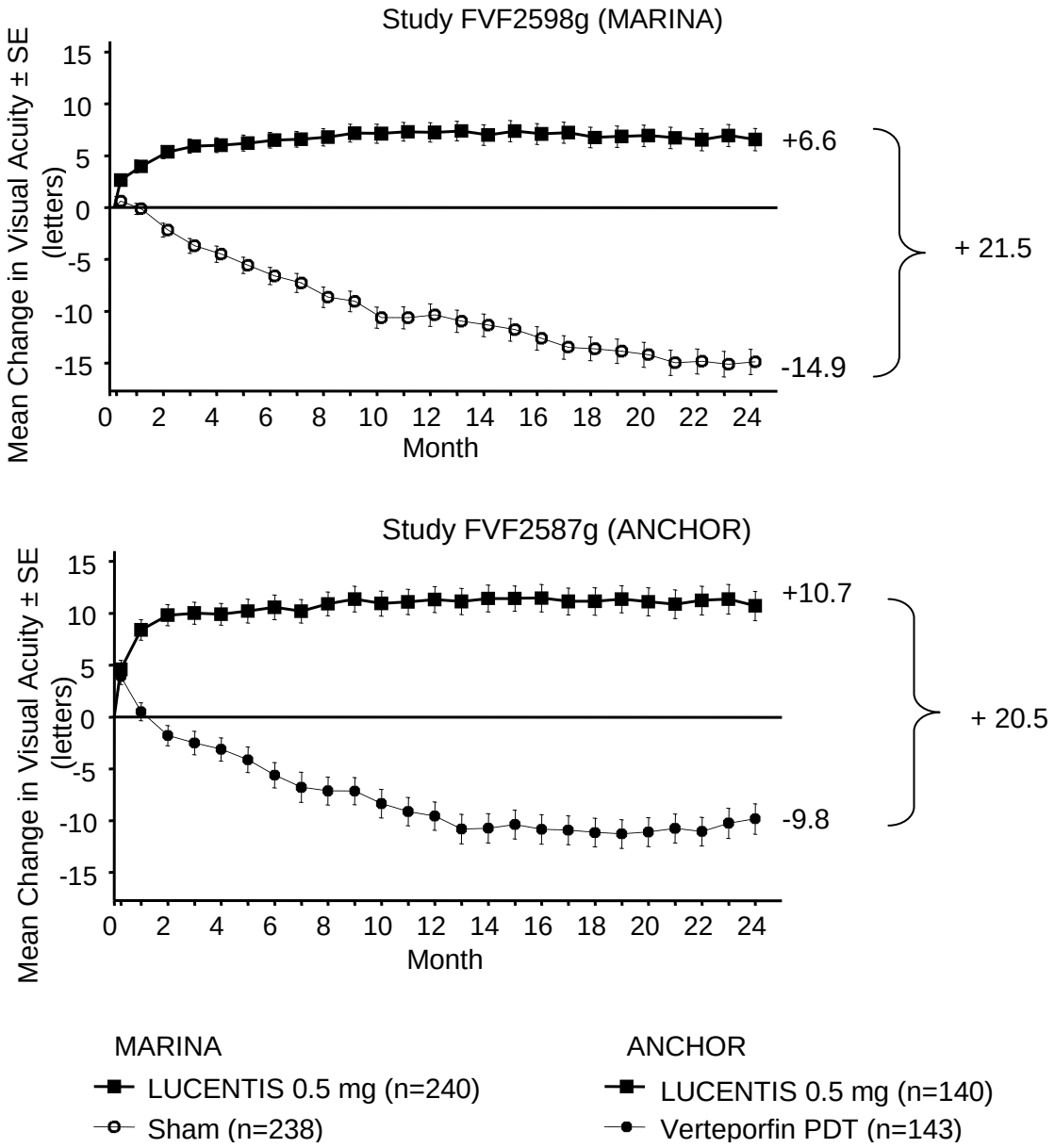
[a] p<0.01

Table 12-2 Outcomes at Month 12 and Month 24 in study FVF2587g (ANCHOR)

Outcome measure	Month	Verteporfin PDT (n=143)	Lucentis 0.5 mg (n=140)
Loss of <15 letters in visual acuity (%)[a] (maintenance of vision)	Month 12	64%	96%
	Month 24	66%	90%
Gain of ≥15 letters in visual acuity (%)[a]	Month 12	6%	40%
	Month 24	6%	41%
Mean change in visual acuity (letters) (SD)[a]	Month 12	-9.5 (16.4)	+11.3 (14.6)
	Month 24	-9.8 (17.6)	+10.7 (16.5)

[a] p<0.01

Figure 12-1 Mean change in visual acuity from baseline to Month 24 in study FVF2598g (MARINA) and study FVF2587g (ANCHOR)



Patients in the group treated with Lucentis had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3 DA for Lucentis versus 2.3-2.6 DA for the control arms.

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

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.

Study FVF3192g (PIER

Study FVF3192g (PIER) Study FVF3192g (PIER) was a randomized, double-masked, sham-controlled,

two-year study designed to assess the safety and efficacy of Lucentis in 184 patients with neovascular AMD. Patients received Lucentis 0.3 mg or 0.5 mg intravitreal injections 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 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 treatments during the study.
The primary efficacy endpoint was mean change in visual acuity at Month 12 compared with baseline. After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with Lucentis lost visual acuity, returning to baseline at Month 12. This effect was maintained in most Lucentis-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.

