



A brief guide to the management of risks associated with intravitreal injections during LUCENTIS® (ranibizumab) treatment

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 <http://www.medicinesauthority.gov.mt/adrportal> and posted to:

Medicines Authority Post-licensing Directorate,
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann. SGN 3000.

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 +356 21222872, by fax on +356 22487219 or e-mail at drug_safety.malta@novartis.com.

Marketing Authorization Holder: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7S4, United Kingdom.

Local Representative: Novartis Pharma Services Inc., Representative Office Malta.
Tel No.: +356 21222872



Introduction

This physician leaflet is part of the educational materials regarding the use of ranibizumab and provides information on the method of administration of ranibizumab, and on the prevention and management of key injection-related risks associated with intravitreal injections.

Complete information regarding the safety profile of ranibizumab is detailed within the local prescribing information¹.

Treatment with ranibizumab

Background

Ranibizumab is a humanized recombinant 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

Ranibizumab is indicated for the treatment of adults with:¹

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

Prevention and management of key injection-related risks associated with ranibizumab intravitreal injection

Intravitreal injections, including those with ranibizumab, have been associated with infectious endophthalmitis, traumatic cataract, intraocular pressure (IOP) increase (see more information below), as well as intraocular inflammation, rhegmatogenous retinal detachment or retinal tear.¹

Proper aseptic injection techniques must always be used when administering ranibizumab. 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 infectious endophthalmitis or any of the above mentioned events without delay.¹

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 ranibizumab treatment is appropriate.

Infectious endophthalmitis

Characteristics

- Infectious endophthalmitis is a serious ocular condition consisting of inflammation of the vitreous cavity, and can potentially lead to blindness^{2,3}
- Infectious endophthalmitis is often caused by an intraocular infection
 - > Frequently implicated pathogens include skin bacteria such as coagulase-negative staphylococci, *Staphylococcus aureus*, and streptococci²
 - > *Streptococcus viridans* (a commensal organism of the throat) has been isolated over three times more frequently in cases of infectious endophthalmitis occurring after intravitreal injection than after intraocular surgery⁴
- Events such as penetrating trauma, surgical procedures and intravitreal injections that disrupt the integrity of the eye globe can potentially lead to infectious endophthalmitis^{2,3}
- Infectious endophthalmitis following ranibizumab injection is uncommon; the reported incidence in ranibizumab clinical trials ranges from $\geq 1/1,000$ to $< 1/100$ patients across all indications¹

Prevention and management

- Ranibizumab should be prepared for intravitreal injection and administered according to the steps outlined in the local prescribing information¹, summarized on pages 8 and 9 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), and the availability of sterile paracentesis (if required) is recommended¹
- Patients should be instructed to report any symptoms suggestive of infectious endophthalmitis without delay¹
- Appropriate management and treatment of infectious endophthalmitis should be followed according to local clinical practice

Iatrogenic traumatic cataract

Characteristics

- Traumatic cataract can be caused by trauma to the intraocular lens following either penetrating or non-penetrating ocular trauma⁵
- Traumatic cataract may lead to loss of vision, and may require surgical intervention^{5,6}

Prevention and management

- To reduce the risk of iatrogenic traumatic cataract, ranibizumab should be prepared for intravitreal injection and administered according to the steps outlined in the local prescribing information¹, summarized on pages 8 and 9 of this leaflet
 - > Care should be taken to ensure the injection is 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
- Patients should be instructed to report any symptoms suggestive of iatrogenic traumatic cataract without delay¹
- Appropriate management and treatment of traumatic cataract should be followed according to local clinical practice

Increases in intraocular pressure

Characteristics

- Transient increases in IOP within 60 minutes of injection of ranibizumab are very common; the reported incidence is $\geq 1/10$ patients in ranibizumab clinical trials across all indications¹
- Increases in IOP are caused by injection of fluid into the eye and are more likely if high volumes are administered⁷
- Post-injection increases in IOP are often asymptomatic and usually resolve quickly (are transient)⁷

