NOVARTIS

Lucentis®

Composition
Active substance: Ranibizumab
Excipients: α,α-trehalose dihydrate, histidine, histidine hydrochloride monohydrate, polysorbate 20, water for injections
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit
Vial: 10 mg/ml ranibizumab (vial containing 2.3 mg ranibizumab in 0.23 ml of solution).
Pre-filled syringe 10 mg/ml ranibizumab (pre-filled syringe containing 1.65 mg ranibizumab in 0.165 ml of solution).

Indications/Potential uses
Lucentis is indicated for the treatment of:
- wet age-related macular degeneration (wet AMD).
- visual impairment due to diabetic macular oedema (DME).
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch retinal vein occlusion, BRVO, or central retinal vein occlusion, CRVO).
- visual impairment due to choroidal neovascularisation (CNV) secondary to pathological myopia (PM).

Dosage/Administration
Dosage
Lucentis may only be administered by a qualified ophthalmologist with access to the appropriate infrastructure. Lucentis is administered by intravitreal injection. A Lucentis vial contains 0.23 ml and a pre-filled syringe contains 0.165 ml. Both are intended for once-only use in a single patient.
The recommended dose of 0.5 mg is given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two injections may not be shorter than one month. The patient should be monitored monthly.

Treatment of wet AMD
If it is not possible to give monthly injections in the long term, treatment may be given as follows:
Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. when visual acuity is stable on Lucentis therapy in at least three consecutive monthly assessments.
Treatment should be resumed when monitoring indicates renewed disease activity (confirmed by renewed loss of visual acuity, or morphological changes), and should continue until visual acuity is stable on Lucentis therapy in at least three consecutive monthly assessments.

Treatment of visual impairment due to DME
Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. when visual acuity is stable on Lucentis therapy in at least three consecutive monthly assessments.
Treatment should be resumed when monitoring indicates renewed disease activity (confirmed by renewed loss of visual acuity, or morphological changes), and should continue until visual acuity is stable on Lucentis therapy in at least three consecutive monthly assessments.

Treatment of visual impairment due to macular oedema secondary to RVO
Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. when visual acuity is stable on Lucentis therapy in at least three consecutive monthly assessments.
Treatment should be resumed when monitoring indicates renewed disease activity (confirmed by renewed loss of visual acuity, or morphological changes), and should continue until visual acuity is stable on Lucentis therapy in at least three consecutive monthly assessments.

Treatment of visual impairment due to CNV secondary to PM
Treatment is initiated with a single injection.
If monitoring reveals signs of disease activity, further treatment is recommended. Monitoring for disease activity may include clinical examinations such as measuring visual acuity, optical coherence tomography (OCT) or fluorescein angiography (FA). In the first year of treatment, monthly monitoring is recommended during the first two months of treatment, and subsequently at least every three months. Following the end of the first year of treatment, the frequency of monitoring should be determined by the treating physician.
Following initial therapy, the interval between two injections may not be shorter than one month.
There is no experience with treatment lasting for more than one year.

Administration
The patient's medical history should be thoroughly evaluated for possible hypersensitivity reactions prior to intravitreal administration (see "Warnings and precautions").
Lucentis must be administered under aseptic conditions (suitable premises, sterile drape, gloves and utensils). Suitable anaesthesia and a topical broad spectrum microbicide to disinfect the skin around the eye, the eyelid and the surface of the eye should be applied before the injection.
The entire contents of the vial are withdrawn using a syringe and a 5 µm filter needle. The filter needle is removed prior to intravitreal injection, and the injection needle (30G x 13 mm) is attached to the syringe. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 ml (50 µl) on the syringe. The contents of one vial are to be used for administration of a single dose. Discard leftover solution.
The injection needle should be fully inserted 3.5-4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming towards the centre of the globe.
The injection volume is delivered slowly, and attention should be paid to changing the scleral injection site for subsequent injections.
The patient's intraocular pressure must be monitored after the injection. Monitoring should consist of a check for perfusion of the optic nerve disc immediately after the injection, tonometry within 30 minutes, and ophthalmoscopy, slit-lamp examination and fundoscopy 2-7 days later. Patients must be instructed to report any signs of endophthalmitis to their doctor immediately (see "Warnings and precautions").

