# A brief guide to the management of risks associated with intravitreal injections during Lucentis® treatment

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## Introduction

This physician leaflet is part of the educational materials regarding the use of Lucentis® (ranibizumab) in its approved indications and provides information on the incidence, prevention and management of risks associated with intravitreal injections. This leaflet will specifically highlight three key ocular risks that have been identified as concerns associated with the intravitreal injection procedure: endophthalmitis, traumatic cataract and increases in intraocular pressure (IOP). This leaflet is not intended to replace the Lucentis® prescribing information: complete information regarding the safety profile of Lucentis®, including all adverse events that may be caused by intravitreal injections of Lucentis®, are detailed within the prescribing information.[1]

## Treatment with Lucentis®

### Background

Lucentis® (ranibizumab) is a fully humanized monoclonal antibody fragment specifically designed for intravitreal use that binds and inhibits multiple isoforms of biologically active vascular endothelial growth factor A (VEGF-A).[1]

### Indications

Lucentis® is indicated for the treatment of adults with:[1]

- Neovascular (wet) age-related macular degeneration (AMD)
- Visual impairment due to diabetic macular edema (DME)
- Visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO)
- Visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

### Contra-indications

Lucentis® must not be administered to patients with any of the following conditions:[1]

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

*Special populations*

- **Hepatic impairment:** Lucentis® has not been studied in patients with hepatic impairment. However, as systemic exposure is negligible, no special measures are considered necessary in this population
- **Renal impairment:** dose adjustment is not needed in patients with renal impairment
- **Geriatric patients:** no dose adjustment is required in the elderly
- **Pediatric 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

## Posology

### In patients with wet AMD:

- Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis® treatment
- Patients should be monitored monthly for visual acuity
- Treatment is resumed with monthly injections when monitoring indicates loss of visual acuity due to wet AMD, and is continued until stable visual acuity is reached again for three consecutive monthly assessments
- The interval between doses should not be shorter than 1 month[1]

### In patients with visual impairment due to DME:

- Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis® treatment
- Patients should be monitored monthly for visual acuity
- Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to DME, and is continued until stable visual acuity is reached again for three consecutive monthly assessments
- The interval between doses should not be shorter than 1 month[1]
- Lucentis® has been used concomitantly with laser photocoagulation in 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

### In patients with visual impairment due to macular edema secondary to RVO:

- Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis® treatment
- Patients should be monitored monthly for visual acuity
- Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular edema secondary to RVO, and is continued until stable visual acuity is reached again for three consecutive monthly assessments
- The interval between doses should not be shorter than 1 month[1]
- Lucentis® has been used concomitantly with laser photocoagulation in 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

### In patients with 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 examination, optical coherence tomography or fluorescein angiography. Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician.

## Administration of Lucentis®

- Lucentis® is available as a vial kit
  - As with all medicinal products for parenteral use, Lucentis® should be inspected visually for particulate matter and discoloration prior to administration
  - Further details on Lucentis® preparation are provided in the Preparation of Lucentis® for intravitreal injection section (page 7)
- One pack contains one vial, one filter needle for withdrawal of the vial content, one needle for the intravitreal injection, one syringe for the withdrawal of the vial contents and the intravitreal injection
- The glass vial (colorless type I glass) contains 0.23 mL Lucentis® solution for injection
- The vial kit is for single use only. Lucentis® is not licensed for multi-dose, further compounding or vial splitting. Use of more than one injection from the vial can lead to contamination and subsequent infection
- Do not use any component if its packaging is damaged
- The injection procedure should be carried out under aseptic conditions
  - The use of surgical hand disinfection, sterile gloves, a sterile drape and sterile eyelid speculum (or equivalent) is recommended
  - The periocular skin, eyelid and ocular surface should be disinfected
  - Adequate anesthesia and broad-spectrum topical microbicide should be administered prior to the injection
  - The patient should be instructed to self-administer antimicrobial drops four times daily for 3 days before and 3 days after each injection
- The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure
- Injection of Lucentis®:
  - 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
  - Any unused product or waste material should be disposed of in accordance with local requirements
  - Further details on Lucentis® injection are provided in the Preparation of the eye and administration of Lucentis® section (page 8)