Study FVF3689g (SAILOR)

Study FVF3689g (SAILOR) was a Phase IIIb, single-masked, one-year multicenter study in naïve and previously treated subjects with CNV secondary to AMD. The primary study objective was to estimate the incidence of ocular and non-ocular serious adverse events in subjects treated for 12 months. Overall, 2378 patients were randomized in a 1:1 ratio to receive one intravitreal injection of 0.3 mg or 0.5mg ranibizumab every month for three consecutive months followed by re-treatment as needed not more often than monthly.

Overall, no imbalances between the two dose groups were observed in the frequency of ocular and non-ocular adverse events. There was a statistically non-significant trend towards a higher stroke rate in the 0.5 mg group compared to the 0.3 mg group. The respective 95% CIs for the overall stroke rate were wide (0.3% to 1.3% for the 0.3 mg group vs. 0.7% to 2.0% for the 0.5 mg group). The number of strokes was small in both dose groups, and there is not sufficient evidence to conclude (or rule out) that there is a true difference in stroke rates among the treatment groups. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke and transient ischemic attack.

Treatment of visual impairment due to DME

The efficacy and safety of Lucentis have been assessed in two randomized, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular edema [Study D2301 (RESTORE) and D2201 (RESOLVE)]. A total of 496 patients (336 active and 160 control) were enrolled in these studies, the majority had type II diabetes, 28 patients treated with ranibizumab had type I diabetes.

Study D2301 (RESTORE)

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular edema were randomized to receive either initial intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation, 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 there was a reduction in BCVA due to DME progression. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before the injection of ranibizumab, and then as needed based on Early Treatment Diabetic Retinopathy study (ETDRS) criteria.
Key outcomes are summarized in Table 12-3 and Figure 12-2.

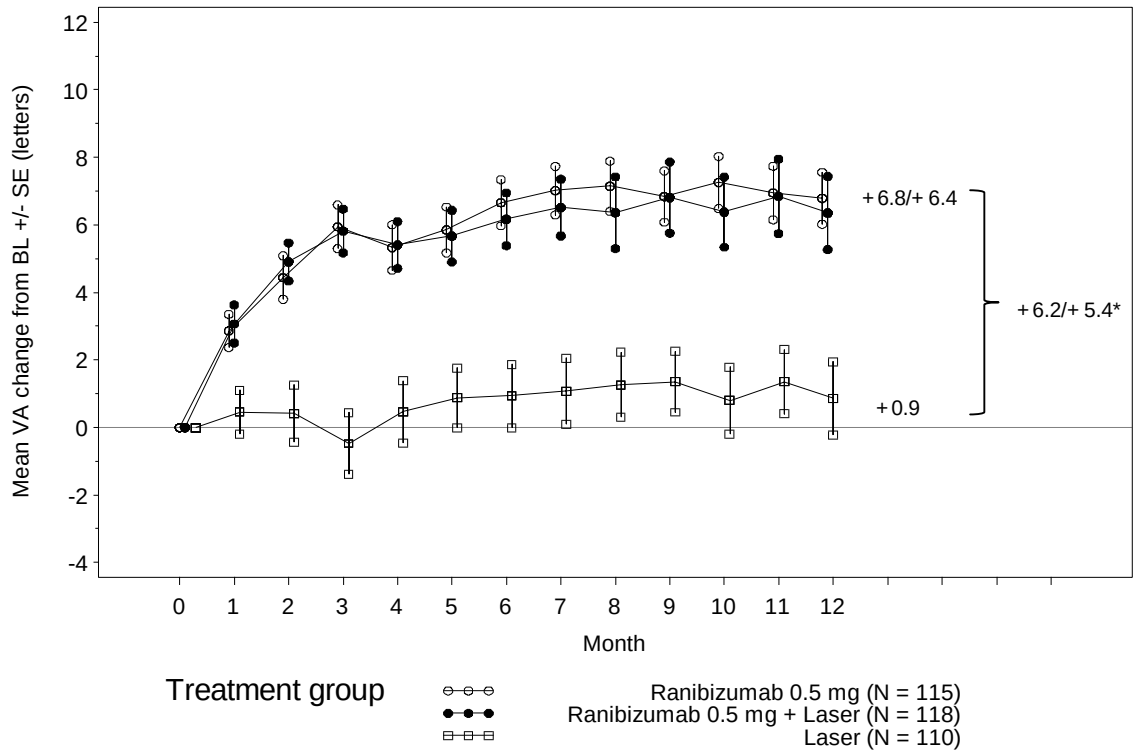
Table 12-3 Outcomes at Month 12 in study D2301 (RESTORE)

Outcome measure	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 compared to baseline (letters) (SD) [b]	+6.1 (6.43)	+5.9 (7.92)	+0.8 (8.56)
Mean change in BCVA at Month 12 compared to baseline (letters) (SD)	+6.8 (8.25)[b]	+6.4 (11.77)[c]	+0.9 (11.44)
Gain of ≥10 letters in BCVA (% of patients) at Month 12	37.4[d]	43.2[b]	15.5
Gain of ≥15 letters in BCVA (% of patients) at Month 12	22.6[e]	22.9[f]	8.2

[b] p<0.0001, [c]p=0.0004, [d]p=0.0001, [e]p=0.0032, [f]p=0.0021

Figure 12-2 Mean BCVA change from baseline over time in study D2301 (RESTORE)



BL=baseline; SE= standard error of mean

Study D2301E1 (RESTORE Extension)

Study D2301E1 (RESTORE Extension) was an open-label, multi-center, 24-month extension study. 240 patients who had completed the 12-month core study entered the extension study and were treated with ranibizumab 0.5 mg *pro re nata* (PRN) in the same eye that was selected as the study eye in the core study. Treatment was administered monthly upon a decrease in BCVA due to DME until stable BCVA was reached. In addition, laser treatment was administered, if deemed necessary by the investigator, and based on ETDRS guidelines.