Additional information for special patient populations
Renal impairment
No dose adjustment is necessary in patients with renal impairment (see "Pharmacokinetics").

Hepatic impairment
No studies are available. No special precautions are considered necessary as systemic exposure is negligible.

Children and adolescents
Data on safety and efficacy are not available. Lucentis is not recommended for use in children and adolescents.

Elderly patients (aged 65 and over)
No dose adjustment is necessary.

Contraindications
Hypersensitivity to ranibizumab or to any of the excipients. Lucentis is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation.

Warnings and precautions
Intravitreal injections have been associated with infectious endophthalmitis and retinal detachment. Aseptic injection techniques must be used when administering Lucentis. In addition, patients should be monitored during the days following the injection to permit early detection and treatment of infection (see "Adverse effects").
Transient increases in intraocular pressure have been seen within 60 minutes of injection of Lucentis. Persistently elevated intraocular pressure has also been reported. Both intraocular pressure and the perfusion of the central retinal artery must be monitored and managed appropriately (see "Adverse effects").
The safety and efficacy of Lucentis treatment administered to both eyes concurrently have not been investigated in experimental studies.
The limited data on bilateral Lucentis use (including administration on the same day) does not suggest an increased risk of systemic adverse events compared with unilateral use.
There is a potential risk of arterial thromboembolic events following intravitreal use of vascular endothelial growth factor (VEGF) inhibitors. Patients with known risk factors for stroke (e.g. a prior stroke or transient ischaemic attack) may be at higher risk.
The pre-treatment incidence of immunoreactivity to Lucentis was 0–3% in all treatment groups. Following monthly administration, low antibody titres were detected in 1-6% of patients after 12-24 months. These immunogenicity data reflect the percentage of patients in whom electrochemiluminescence assay results were positive. The data were highly dependent on the sensitivity and specificity of the assay. The clinical significance of immunoreactivity to Lucentis is unclear at this time. Iritis and vitritis were reported in some patients with the highest levels of immunoreactivity.
Lucentis has not yet been studied in patients with active systemic infections or concurrent eye conditions such as retinal detachment or macular hole.
There is limited experience in patients with prior episodes of RVO and patients with ischaemic RVO. In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended.
Use of Lucentis in patients who have previously received laser photocoagulation, and co-administration of Lucentis with laser photocoagulation were studied. If Lucentis is to be given on the same day as laser photocoagulation, the injection may not be administered until at least 30 minutes after laser photocoagulation.

Interactions
No specific interaction studies have been performed.

Pregnancy/Breast-feeding
Pregnancy
There are no data on the use of ranibizumab in pregnant women.
Studies in cynomolgus monkeys did not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/fetal development (see "Preclinical data"). Ranibizumab inhibits VEGF-A, a major angiogenic factor in the formation of new blood vessels during embryonic and fetal development and placentation. Systemic exposure to ranibizumab is low after ocular administration. Owing to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryotoxic/fetotoxic, and must not be used during pregnancy unless clearly necessary. Women who wish to become pregnant should stop receiving ranibizumab three months before conception.

Women of child-bearing potential
Women of childbearing potential should use effective contraception during treatment, and for up to 30 days after treatment has ended.

Breast-feeding
It is not known whether Lucentis is excreted in breast milk. As many substances are excreted in breast milk and there is potential for absorption and impairment of infant growth and development, breast-feeding is not recommended during treatment with Lucentis.

Fertility
The effect of Lucentis on male and female fertility has not been investigated.

Effects on the ability to drive and use machines
Treatment with Lucentis may induce temporary visual disturbances, which may affect the ability to drive or use machines (see "Adverse effects"). Patients who experience such effects must not drive or use machines until the temporary visual disturbances subside.