Prevention and management

- Ranibizumab should be administered as a single intravitreal injection with an injection volume of 0.05 mL¹
 - > 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 attending physician¹
- IOP and perfusion of the optic nerve head must be monitored and managed appropriately¹
 - > 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 vision⁸

Overdose due to overfill of the pre-filled syringe

Characteristics

- The pre-filled syringe contains more ranibizumab solution than is required for a single dose¹
- The extra volume is present to aid priming the needle and syringe in preparation for the injection¹

Prevention and management

- The instructions for use in the local prescribing information should be closely followed to ensure accurate setting of the dose in the syringe¹
- If an overdose occurs, IOP should be monitored and treated, if deemed necessary by the physician¹
- IOP and perfusion of the optic nerve head must be monitored and managed appropriately
 - > Paracentesis should only be carried out in cases in which the degree of increase in IOP poses a threat to vision⁸

References

1. Novartis Europharm Ltd. Lucentis® Summary of Product Characteristics; 2. Kernt M, Kampik A. *Clin Ophthalmol.* 2010; 4: 121-135; 3. Spadea L. *US Ophthalmic Rev.* 2014; 7(2): 146-153; 4. Chen E, et al. *Retina.* 2011; 31(8): 1525-1533; 5. Shah M, et al. *Indian J Ophthalmol.* 2011; 59(3): 217-222; 6. Thylefors B. *Aust N Z J Ophthalmol.* 1992; 20(2): 95-98; 7. Abedi G, et al. *Semin Ophthalmol.* 2013; 28(3): 126-130; 8. Aiello LP, et al. *Retina.* 2004; 24(5 Suppl): S3-S19.

Administration of ranibizumab

- Ranibizumab is available as a vial kit, vial with a filter needle or pre-filled syringe
- Ranibizumab should be inspected visually for particulate matter and discoloration prior to administration
- Both the vial and the pre-filled syringe are for single use only. Ranibizumab is not licensed for multi-dose, further compounding or vial splitting. Use of more than one injection from the vial may lead to contamination and subsequent infection
- 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 a broad-spectrum topical microbicide should be administered prior to the injection
- Prophylactic topical antibiotics should be used according to local clinical practice
- The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure

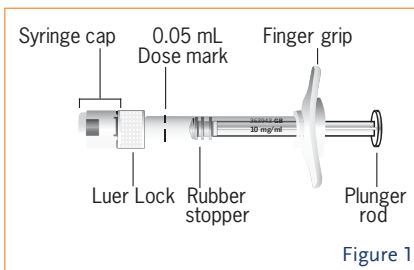
Preparation of ranibizumab for intravitreal injection using the pre-filled syringe

To prepare the ranibizumab pre-filled syringe for intravitreal administration, please adhere to the following instructions for use:

The single-use pre-filled syringe is for intravitreal use only. The pre-filled syringe contains more than the recommended dose of 0.5 mg.

Read all the instructions carefully before using the pre-filled syringe.

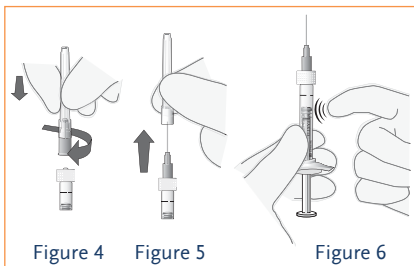
The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The opening of the sealed tray and all subsequent steps should be done under aseptic conditions. **Note: the dose must be set to 0.05 mL.**



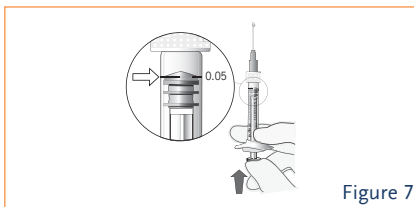
1. Make sure that your pack contains a sterile pre-filled syringe in a sealed tray.
2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe.
3. Check that:
 - The syringe cap is not detached from the Luer Lock
 - The syringe is not damaged
 - The solution looks clear, colorless to pale yellow and does not contain any particulates.



4. If any of the above is not true, discard the pre-filled syringe (**Figure 1**) and use a new one.
5. Snap off (do not turn or twist) the syringe cap (**Figure 2**).
6. Dispose of the syringe cap (**Figure 3**).