## Ocular and systemic safety profile of Lucentis®

The safety profile and tolerability of Lucentis® have been established through clinical trials and post-marketing experience. Detailed information regarding the safety profile and tolerability of Lucentis® is provided in the prescribing information.[1] Serious adverse events related to the injection procedure included endophthalmitis, iatrogenic traumatic cataract and increased IOP. Other serious ocular events observed among Lucentis®-treated patients included intraocular inflammation, rhegmatogenous retinal detachment and retinal tear.

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 previously mentioned without delay.

Although this leaflet focusses on key ocular risks, there is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. 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. These patients should be carefully evaluated as to whether Lucentis® treatment is appropriate.

## Prevention and management of key injection-related risks with Lucentis®

### Endophthalmitis

*Characteristics*

- Endophthalmitis is a serious ocular condition consisting of inflammation of the vitreous cavity and can potentially lead to blindness[2]
- Endophthalmitis is often caused by an intraocular infection
  - Frequently implicated pathogens include skin bacteria such as coagulase-negative staphylococci, *Staphylococcus aureus* and streptococci[2]
  - *Streptococcus viridans* (a commensal organism of the throat) has been isolated over three times more frequently in cases of endophthalmitis occurring after intravitreal injection than after intraocular surgery[3]
- Events such as penetrating trauma, surgical procedures and intravitreal injections that disrupt the integrity of the eye globe can potentially lead to endophthalmitis[2]
- Endophthalmitis following Lucentis® injection is uncommon and the reported incidence in Lucentis® clinical trials ranges from ≥1/1000 to <1/100 patients across all indications[1]

*Prevention and management*

- Antimicrobial eye drops are recommended before and after each Lucentis® injection to prevent possible eye infection[1]
- Lucentis® should be prepared for intravitreal injection and administered according to the steps outlined in the prescribing information, summarized on pages 7 and 8 of this leaflet
  - It is essential to perform the injection procedure under aseptic conditions to prevent contamination of the eye
  - The use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) is recommended[1]
- Physicians should inform patients to contact their clinic immediately 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[1]
- Appropriate management and treatment of endophthalmitis should be followed according to local clinical practice

### Traumatic cataract

*Characteristics*

- Traumatic cataract can be caused by blunt trauma to the intraocular lens following either penetrating or non-penetrating ocular trauma
- Cataract incidence in Lucentis® clinical trials was reported to occur in ≥1/1000 to <1/100 of patients in clinical trials across all indications[1]
- Cataract may lead to loss of vision, and may require surgical intervention[4]

*Prevention and management*

- To reduce the risk of traumatic cataract, Lucentis® should be prepared for intravitreal injection and administered according to the steps outlined in the prescribing information, summarized on pages 7 and 8 of this leaflet[1]
  - Care should be taken to ensure the injection is inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, aiming towards the center of the globe, avoiding contact with the lens
- Physicians should inform patients to contact their clinic immediately if they develop symptoms such as sudden blurred or decreased vision[1]
- Appropriate management and treatment of traumatic cataract should be followed according to local clinical practice

### Increases in IOP

*Characteristics*

- Increases in IOP within 60 minutes of injection of Lucentis® are very common and the reported incidence is ≥1/10 patients in Lucentis® clinical trials across all indications[1]
- Increases in IOP are caused by injection of fluid into the eye and are more likely if high volumes are administered
- Post-injection increases in IOP are often asymptomatic and usually resolve quickly (are transient)