Adverse effects
A total of 1,315 patients constituted the safety population in the three phase III clinical studies on the treatment of wet AMD. All the patients were treated with Lucentis for at least 24 months. 440 patients were treated with the recommended dose of 0.5 mg.
Serious adverse events related to the injection procedure were: endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see "Warnings and precautions").
Intraocular inflammation and increased intraocular pressure were also seen in patients treated with Lucentis (see "Warnings and precautions").
In the controlled phase III studies of wet AMD – FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER) – the adverse events listed below occurred at a higher rate (at least two percentage points higher) in patients with wet AMD receiving treatment with 0.5 mg Lucentis than in patients in the control groups (sham injection [see "Properties/Actions"] or verteporfin PDT). They were therefore considered potential adverse drug reactions (ADRs). The safety data provided below also include all adverse events suspected to be at least potentially caused by the injection procedure or the medicinal product in the 440 patients in the combined 0.5 mg Lucentis treatment groups in wet AMD.

CNV secondary to PM patient population
The safety of Lucentis was studied in the 12-month clinical study RADIANCE, which included 224 ranibizumab-treated patients with CNV secondary to PM (see "Properties/Actions"). Ocular and non-ocular events in this trial were reported with a frequency and severity similar to those seen in the wet AMD trials.
Frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/100 to < 1/1,000); rare (≥ 1,000 to < 1/10,000); very rare (< 10,000).

Infections
Very common: Nasopharyngitis (12.5–16.4%).
Common: Influenza, urinary tract infection.

Blood and lymphatic system disorders
Common: Anaemia.

Immune system disorders
Common: Hypersensitivity reactions.

Psychiatric disorders
Common: Anxiety.

Nervous system disorders
Very common: Headache (8-15%).
Common: Stroke.

Eye disorders
Very common: Intraocular inflammation (10-18%), vitritis (2.3-10%), vitreous detachment (18-19%), retinal haemorrhage (25%), visual disturbances (6.6-10.5%), eye pain (27-32%), vitreous floaters (7-25%), conjunctival haemorrhage (55-72%), eye irritation (12-15%), foreign body sensation in eyes (12-15%), increased lacrimation (10-14%), blepharitis (8-11%), eye pruritus (8.5-10%).
Common: Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of retinal pigment epithelium, tear in retinal pigment epithelium, reduced visual acuity, vitreous haemorrhage, vitreous disorders, uveitis, iritis, iridocyclitis, (subcapsular) cataract, posterior capsule opacification, punctate keratitis, corneal abrasion, opacification of aqueous humour, blurred vision, injection site haemorrhage, eye haemorrhage, (allergic) conjunctivitis, eye discharge, photopsia, photophobia, ocular discomfort, eyelid pain, eyelid oedema, conjunctival hyperaemia.
Uncommon: Endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesions, corneal melt, corneal oedema, corneal striae, injection site pain and irritation, blindness, eyelid irritation.

Cardiovascular disorders
Arterial thromboembolic events, as defined by the Antiplatelet Trialists' Collaboration (1994), including vascular deaths, non-fatal myocardial infarctions, non-fatal ischaemic strokes and non-fatal haemorrhagic strokes, have been linked to the systemic availability of highly potent VEGF inhibitors. In the first year, the incidence of thromboembolic events in both of the patient groups treated with Lucentis (0.3 and 0.5 mg) was 2.3%, compared with 1.3% in the control group. In the second year of the MARINA study, it was 3.0% in both treatment groups and 3.2% in the control group.

Respiratory, thoracic and mediastinal disorders
Common: Cough.

Gastrointestinal disorders
Common: Nausea.

Skin and subcutaneous tissue disorders
Uncommon: Allergic reactions (rash, urticaria, pruritus, erythema).

Musculoskeletal disorders
Very common: Arthralgia (8–12%).

Investigations
Increased intraocular pressure.

Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with Lucentis. The immunogenicity data reflect the percentage of patients testing positive for antibodies to ranibizumab in immunoassays and were highly dependent on the sensitivity and specificity of the assays.
In the AMD studies, the pre-treatment incidence of immunoreactivity to Lucentis was 0-3% in all treatment groups. After monthly administration of Lucentis for 12 to 24 months, antibodies to ranibizumab were detected in approximately 1-8% of patients with neovascular AMD.
In the DME studies, the pre-treatment incidence of immunoreactivity to Lucentis was 0-2% in all treatment groups. After monthly administration of Lucentis for 12 months, antibodies to ranibizumab were detected in approximately 2-4% of patients with DME.
In the RVO studies, the pre-treatment incidence of immunoreactivity to Lucentis was 2-3% in all treatment groups. After monthly administration of Lucentis for 12 months, antibodies to ranibizumab were detected in approximately 4-5% of patients with RVO.
The clinical significance of immunoreactivity to Lucentis is unclear at this time.