On average, 6.4 ranibizumab injections were administered per patient in the 24-month extension period in patients who were treated with ranibizumab in the core study. Of the 74 patients from the core study laser

treatment arm, 59 (79%) patients received ranibizumab at some point during the extension phase. On average, these 59 patients received 8.1 ranibizumab injections per patient over the 24 months of the extension study. The proportions of patients who did not require any ranibizumab treatment during the extension phase were 19%, 25% and 20% in the prior ranibizumab, prior ranibizumab + laser, and prior laser group, respectively.

Key outcome measures are summarized in Table 12-4.

Table 12-4 Outcomes at Month 36 in study D2301E1 (RESTORE Extension)

Outcome measure compared to core baseline	**Prior ranibizumab 0.5 mg n=83**	**Prior ranibizumab 0.5 mg + Laser n=83**	**Prior laser n=74***
Mean change in BCVA from baseline in the core study at Month 36 (SD)	+8.0 (10.09)	+6.7 (9.59)	+6.0 (9.35)
Gain of ≥10 letters from core baseline or BCVA ≥84 (%) at Month 36	39 (47.0)	37 (44.6)	31 (41.9)
Gain of ≥15 letters from core baseline or BCVA ≥84 (%) at Month 36	23 (27.7)	25 (30.1)	16 (21.6)

n The number of patients with a value both at core baseline (Month 0) and at the Month 36 visit.

* Of the 74 patients with prior laser treatment, 59 (79%) patients received ranibizumab in the extension study

VFQ-25 scores in patients who were previously treated with ranibizumab PRN in the core study stabilized during the extension phase. Those treated with laser in the core study control group, and then switched to ranibizumab PRN treatment in the extension phase, demonstrated an improvement in VFQ-25 scores.

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

Study D2201 (RESOLVE)

In study D2201 (RESOLVE), a total of 151 patients with macular center involvement causing visual impairment 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 (0.3mg or 0.5mg) could be doubled at any time during the study after the first injection if the investigator evaluated that response to treatment was not sufficiently achieved. Laser photocoagulation rescue treatment was allowed from Month 3 in both treatment arms.

The study was comprised of two parts: an exploratory part (the first 42 patients analyzed at Month 6), and a confirmatory part (the remaining 109 patients analyzed at Month 12).

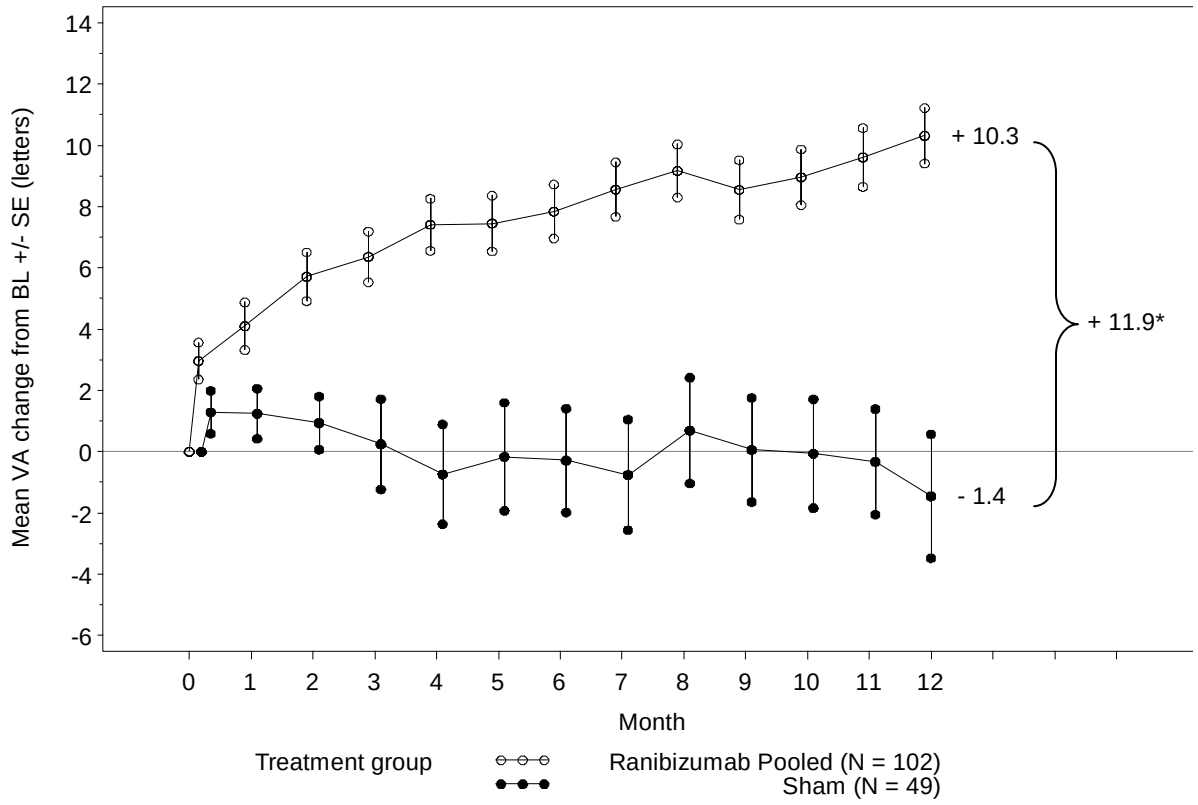
Key outcomes from the confirmatory part of the study (2/3 of the patients) are summarized in Table 12-5 and Figure 12-3.