*Prevention and management*

- Lucentis® should be administered as a single intravitreal injection with an injection volume of 0.05 mL
  - Injection volume should be accurately checked to minimize the risk of increases in IOP
  - If an overdose occurs, IOP should be monitored and treated, if deemed necessary by the physician[1]
- IOP and perfusion of the optic nerve head should be monitored and managed appropriately[1]
  - The treatment of increases in IOP should follow local clinical practice
  - Paracentesis should only be carried out in cases in which the degree of increase in IOP poses a threat to vision[5]

## References

1. Novartis Europharm Ltd. Lucentis® (ranibizumab) Summary of Product Characteristics.
2. Kernt M, Kampik A. Endophthalmitis: pathogenesis, clinical presentation, management, and perspectives. *Clin Ophthalmol* 2010;4:121-35.
3. Chen E, Lin MY, Cox J, Brown DM. Endophthalmitis after intravitreal injection: the importance of viridans streptococci. *Retina* 2011;31:1525-33.
4. Thylefors B. Epidemiological patterns of ocular trauma. *Aust N Z J Ophthalmol* 1992;20:95-8.
5. Aiello LP, Brucker AJ, Chang S *et al*. Evolving guidelines for intravitreous injections. *Retina* 2004;24:S3-S19.

## Preparation of Lucentis® for intravitreal injection

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

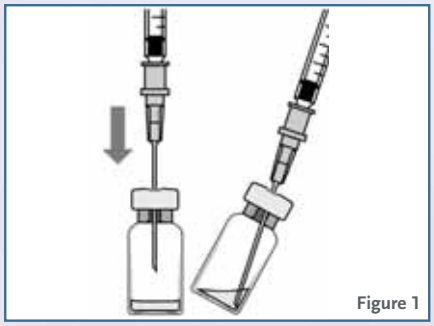


Figure 1

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.
2. Assemble the 5 µm filter needle (provided) onto the 1 mL syringe (provided) using aseptic technique. Push the blunt filter needle into the 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 (Figure 1).

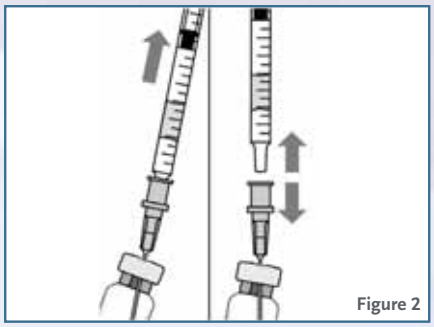


Figure 2

4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection (Figure 2).

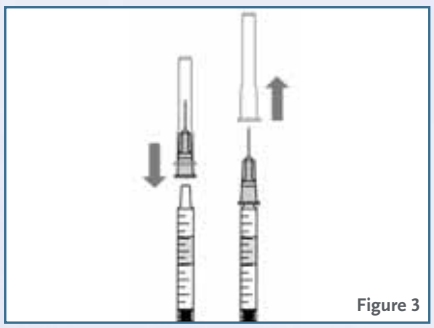


Figure 3

6. Aseptically and firmly assemble the injection needle (provided) onto the syringe.
7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe (Figure 3).

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

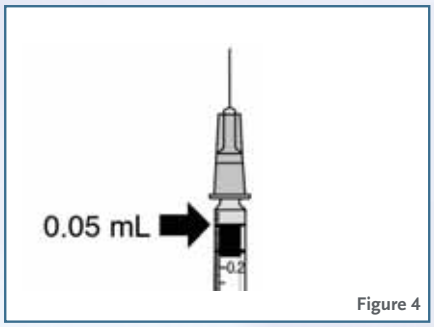



Figure 4

8. Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark on the syringe (Figure 4). The syringe is ready for injection.

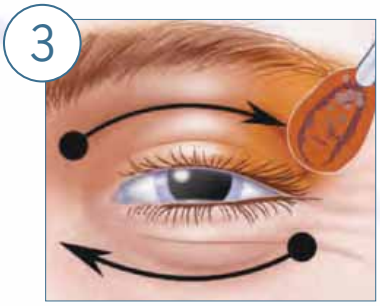
   **Note: do not wipe the injection needle. Do not pull back on the plunger.**

   The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. The injection volume of 0.05 mL is then delivered; a different scleral site should be used for subsequent injections.