7. Attach a 30 gauge x 1/2 inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer Lock (**Figure 4**).
8. Carefully remove the needle cap by pulling it straight off (**Figure 5**). **Note: do not wipe the needle at any time.**
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 (**Figure 6**).



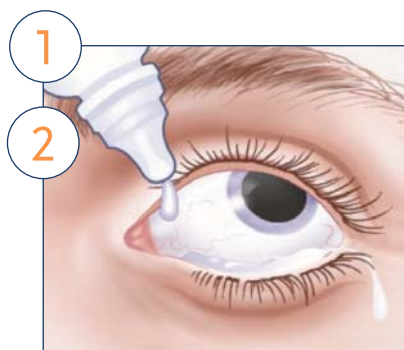
11. Hold the syringe at eye level and carefully push the plunger until the **edge below the dome of the rubber stopper** is aligned with the dose mark (**Figure 7**). This will expel the air and the excess solution and set the dose to 0.05 mL. **Note: the plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.**

The injection procedure should be carried out under aseptic conditions.

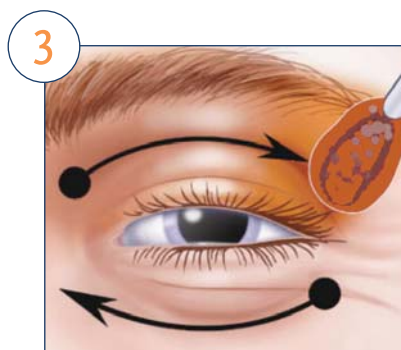
12. The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe.
13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL.
14. A different 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.

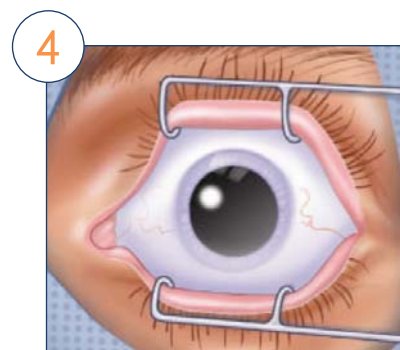
Preparation of the eye and administration of ranibizumab



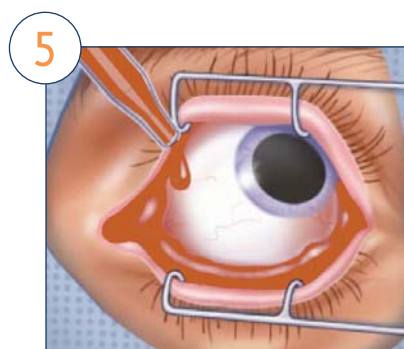
1. Dilate the pupil.
2. Apply topical anesthesia.



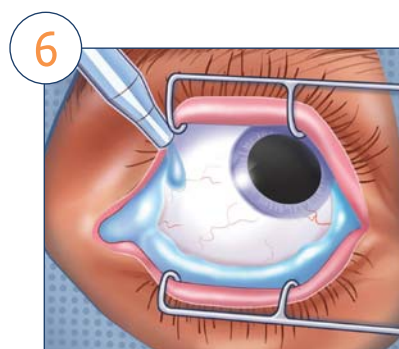
3. Apply 10% povidone iodine solution to periocular skin, lids and eyelashes, and place sterile drape over eye.



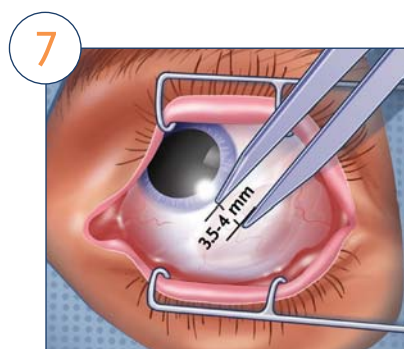
4. Apply sterile eyelid speculum.