Table 12-5 Outcomes at Month 12 in study D2201 (RESOLVE) (overall study population)

Outcome measure	Ranibizumab pooled (n=102)	Sham (n=49)
Mean average change in BCVA from Month 1 to Month 12 compared to baseline (letters) (SD)[b]	+7.8 (7.72)	-0.1 (9.77)
Mean change in BCVA at Month 12 compared to baseline (letters) (SD) [b]	+10.3 (9.14)	-1.4 (14.16)
Gain of ≥10 letters in BCVA (% patients) at Month 12[b]	60.8	18.4
Gain of ≥15 letters in BCVA (% patients) at Month 12[g]	32.4	10.2

[b] p<0.0001, [g]p=0.0043

Figure 12-3 Mean change in visual acuity from baseline over time in study D2201 (RESOLVE) (overall population)



BL=baseline; SE= standard error of mean

Patients treated with ranibizumab experienced a continuous reduction in central retina thickness (CRT). At Month 12, the mean CRT change from baseline was -194 micrometers for ranibizumab versus -48 micrometers for sham control.

Overall, ocular and non-ocular safety findings in DME patients of both studies D2201 and D2301 were comparable with the previously known safety profile observed in wet AMD patients.

Study D2304 (RETAIN)

In the phase IIIb study D2304 (RETAIN), 372 patients with visual impairment due to DME were randomized to receive either intravitreal injection of

- ranibizumab 0.5 mg with concomitant laser photocoagulation on a treat-and-extend (TE) regimen (n=121),
- ranibizumab 0.5 mg monotherapy on a TE regimen (n=128), or
- ranibizumab 0.5 mg monotherapy on a *pro re nata* (PRN) regimen (n=123).

In all groups, treatment with ranibizumab was initiated with monthly intravitreal injections and continued until BCVA was stable for at least three consecutive monthly assessments. Laser photocoagulation was administered at baseline on the same day as the first ranibizumab injection and then as needed based on ETDRS criteria. On TE regimen, ranibizumab was then administered, at scheduled treatment at intervals of 2-3 months. On PRN regimen, BCVA was assessed monthly and ranibizumab was administered during the same visit, if needed. 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 duration of the study was 24 months.

In the RETAIN study the number of scheduled treatment visits required by the TE regimen was 40% lower than the number of monthly visits required by the PRN regimen. With both regimens, more than 70% of patients were able to maintain their BCVA with a visit frequency of $\geq$ 2 months.

Key outcome measures are summarized in Table 12-6.

Table 12-1 Outcomes in study D2304 (RETAIN)

Outcome measure compared to baseline	TE Ranibizumab 0.5 mg + Laser n=117	TE Ranibizumab 0.5 mg 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)[b]	+6.1 (5.7)[b]	+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 ≥10 letters or BCVA ≥84 (%) at Month 24	43.6	40.8	45.3
Gain of ≥15 letters or BCVA ≥84 (%) at Month 24	25.6	28.0	30.8

[b]p<0.0001

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

There was no difference in the BCVA or CRT outcomes of patients in RETAIN study who received or did not receive concomitant thiazolidinediones.

Study D2303 (REVEAL)

The study D2303 (REVEAL), was a 12 month, randomized, double-masked Phase IIIb trial conducted in Asian patients. Similar to the RESTORE 12 month core study in trial design and inclusion/exclusion criteria, 390 patients with visual impairment due to macular edema were randomized to receive either ranibizumab 0.5 mg injection as monotherapy and sham laser photocoagulation (n=133), ranibizumab 0.5 mg injection and laser photocoagulation (n=129), or sham injection and laser photocoagulation (n=128). Mean change in visual acuity at Month 12 compared to baseline were +6.6 letters in the ranibizumab monotherapy group, +6.4 letters in the ranibizumab plus laser group and +1.8 letters in the laser group. Overall, the efficacy and safety results of the REVEAL study in Asian DME patients are consistent with those of the RESTORE study in Caucasian DME patients.

Treatment of visual impairment due to macular edema secondary to RVO

Study FVF4165g (BRAVO) and study FVF4166g CRUISE

The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular edema secondary to RVO have been assessed in the randomized, 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.