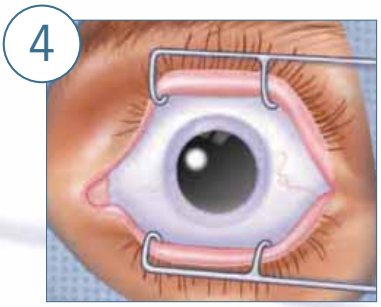
Any unused product or waste material should be disposed of in accordance with local requirements.

## Preparation of the eye and administration of Lucentis®

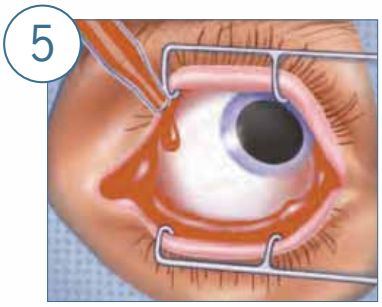

1. Dilate the pupil.
2. Apply topical anesthesia, and administer broad-spectrum antimicrobial eye drops.



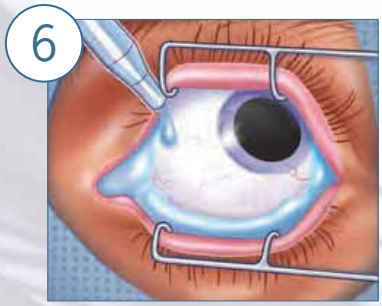

3. Apply 10% povidone iodine solution to periocular skin, lids and eyelashes, and place sterile drape over eye.



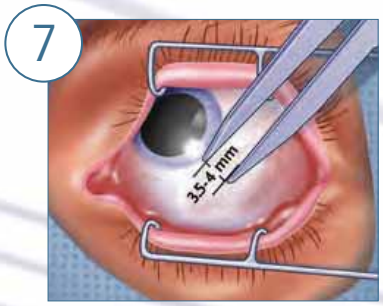

4. Apply sterile lid speculum.



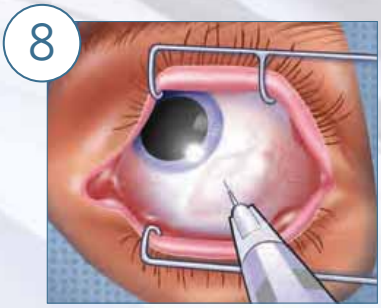

5. Instill 5% povidone iodine ophthalmic solution, and wait for 90 seconds.



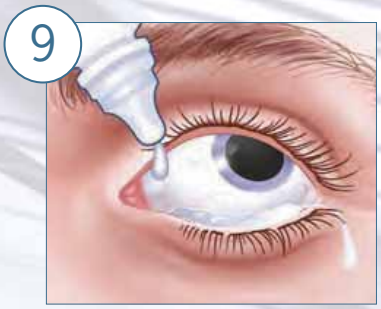

6. Rinse the eye with ophthalmic saline solution.




7. Direct the patient to look away from the injection site. Mark an injection site at an area 3.5-4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe.




8. Slowly deliver the injection volume, then remove the needle slowly.
   – Rotate the scleral site for subsequent intravitreal injections so that the same site is not injected repeatedly.