Overdose
Cases of accidental overdose have been reported from the clinical studies in wet AMD, and from post-marketing. Eye pain and increased intraocular pressure are the most common of these adverse effects. If an overdose occurs, intraocular pressure should be monitored and – if deemed necessary by the attending physician – treated.

Properties/Actions
ATC code: S01LA04

Mechanism of action
The active substance of Lucentis (ranibizumab) is a humanised recombinant monoclonal antibody fragment (Fab) targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to VEGF-A and its isoforms. The isoforms – e.g. $VEGF_{121}$ and $VEGF_{165}$ – are generated by alternative mRNA splicing; isoform $VEGF_{110}$ is generated by proteolysis. The binding of ranibizumab to VEGF-A and its isoforms inhibits the activation of the VEGFR-1 and VEGFR-2 receptors on the surface of endothelial cells. The activation of the VEGFR-1 and VEGFR-2 receptors leads to endothelial cell proliferation, neovascularisation and vascular leakage, all of which are assumed to contribute to the progression of the neovascular form of age-related macular degeneration (AMD) and pathological myopia (PM), diabetic macular oedema (DME) and retinal vein occlusion leading to visual impairment (RVO).

Treatment of wet AMD
The clinical safety and efficacy of ranibizumab in the treatment of wet AMD have been assessed in three randomised, double-masked studies in a total of 1,323 patients with neovascular AMD (Lucentis: N = 879; control groups: N = 444). Sham treatment served as a control arm in the MARINA study, while photodynamic therapy (PDT) with Visudyne served as an active control in the ANCHOR study. Patients with lesions up to 12 disc areas in total size, and with visual acuity in the study eye ranging between 20/40 and 20/320 (Snellen), were enrolled. The average age of the patients was 77 years. In the clinical trials, patients were instructed to self-administer antimicrobial eye drops four times daily for three days before and after each injection.
A total of 716 patients with minimally classic choroidal neovascularisation (CNV) or occult CNV were enrolled in the MARINA study. They received monthly intravitreal injections of 0.3 mg Lucentis (N = 238), 0.5 mg Lucentis (N = 240) or sham injections (N = 238). During the 24-month treatment phase, the patients received an average of 22 out of a possible 24 treatments. The results of the MARINA study after 12 months of treatment were also essentially confirmed after 24 months of treatment (once per month) in 90% of the patients.
A total of 423 patients with predominantly classic CNV lesions were enrolled in the ANCHOR study. They received monthly intravitreal injections of either 0.3 mg Lucentis and sham PDT (N = 143), intravitreal injections of 0.5 mg Lucentis and sham PDT (N = 140), or sham intravitreal injections and active verteporfin PDT (N = 143). The initial sham or active verteporfin PDT was given with the initial Lucentis injection. Treatment was given every three months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage in the study eye. For the ANCHOR study, data are available up to the end of Month 12. During this time, patients received an average of 12 out of a possible 13 treatments.

The results are summarised in the following tables:

Table 0-1 MARINA study: Results at Months 12 and 24

Change in visual acuity (in letters, ETDRS)	Month	Sham (N = 238)	Ranibizumab 0.5 mg (N = 240)	Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	Month 12	62%	95%	32% (26%, 39%)
	Month 24	53%	90%	37% (29%, 44%)
Gain of ≥ 15 letters in visual acuity (%)[b]	Month 12	5%	34%	29% (22%, 35%)
	Month 24	4%	33%	29% (23%, 35%)
Mean change in visual acuity[b] (letters)	Month 12	-10.5 (16.6)	+7.2 (14.4)	17.5 (14.8, 20.2)
	Month 24	-14.9 (18.7)	+6.6 (16.5)	21.1 (18.1, 24.2)