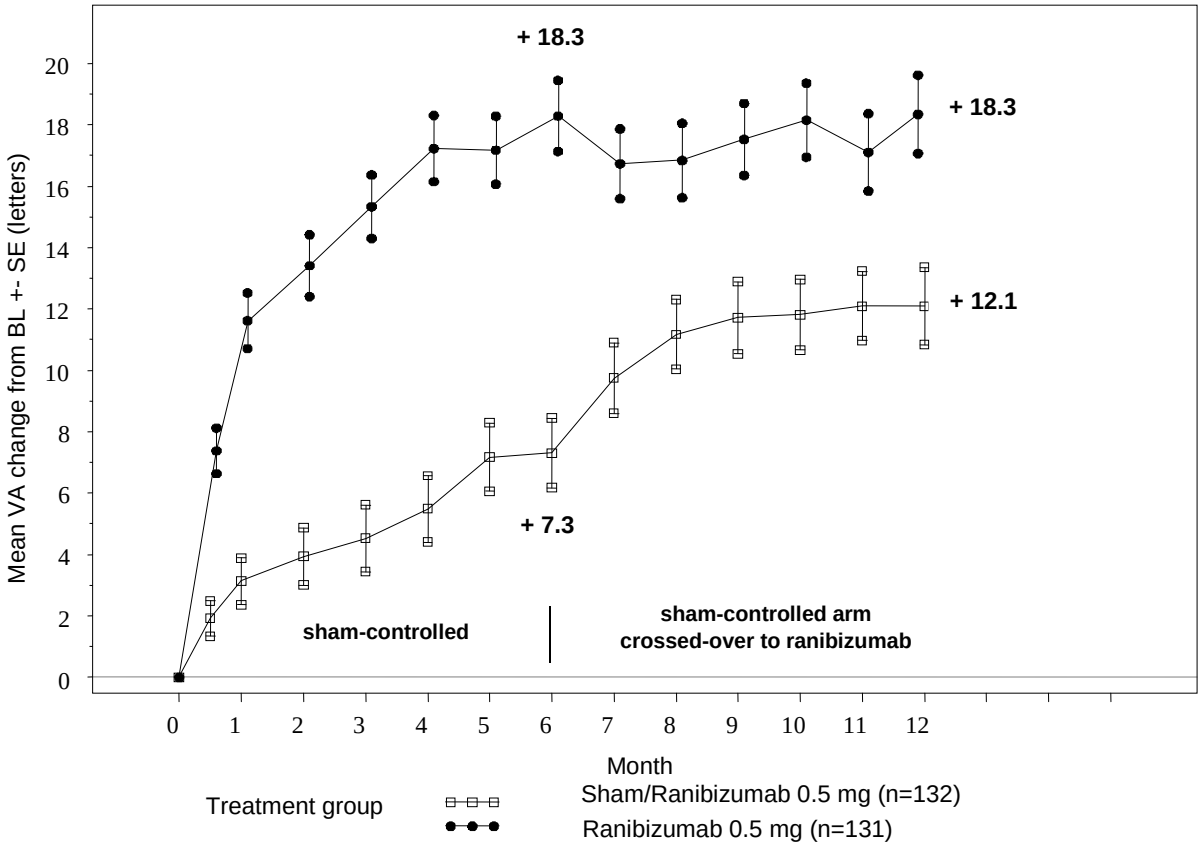
Key outcomes from BRAVO and CRUISE are summarized in Tables 12-7and 12-8, and Figures 12-4 and 12-5.

Table 12-7 Outcomes at Month 6 and Month 12 (BRAVO)

	Sham/Lucentis (n=132)	Lucentis 0.5 mg (n=131)
Mean change in visual acuity from baseline at Month 6[b] (letters) (primary endpoint)	+7.3	+18.3
Mean change in visual acuity from baseline at Month 12 (letters)	+12.1	+18.3
Proportion of patients gained ≥15 letters in BCVA from baseline at Month 6[b]	28.8 %	61.1 %
Proportion of patients gained ≥15 letters in BCVA from baseline at Month 12	43.9 %	60.3 %
Proportion of patients receiving laser rescue over 12 months	61.4 %	34.4 %

[b] $p<0.0001$

Figure 12-4 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (BRAVO)



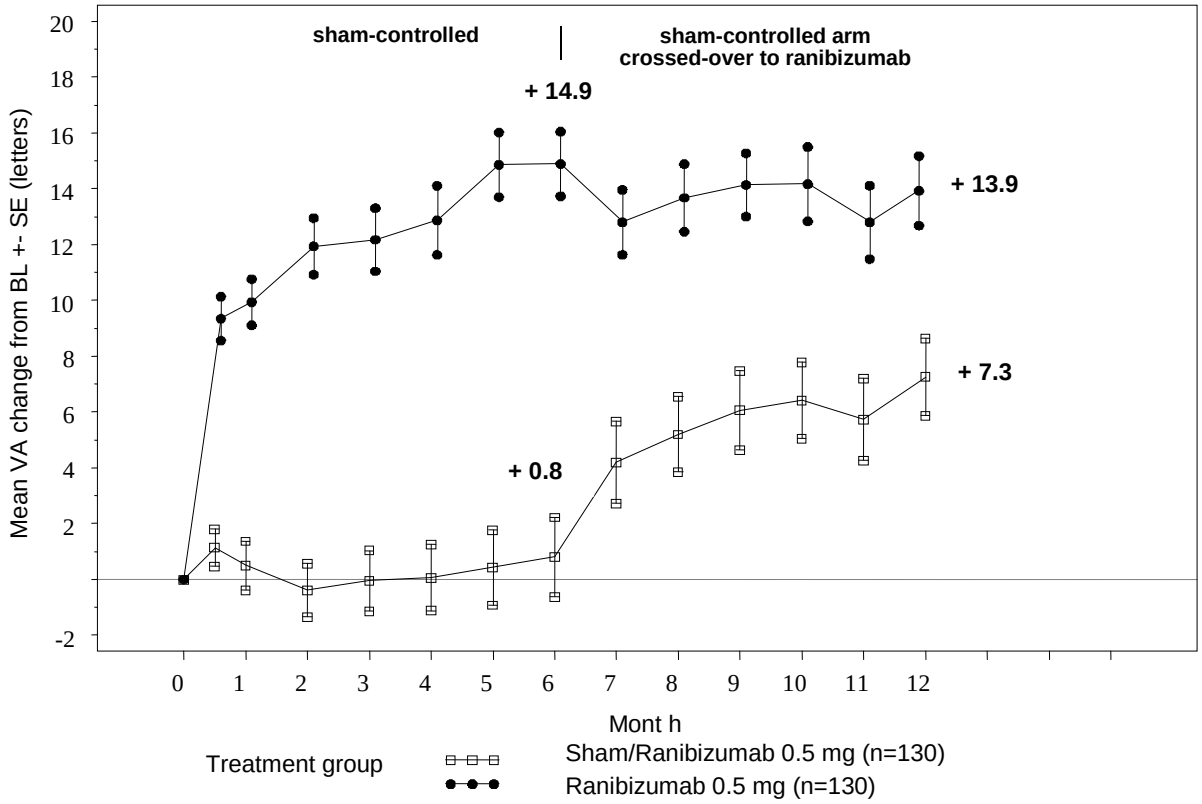
BL=baseline; SE=standard error of mean.