9. Administer broad-spectrum antimicrobial eye drops.

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

**PRESENTATION:** A glass single-use vial containing:
0.23ml solution - 2.3mg of ranibizumab (10mg/ml).
**INDICATIONS**: Lucentis is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD), the treatment of visual impairment due to diabetic macular oedema (DME), the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO (see section 5.1) and the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM).
**DOSAGE AND ADMINISTRATION**: Single-use vial for intravitreal use only. Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections under aseptic conditions. In wet AMD the recommended dose is 0.5mg (0.05ml) is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment The interval between two doses should not be shorter than 1 month. Before treatment, evaluate the patients medical history for hypersensitivity. The patient should also be instructed to self-administer antimicrobial drops, four times daily for 3 days before and following each injection. In visual impairment due to either DME or macular oedema secondary to RVO, the recommended dose for Lucentis is 0.5 mg (0.05ml) given as a single intravitreal injection. Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD, DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month. For cases 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. The interval between two doses should not be shorter than one month. **Paediatric population:** The safety and efficacy of Lucentis in children and adolescents below 18 years of age have not been established. No data are available.. Renal Impairment and **Elderly:** No dose adjustment is required. There is limited experience in patients older than 75 years with DME. Consult SmPC for full administration details before using Lucentis.
**CONTRAINDICATIONS:** Hypersensitivity to the active substance or excipients. Patients with active or suspected ocular or periocular infections. Patients with active severe intraocular inflammation.
**WARNINGS/PRECAUTIONS:** Lucentis is for intravitreal injection only. Intravitreous injections have been associated with endophthalmitus, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Monitor during week following injection for infections. Patients should be instructed to report symptoms suggestive of any of the above without delay. Transient increases in intraocular pressure (IOP) have been seen within 1 hour of injection. Sustained IOP increases have also been identified. Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. Concurrent use in both eyes has not been studied. Bilateral treatment at the same time could lead to an increased systemic exposure. There is a potential for immunogenicity and patients should report an increase in severity of intraocular inflammation. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. There are limited data on safety in the treatment of DME and macular oedema due to RVO patients with prior history of stroke or transient ischaemic attacks. There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischaemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended. Lucentis should not be administered concurrently with other anti-VEGF agents (systemic or ocular). Withhold dose and do not resume treatment earlier than the next scheduled treatment in the event of the following: a decrease in 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. 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. Discontinue treatment in cases of rhegmatogenous retinal detachment or stage 3 or 4 macular holes. Ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. Women of child-bearing potential should use effective contraception during treatment. Breast-feeding is not recommended during treatment. The treatment procedure may induce temporary visual disturbances and patients who experience these signs must not drive or use machines until these disturbances subside. The vial, injection needle, filter needle and syringe are for single use only. Re-use may lead to infection or other illness/injury. All components are sterile. Any component with packaging showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the component packaging seal remains intact.
**INTERACTIONS:** No formal interaction studies have been performed. Adjunctive use of verteporfin photodynamic therapy (PDT) and Lucentis in an open study showed a low incidence of intraocular inflammation following initial combination treatment.
**ADVERSE REACTIONS:** 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. Serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Other serious ocular events included intraocular inflammation and increased intraocular pressure. **Very Common:** Intraocular pressure increased**,** headache**,** vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus, arthralgia**,** nasopharyngitis, urinary tract infections**.** **Common:** Anaemia**,** retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia, cough, nausea, allergic reactions (rash, urticaria, pruritus, erythema), hypersensitivity, anxiety. **Uncommon:** Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. Please refer to SmPC for full listing of all undesirable effects.
**LEGAL CATEGORY:** POM
**PACK SIZES:** Lucentis is supplied in packs containing 1 vial.
**MARKETING AUTHORISATION HOLDER**: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.
**MARKETING AUTHORISATION NUMBER**:
EU/1/06/374/001

**Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. 24, MRS 1000, Marsa, Malta. Tel: +356 22983217/+35621222872

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Any suspected adverse reactions and medication errors can be reported via the National Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA or sent by e-mail to postlicensing.medicinesauthority@gov.mt.

Healthcare professionals may also report any adverse events suspected to be associated with the use of Lucentis to Novartis Pharma Services Inc. Representative Office Malta by phone on 22983217 or 21222872, by fax on 22487219 or e-mail at drug_safety.malta@novartis.com

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