[a] after stratification
[b] p < 0.01

Table 0-2 ANCHOR study: Results at Months 12 and 24

Change in visual acuity		Verteporfin PDT (N = 143)	Ranibizumab 0.5 mg (N = 140)	Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	Month 12	64%	96%	33% (25%, 41%)
	Month 24	66%	90%	25% (16%, 34%)
Gain of ≥ 15 letters in visual acuity (%)[b]	Month 12	6%	40%	35% (26 %, 44 %)
	Month 24	6%	41%	35% (26 %, 44 %)
Mean change in visual acuity[b] (letters)	Month 12	-9.5 (16.4)	+11.3 (14.6)	21.1 (17.5, 24.6)
	Month 24	-9.8 (16.4)	+10.7 (16.5)	20.7 (16.8, 24.7)

[a] after stratification
[b] p < 0.01

The improvement in vision reported at Month 12 in both the MARINA and ANCHOR study on treatment with 0.5 mg Lucentis resulted in a benefit for patients, as measured by the three subscales of the National Eye Institute Visual Function Questionnaire (VFQ-25), which had been established previously as secondary endpoints for efficacy (activities related to near vision and distance vision, as well as other vision-dependent activities). All differences between 0.5 mg Lucentis and the two control groups were statistically significant and clinically relevant, with p-values between 0.009 and < 0.0001.
The PIER study included 184 patients with CNV lesions (with and without classic components). They received an intravitreal injection of 0.3 mg or 0.5 mg Lucentis, or a sham intravitreal injection, once a month for the first three months. Additional injections of Lucentis were administered once every three months. From Month 14, patients who received a sham injection were also able to be treated with Lucentis, and from Month 19 more frequent injections of Lucentis were possible. Patients treated with Lucentis in PIER received an average of 10 treatments over 24 months.
The primary efficacy endpoint was mean change in visual acuity over the 12 months. After an initial increase during the monthly injection phase, patients' visual acuity declined during the quarterly injection phase, returning to baseline after 12 months. This effect was maintained in most patients (82%) treated with Lucentis at Month 24. Data from a limited number of patients who switched over to treatment with Lucentis after more than a year of sham treatment suggest that early initiation of treatment is associated with better preservation of visual acuity.

Table 0-3 PIER study: Results at Month 12

Change in visual acuity	Sham (N = 63)	Ranibizumab 0.5 mg (N = 61)	Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	49	90	37 (23, 52)
Gain of ≥ 15 letters in visual acuity (%)[b]	10	13	2 (-8, 12)
Mean change in visual acuity[b]	-16.3 (22.3)	-0.2 (13.1)	14.7 (8.2, 21.2)

[a] after stratification
[b] p < 0.0001

The phase IIIb SAILOR study was carried out in treatment-naive and previously treated patients with CNV secondary to AMD. SAILOR was a one-year multicentre study. The primary study objective was to estimate the incidence of ocular and non-ocular adverse effects during 12 months of treatment. 2,378 patients, randomised to two groups, were given one 0.3 mg or 0.5 mg dose of Lucentis every month for three months. Depending on the findings, this was followed by further treatment at intervals of not less than one month.
There was no imbalance between the two groups with regard either to the overall incidence of ocular and non-ocular adverse effects or to the incidence of stroke in particular, which occurred in 8 of 1,169 patients given 0.3 mg doses (0.7%; 95% CI: 0.3% to 1.3%) . 15 of 1,209 patients given 0.5 mg doses (1.2%; 95% CI: 0.7% - 2%). Patients with known risk factors (e.g. a prior stroke or transient ischaemic attack) are presumably at greater risk for stroke during treatment with Lucentis.

Treatment of visual impairment due to DME
The clinical efficacy and safety of Lucentis in patients with visual impairment due to diabetic macular oedema (DME) were assessed in the RESTORE study involving a total of 345 patients with visual impairment due to DME. The study had three arms: Patients in arm 1 (N = 116) initially received intravitreal injections of 0.5 mg ranibizumab as monotherapy and sham laser photocoagulation. Patients in arm 2 (N = 118) initially received intravitreal injections of 0.5 mg ranibizumab and laser photocoagulation. Patients in arm 3 (N = 111) initially received laser photocoagulation monotherapy and a sham injection.
Treatment with ranibizumab continued with monthly intravitreal injections and was suspended when visual acuity on Lucentis had stabilised at three consecutive visits. Treatment was reinitiated when there was a reduction in visual acuity due to DME progression. Repeat treatment with laser photocoagulation was carried out on the same day, at least 30 minutes before injection of ranibizumab, according to ETDRS criteria.