Table 12-8 Outcomes at Month 6 and Month 12 (CRUISE)

	Sham/Lucentis 0.5mg (n=130)	**Lucentis 0.5 mg (n=130)**
Mean change in visual acuity from baseline at Month 6[b] (letters)	+0.8	+14.9
Mean change in visual acuity from baseline at Month 12 (letters)	+7.3	+13.9
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6[b]	16.9 %	47.7 %
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12	33.1%	50.8%

[b]: p<0.0001

Figure 12-5 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 decrease in the macular edema as measured by central retinal thickness.

The improvement in visual acuity seen with ranibizumab treatment at 6 and 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) sub-scales related to near and distance activity, a pre-specified secondary efficacy endpoint. 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.

Treatment of visual impairment due to CNV secondary to PM

Study F2301 (RADIANCE)

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 randomised, double-masked, controlled pivotal study F2301 (RADIANCE). This study was designed to evaluate two different dosing regimens of 0.5 mg ranibizumab given as an intravitreal injection in comparison to verteporfin PDT (vPDT, Visudyne photodynamic therapy). The 277 patients were randomised to one of 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 OCT and/or FA).
- Group III (vPDT - patients were allowed to receive ranibizumab treatment as of Month 3).

During the 12 months of the study, patients received on average 4.6 injections (range 1-11) in Group I and 3.5 injections (range 1-12) in Group II. In Group II, which is the recommended posology (see section 4), 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 summarized in Table 12-9 and Figure12-6.

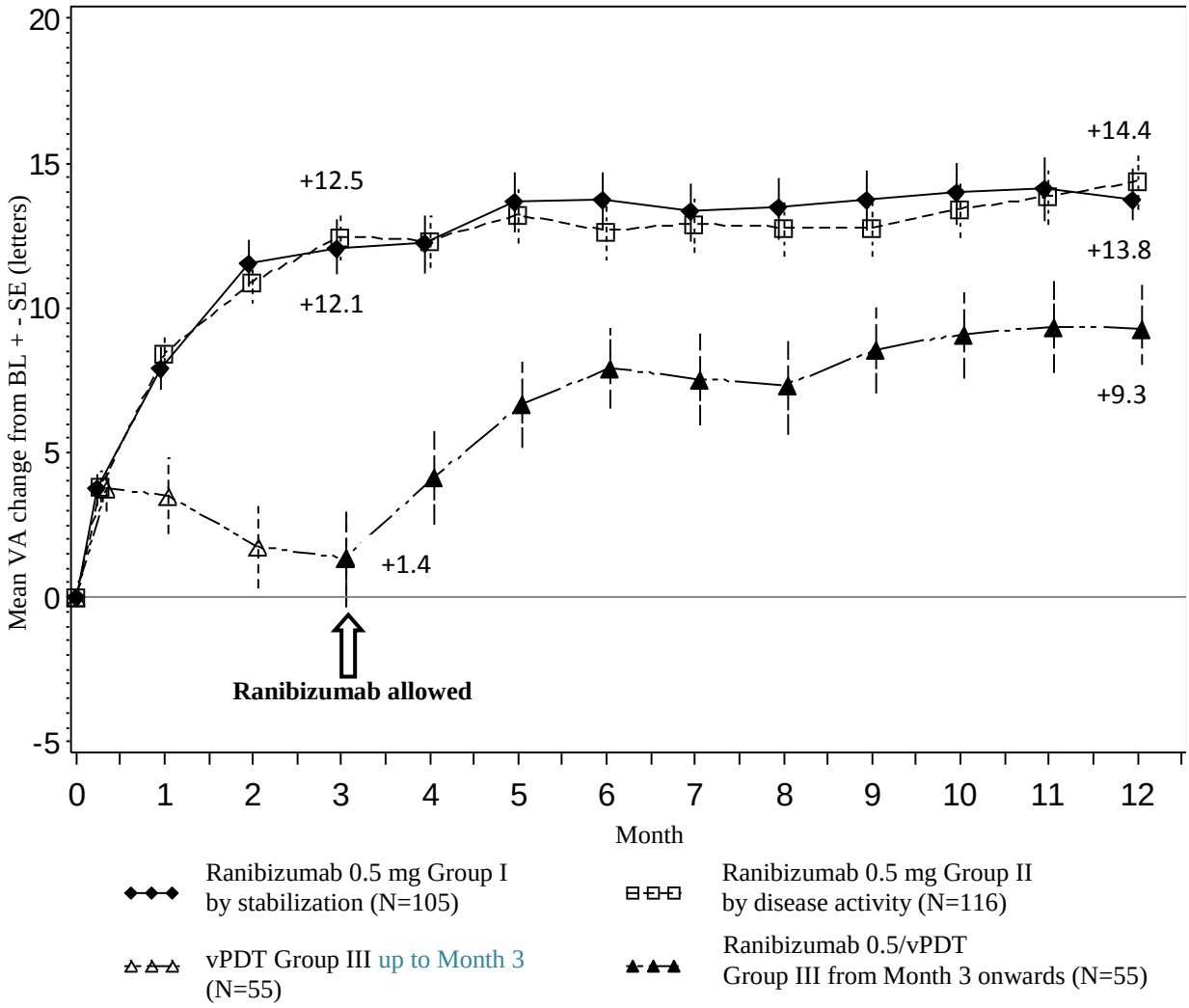
Table 12-9 Outcomes at Month 3 and 12 (RADIANCE)