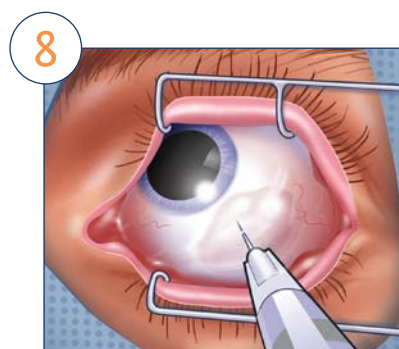
5. Instill 5% povidone iodine ophthalmic solution and wait for 90 seconds.



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 mm to 4.0 mm posterior to the limbus, avoiding the horizontal meridian.



8. The injection needle should be inserted aiming towards the center of the globe. Slowly deliver the injection volume, then remove the needle slowly.
 - A different scleral site should be used for subsequent intravitreal injections so that the same site is not injected repeatedly.

Note: prophylactic topical antibiotics should be used according to local clinical practice

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

PRESENTATION: One ml contains 10mg ranibizumab. One pre-filled syringe contains 0.165ml equivalent to 1.65mg ranibizumab.

INDICATIONS: For the treatments of: neovascular (wet) age-related macular degeneration (AMD), visual impairment due to choroidal neovascularisation (CNV), visual impairment due to diabetic macular oedema (DME) and visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

DOSAGE: 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 be at least four weeks. Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. Monitoring may include clinical examination, functional testing, or imaging techniques. While applying the treat-and-extend regimen, the treatment interval should be extended by 2 weeks for wAMD and by 1 month for DME. Treatment intervals may also be gradually extended for RVO. Treatment for CNV should be determined individually per patient depending on disease activity. *Special populations* -*Hepatic impairment:* No special considerations. *Renal impairment:* Dosage adjustment is not needed. *Elderly:* Dose adjustment is not required, limited experience in elderly with DME older than 75 years. *Paediatric population:* The safety and efficacy of Lucentis in patients below 18 years of age have not been established.

CONTRAINDICATIONS: Hypersensitivity to the active substance or the excipients, in patients with active or suspected ocular or periocular infection and in patients with active severe intraocular inflammation.

WARNINGS/PRECAUTIONS: *Intravitreal injection-related reactions:* Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Therefore proper aseptic injection techniques must be used when administering Lucentis. *Intraocular pressure (IOP) increases:* Monitor and manage appropriately the intraocular pressure and optic nerve head perfusion. Inform patients to report signs of IOP such as eye pain, worsening eye redness, blurred vision and increased light sensitivity. *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. *Concomitant use of other anti-VEGF (vascular endothelial growth factor):* Lucentis should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular). *Withholding Lucentis:* The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of: ● a decrease in best-corrected visual acuity (BCVA) of ≥ 30 letters compared with the last assessment of visual acuity; ● an intraocular pressure of ≥ 30 mmHg; ● a retinal break; ● a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is $\geq 50\%$, of the total lesion area; ● performed or planned intraocular surgery within the previous or next 28 days. *Retinal pigment epithelial tear:* Caution should be used in patients with 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. *Systemic effects following intravitreal use:* Use caution when treating patients with prior history of stroke or transient ischaemic attacks. *Women of childbearing potential/contraception in females:* Women of childbearing potential should use effective contraception during treatment. *Pregnancy:* It is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child. *Breast-feeding:* Not recommended. *Effects on ability to drive and use machines:* Patients who experience temporary visual disturbances must not drive or use machines until these subside.

INTERACTIONS: No formal interaction studies have been performed. *Lucentis and laser photocoagulation in DME and in macular oedema secondary to BRVO:* When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation. *Lucentis and verteporfin photodynamic therapy in CNV secondary to PM:* No experience of concomitant administration.

ADVERSE REACTIONS: *Very common:* Nasopharyngitis, 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, intraocular pressure increased. *Common:* Urinary tract infection, anaemia, hypersensitivity, anxiety, 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). *Please refer to the Summary of Product Characteristics for a full list of adverse events.*

LEGAL CATEGORY: POM.

PACK SIZES: one pre-filled syringe packed in a sealed tray.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom.

MARKETING AUTHORISATION NUMBERS: EU/1/06/374/003

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. Box 4, MRS 1000, Marsa, Malta. Tel+356 21222872.

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