The results are summarized in the following tables:

Table 0-4 RESTORE study: Results at Month 12

Change in best-corrected visual acuity (BCVA)	Ranibizumab 0.5 mg (n=115)	Ranibizumab 0.5 mg + laser (n=118)	Laser (n=110)
Mean change in BCVA (in letters) from Month 1 to Month 12 compared to baseline (standard deviation)[a]	6.1 (6.4)	5.9 (7.9)	0.8 (8.6)
Mean change in BCVA (in letters) at Month 12 compared to baseline (standard deviation)[a]	6.8 (8.3)[a]	6.4 (11.8)[b]	0.9 (11.4)
Gain of ≥ 10 letters in BCVA (% of patients)	37.4[c]	43.2	15.5
Gain of ≥ 15 letters in BCVA (% of patients)	22.6[d]	22.9[e]	8.2

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

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 retinal vein occlusion (RVO) have been assessed in two randomised, double-masked, controlled studies: BRAVO (N = 397) and CRUISE (N = 392). In both studies, patients received either 0.3 mg or 0.5 mg ranibizumab, or sham treatment. In BRAVO, laser photocoagulation was allowed as rescue treatment at any time in the study from Month 3 in all study arms. The results of BRAVO and CRUISE are summarised in the following tables:

Table 0-5 BRAVO study: Results at Months 6 and 12

Change in visual acuity	Sham (n=132)	Ranibizumab 0.5 mg (n=131)
Mean change in BCVA (in letters) at Month 6 compared to baseline[a]	+7.3	+18.3
Mean change in BCVA (in letters) at Month 12 compared to baseline	+12.1	+18.3
Proportion of patients with gain of ≥15 letters in visual acuity (%) at Month 6	28.8%	61.1%
Proportion of patients with gain of ≥15 letters in visual acuity (%) at Month 12	43.9%	60.3%
Proportion of patients with laser rescue over 12 months	61.4%	34.4%

[a] p<0.0001

Table 0-6 CRUISE study: Results at Months 6 and 12

Change in visual acuity	Sham (n=132)	Ranibizumab 0.5 mg (n=131)
Mean change in BCVA (in letters) at Month 6 compared to baseline[a]	+0.8	+14.9
Mean change in BCVA (in letters) at Month 12 compared to baseline	+7.3	+13.9
Proportion of patients with gain of ≥15 letters in visual acuity (%) at Month 6	16.9%	47.7%
Proportion of patients with gain of ≥15 letters in visual acuity (%) at Month 12	33.1%	50.8%

[a] p<0.0001

Patients treated with ranibizumab showed a continuous reduction in central retinal thickness (CRT) in both the BRAVO and CRUISE studies.
Apart from improvement in visual acuity after treatment with ranibizumab at Month 6 and 12, the patients' quality of life was also evaluated using the National Eye Institute Visual Function Questionnaire (VFQ-25). The differences between the 0.5 mg ranibizumab group and the control group were assessed at Month 6 with p-values between 0.02 and 0.0002.
The 12-month results of the HORIZON extension study for BRAVO and CRUISE (i.e. 24 months from BRAVO/CRUISE baseline) showed the following:
The reduced frequency of treatment in the HORIZON trial had little impact on BRVO (branch retinal vein occlusion) patients, who maintained their initial visual acuity improvement observed in the BRAVO study (+17.5 letters at 24 months with a dose of 0.5 mg and an average of 2.4 injections in the second year).
In contrast, in CRVO (central retinal vein occlusion) patients, the reduced frequency of treatment was associated with a reduction in the visual acuity gained in the CRUISE study (+12 letters at 24 months with a dose of 0.5 mg and an average of 3.8 injections in the second year).

Treatment of visual impairment due to CNV secondary to PM
The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV secondary to PM were assessed based on the 12-month data of the randomised, double-masked controlled pivotal study RADIANCE, which 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).