	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[h] (letters)	+10.5	+10.6	+2.2
Proportion of patients who gained:			
≥10 letters, or reached ≥84 letters in BCVA	61.9%	65.5%	27.3%
≥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	2.0	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:			
≥10 letters, or reached ≥84 letters in BCVA	69.5%	69.0%	N/A
≥15 letters, or reached ≥84 letters in BCVA	53.3%	51.7%	N/A

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

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

Figure 12-6 Mean change from baseline BCVA over time to Month 12 (RADIANCE)



BL = baseline; SE = standard error of the mean.

Patients randomized to vPDT were allowed to receive ranibizumab from Month 3 onwards.

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

Patient-reported benefits were observed with the 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.

Paediatric population
The safety and efficacy of ranibizumab have not yet 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 secondary to PM (see section 4 for information on paediatric use).

13 Non-clinical 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 and mutagenicity data are available.
In pregnant monkeys, IVT 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-fetotoxic.
However due to restrictions dictated by the intravitreal route of administration the feasible doses used in this study did not reach maternal toxicity but only a multiple with respect to human systemic exposure. The absence of ranibizumab-mediated effects on the embryo-fetal 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 fetal serum, suggesting that the anti-ranibizumab antibody acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer. As the embryo-fetal development investigations were performed in healthy pregnant animals and disease (such as diabetes) may modify the permeability of the placenta towards a Fab fragment (see recommendations in section 9 Women of child-bearing potential, pregnancy, breast-feeding and fertility), the study should be interpreted with caution.

14 Pharmaceutical information

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

Special precautions for storage
Vial
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Lucentis must be kept out of the reach and sight of children.

Pre-filled syringe
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.
Lucentis must be kept out of the reach and sight of children.

Nature and contents of container

Vial kit

0.23 ml Lucentis solution for injection in a glass vial (colorless type I glass) with chlorobutyl rubber stopper. One pack contains one vial, one filter needle for withdrawal of the vial content, one needle for intravitreal injection, one syringe for withdrawal of the vial contents and for intravitreal injection.

Vial

0.23 mL Lucentis solution for injection in a glass vial (colorless type I glass) with chlorobutyl rubber stopper. One pack contains one vial.

Vial with filter needle

0.23 mL Lucentis solution for injection in a glass vial (colorless type I glass) with chlorobutyl rubber stopper. One pack contains one vial and one filter needle for withdrawal of the vial content.

Pre-filled syringe
0.165 mL sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap and a Luer Lock adaptor. The pre-filled syringe has a plunger rod and a finger grip, and is packed in a sealed tray. One pack contains one pre-filled syringe.

Special precautions for disposal and other handling

Vial
Vials are for single use only (see section 4 Dosage and administration). After injection any unused product must be discarded.

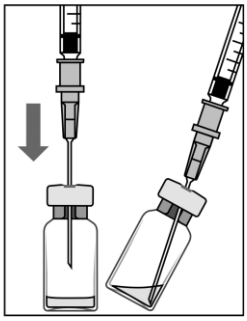
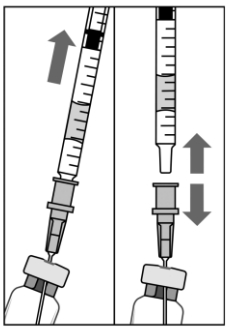
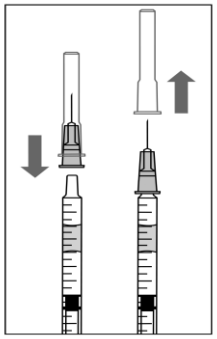
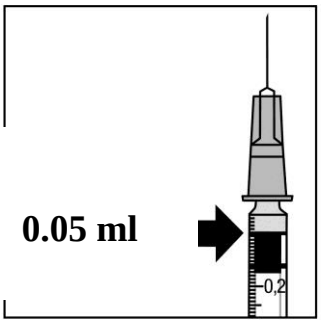
The vial is sterile. Re-use may lead to infection or other illness/injury. Do not use the vial if the packaging is damaged. The sterility of the vial cannot be guaranteed unless the packaging seal remains intact. Do not use the vial if the solution is discolored, cloudy, or contains particulates.

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

- a 5 micrometer filter needle (18G)
- a 1 mL sterile syringe
- an injection needle (30G x 1/2 inch)

These medical devices are not supplied in the Lucentis pack that contains only the vial.

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

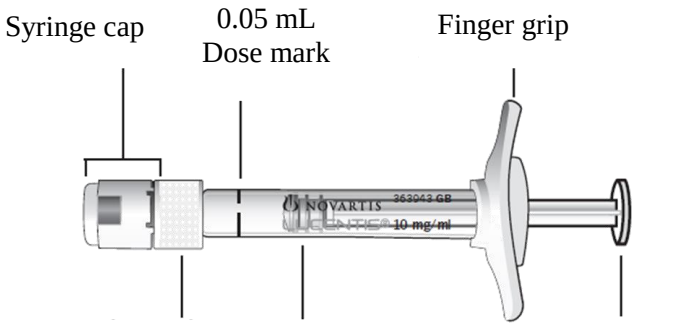
A. 	1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected. 2. Attach a 5 micrometer filter needle (18G) to a 1 ml syringe using aseptic technique. Push the blunt filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial. 3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.
B. 	4. Ensure that the plunger rod is drawn back sufficiently 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.
C. 	6. Aseptically and firmly attach an injection needle (30G x 1/2 inch) to 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.
D. 	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.
	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. After injection any unused product must be discarded.

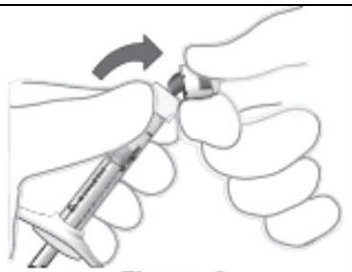
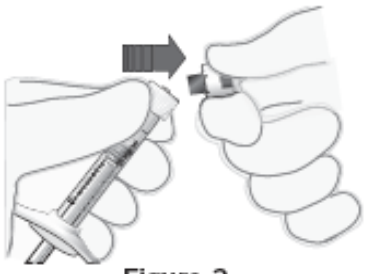
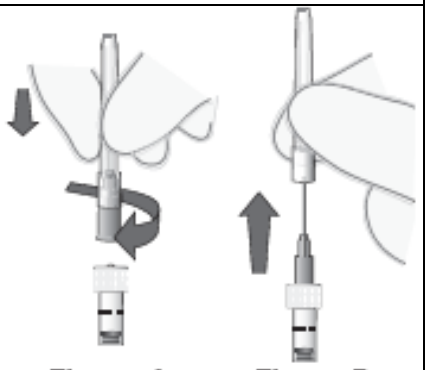
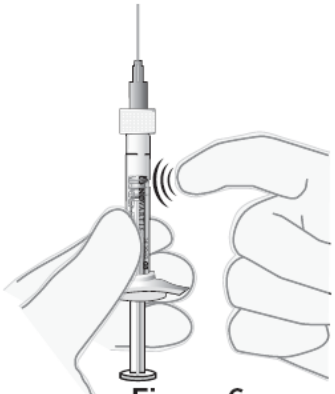
Pre-filled syringe

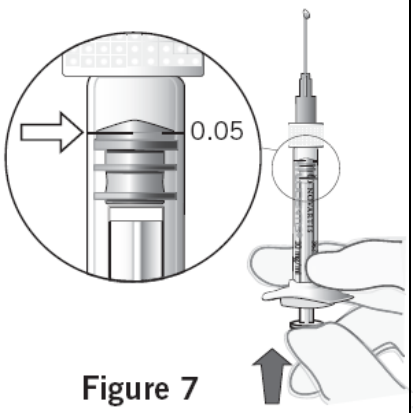
The pre-filled syringe is for single use only (see section 4 Dosage and administration).
The pre-filled syringe is sterile. Do not use the pre-filled syringe if the packaging is damaged. The sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discolored, cloudy, or contains particulates.

For the intravitreal injection, a 30G x 1/2 inch injection needle should be used.

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

Heading	Instructions	Diagram/Image
	Read all the instructions carefully before using the prefilled syringe. The prefilled 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. **Note: The dose must be set to 0.05 mL**	
Pre-filled syringe description	 **Figure 1**	
Prepare	1. Make sure that your pack contains: • a sterile pre-filled syringe in a sealed tray. 2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe.	*(no diagram/image)*
Check syringe	3. Check that: • the syringe cap is not detached from the Luer Lock. • the syringe is not damaged. • the drug solution looks clear, colorless to pale yellow and does not contain	

Heading	Instructions	Diagram/Image
	any particulates. 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). 6. Dispose of the syringe cap (see Figure 3).	 Figure 2  Figure 3
Attach needle	7. Attach a 30G x 1/2 inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer Lock (see Figure 4). 8. Carefully remove the needle cap by pulling it straight off (see Figure 5). **Note: Do not wipe the needle at any time.**	 Figure 4 Figure 5
Dislodge air bubbles	9. Hold the syringe upright. 10. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).	 Figure 6

Heading	Instructions	Diagram/Image
Set dose	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. **Note: the plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.**	 Figure 7
Inject	The injection procedure should be carried out under aseptic conditions 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 center of the globe. 13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL. 14. A different scleral site should be used for subsequent injections. 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.	

15. Manufacturer

Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

16. License Number

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17. License Holder

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