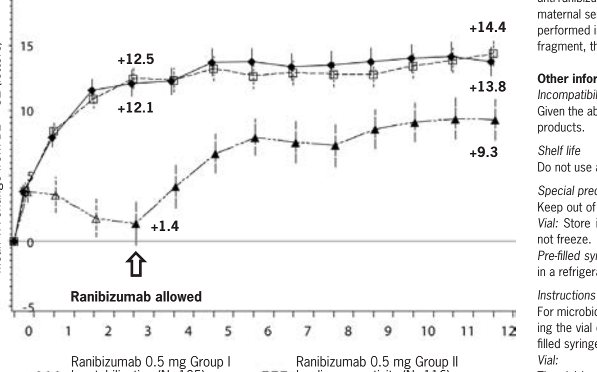
The 277 patients were randomised to one of the following arms:
Group I (ranibizumab 0.5 mg, dosing regimen driven by stability criteria defined as no change in BCVA compared to two preceding monthly evaluations)
Group II (ranibizumab 0.5 mg, dosing regimen driven by disease activity criteria defined as visual 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 three)
Over 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 (in which patients received the recommended treatment regimen based on disease activity, see "Dosage/Administration"), 50.9% of patients required one or two injections, 34.5% required three to five injections and 14.7% required six to twelve injections over the 12-month study period. In Group II, 62.9% of patients did not require injections in the last six months of the study.
Key outcomes from RADIANCE are summarised in Table 0-7 and Figure 0-1.

Table 0-7 Outcomes at Month 3 and Month 12 (RADIANCE)

	Group I 0.5 mg Ranibizumab Visual acuity stability (n=105)	Group II 0.5 mg Ranibizumab Disease activity (n=116)	Group III vPDT* (n=55)
Month 3			
Mean average BCVA change from Month 1 to Month 3 compared to baseline[a] (letters)	+10.5	+10.6	+2.2
Proportion of patients who gained			
≥ 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	4.0	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

* Comparative control up to Month 3. Patients randomised to vPDT were allowed to receive ranibizumab as of Month 3 (in Group III, 38 patients received ranibizumab from Month 3 onwards): p<0.00001 comparison with vPDT control

Figure 0-1 Mean change from baseline BCVA over time up to Month 12 (RADIANCE)



BL = baseline; SE = standard error of the mean.
Figure:
Mean VA change from BL ± SE (letters)
Ranibizumab 0.5 mg Group I by stabilisation (N=105)
Ranibizumab 0.5 mg Group II by stabilisation (N=116)
vPDT Group III up to Month 3 (N=55)

Patients randomised to vPDT were allowed to receive ranibizumab from Month 3 onwards.
The improvement in visual acuity 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 independent functionality) of the VFQ-25 questionnaire.

Pharmacokinetics
Absorption/Distribution
Monthly intravitreal administration of Lucentis in patients with neovascular AMD leads to generally low serum concentrations of ranibizumab, with the peak serum concentration (C_{max}) clearly below the concentration that inhibited VEGF by 50% (11-27 ng/ml, as assessed in a cellular proliferation assay). Peak serum concentrations (C_{max}) generally range from 0.46 to 1.76 ng/ml, and trough serum concentrations (C_{min}) from 0.04 to 0.29 ng/litre. Serum C_{max} was dose-proportional over a dose range of 0.05 to 1.0 mg/eye. The serum concentration in DME and RVO patients was similar to that in neovascular AMD patients. Based on serum concentrations of ranibizumab, the average vitreous elimination half-life of ranibizumab in neovascular AMD patients is about 9 days. Serum concentrations of ranibizumab are assumed to be 90,000 times lower than in the vitreous body.

Pharmacokinetics in special populations
Patients with renal impairment
There have been no prospective studies on the pharmacokinetics of Lucentis in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (N = 136/200) had renal impairment (46.5% mild, 20% moderate and 1.5% severe). Of the studied RVO patients, 48.2% (N = 253/525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). The reported reduction in systemic clearance of ranibizumab was not statistically significant.

Patients with hepatic impairment
There have been no specific studies.

Preclinical 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.
There were dose-dependent increases in anterior chamber flare and cells, with a peak two days after injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery, but was not fully reversible in all cases. In the posterior chamber, there was reversible focal perivenous retinal haemorrhage, which mainly occurred after the first injection, as well as vitreal cell infiltration and floaters, which tended to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study, the severity of inflammation increased with the number of injections and it was necessary to discontinue the study prematurely. Evidence of reversibility was observed during the recovery period. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were more likely to be secondary to severe inflammation. A transient increase in post-dose intraocular pressure was observed following intravitreal injections, irrespective of dose.
Microscopic changes in ocular tissues were all related to inflammation and were not indicative of degenerative processes in any ocular structures. Some cases of granulomatous inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished, and in some instances completely resolved, during the recovery period.
Following intravitreal injection, no signs of systemic toxicity were detected with serum concentrations that were more than 100 times higher than those observed with normal therapeutic use in humans. Serum and vitreous antibodies to ranibizumab were not found in all animals treated.
The preclinical documentation only covers systemic exposure following intravitreal administration. No data are available on the mutagenicity, carcinogenicity or immunotoxicity of Lucentis in animals.
Intravitreal dosing of pregnant monkeys with ranibizumab at maximum systemic exposure levels equivalent to 0.9-7 times the presumed worst-case clinical exposure did not elicit embryo-/fetotoxic or teratogenic effects, and did not affect placental weight or structure. Nevertheless, based on its pharmacological effect, ranibizumab should be regarded as potentially teratogenic and embryo-/fetotoxic.
The absence of ranibizumab-mediated effects on embryo-fetal development is probably mainly due 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 carrier protein (with Fc region) for ranibizumab, thereby decreasing maternal serum clearance and enabling placental transfer. As the embryo-fetal development studies were performed in healthy pregnant animals and disease may modify the permeability of the placenta to a Fab fragment, the study results should be assessed with caution.

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

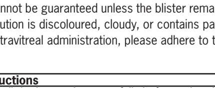
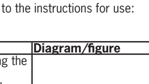
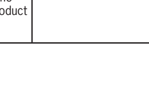
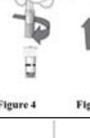
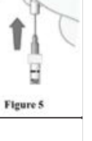
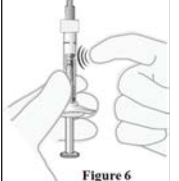
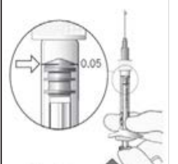
Shelf life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Keep out of the reach of children.
Vial: Store in the original pack to protect the contents from light. Store in a refrigerator (2-8°C). Do not freeze.
Pre-filled syringe Store in the sealed blister in the original pack to protect the contents from light. Store in a refrigerator (2-8°C). Do not freeze.

Instructions for use and handling
For microbiological reasons, the ready-to-use solution for injection should be used immediately after opening the vial or pre-filled syringe. Discard leftover solution (see "Dosage/Administration"). One vial or pre-filled syringe is to be used for administration of a single dose.
Vial:
The vial is sterile. 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 discoloured, cloudy or contains particulates.
The following single-use components are needed to prepare and carry out the intravitreal injection:
- a 5 µm filter needle (18G)
- a 1 ml sterile syringe with Luer Lock
- an injection needle (30G x 13 mm)

These components are not supplied in the Lucentis pack that only contains the vial.
Pre-filled syringe The unopened Lucentis pre-filled syringe can be stored at room temperature (25°C) for up to 24 hours prior to use.

Pre-filled syringe
The pre-filled syringe is for single use only (see "Dosage/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 blister remains sealed and intact. Do not use the pre-filled syringe if the solution is discoloured, cloudy, or contains particulates.
To prepare Lucentis for intravitreal administration, please adhere to the instructions for use:

Heading	Instructions	Diagram/figure
	Read all the instructions carefully before using the pre-filled syringe. The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. **Note: The dose must be set to 0.05 ml.**	
Pre-filled syringe description	 Figure 1	
What you need	1. Make sure that your pack contains: • a sterile pre-filled syringe in a sealed blister. 2. Peel the lid off the blister 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, colourless to pale yellow and does not contain any particulates. 4. If any of the above points are not met, 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 1.3 cm sterile injection needle firmly to 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
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
Injection	The injection procedure must 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 centre 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.	

Pack sizes
Country specific pack sizes.
Not all presentations may be available in the countries.

Manufacturer
See folding box.

Information last revised
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® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists