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

NOVARTIS

LUCENTIS® RANIBIZUMAB

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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 Summary of Product Characteristics[1].

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 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)

PRE-FILLED SYRINGE / VIAL KIT / VIAL & FILTER NEEDLE –
RISK PREVENTION AND MANAGEMENT

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

Intravitreal injections, including those with ranibizumab, have been associated with 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 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.

Endophthalmitis

Characteristics

- Endophthalmitis is a serious ocular condition consisting of inflammation of the vitreous cavity, and can potentially lead to blindness[2,3]
- 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[4]
- Events such as penetrating trauma, surgical procedures and intravitreal injections that disrupt the integrity of the eye globe can potentially lead to endophthalmitis[2,3]
- Endophthalmitis following ranibizumab injection is uncommon; the reported incidence in ranibizumab clinical trials ranges from ≥1/1,000 to <1/100 patients across all indications[1]

Prevention and management

- Ranibizumab should be prepared for intravitreal injection and administered according to the steps outlined in the Summary of Product Characteristics[1], summarized on pages □t□ □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 recommended[1]
- Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay[1]
- Appropriate management and treatment of 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 trauma[5]
- Cataract may lead to loss of vision, and may require surgical intervention[5,6]

PRE-FILLED SYRINGE / VIAL KIT / VIAL & FILTER NEEDLE – RISK PREVENTION AND MANAGEMENT

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 Summary of Product Characteristics[1], summarized on pages □t□ □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 delay[1]
- 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 ≥1/10 patients in ranibizumab 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[7]
- 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 mL[1]
  - > 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 physician[1]
- IOP and perfusion of the optic nerve head must 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[8]

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Overdose due to overfill of the pre-filled syringe

Characteristics

- The pre-filled syringe contains more ranibizumab solution than is required for a single dose[1]
- The extra volume is present to aid priming the needle and syringe in preparation for the injection[1]

Prevention and management

- The instructions for use in the Summary of Product Characteristics should be closely followed to ensure accurate setting of the dose in the syringe[1]
- 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 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 vision[8]

References

1. Novartis Pharma AG. Lucentis® Summary of Product Characteristics. September 2015; **2.** Kernt M, Kampik A. Clin Ophthalmol 2010;4:121-35; **3.** Spadea L. US Ophthalmic Rev 2014;7:146-53; **4.** Chen E, et al. Retina 2011;31:1525-33; **5.** Shah M, et al. Indian J Ophthalmol 2011;59:217-22; **6.** Thylefors B. Aust N Z J Ophthalmol 1992;20:95-8; **7.** Abedi G, et al. Semin Ophthalmol 2013;28:126-30; **8.** Aiello LP, et al. Retina 2004;24:S3-19.

PRE-FILLED SYRINGE / VIAL KIT / VIAL & FILTER NEEDLE – ADMINISTRATION OF RANIBIZUMAB

Administration of ranibizumab

- Ranibizumab is available as a vial kit, vial with 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.**

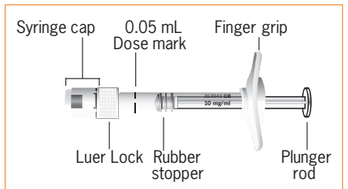

Figure 1


Figure 2

Figure 3

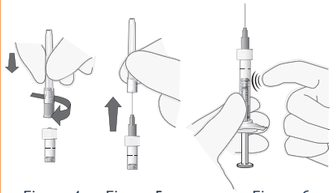
Figure 4

Figure 5

Figure 6

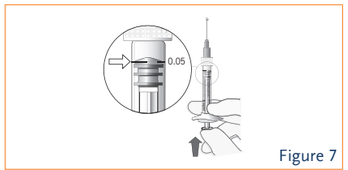

Figure 7

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 × ½-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.

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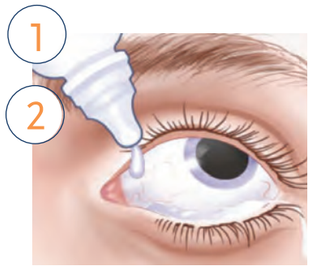
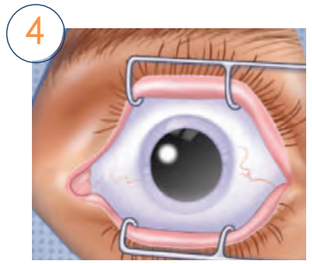
Preparation of the eye and administration of ranibizumab

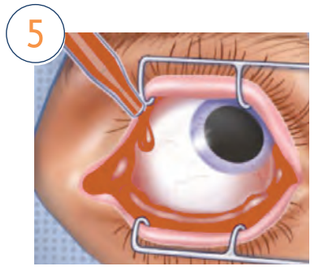


1. Dilate the pupil.
2. Apply topical anesthesia.

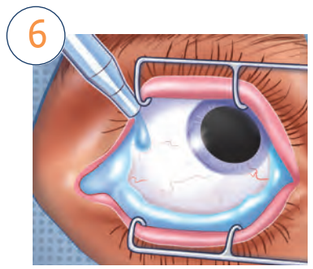
3. Apply 10% povidone iodine solution to periocular skin, lids and eyelashes, and place sterile drape over eye.



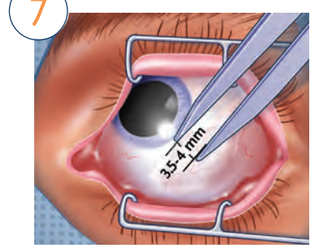
4. Apply sterile eyelid speculum.



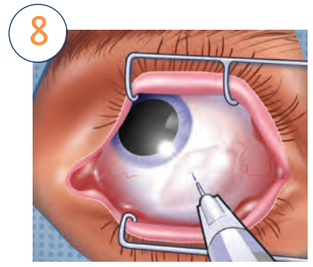
5. Instill 5% povidone iodine ophthalmic solution and wait for 90 seconds.



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 toward 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

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Lucentis® 10mg/ml pre-filled syringe

PRESENTATION: 10mg/ml solution for injection in pre-filled syringe. Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution.

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

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 i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed. 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. *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. *Hepatic impairment:* Lucentis has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population. *Renal impairment:* Dose adjustment is not needed in patients with renal impairment. *Elderly:* No dose adjustment is required in the elderly. *Paediatric population:* The safety and efficacy of Lucentis in children and adolescents below 18 years of age have not been established.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients. Patients with active or suspected ocular or periocular infections. Patients with active severe intraocular inflammation.

WARNINGS/PRECAUTIONS: *Intravitreal injection-related reactions*: Intravitreous injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must always be used when administering Lucentis. *Intraocular pressure increases:* Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis. Sustained IOP increases have also been identified. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. *Bilateral treatment:* Limited data on bilateral use of Lucentis (including same-day administration) do not suggest an increased risk of systemic adverse events compared with unilateral treatment. *Immunogenicity:* There is a potential for immunogenicity with Lucentis. Since there is a potential for an increased systemic exposure in subjects with DME, an increased risk for developing hypersensitivity in this patient population cannot be excluded. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation. *Concomitant use of other anti-VEGF (vascular endothelial growth factor):* Lucentis should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular). *Withholding Lucentis:* The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of: ●a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity; ● an intraocular pressure of ≥30 mmHg; ● a retinal break; ● a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area; ● performed or planned intraocular surgery within the previous or next 28 days. *Retinal pigment epithelial tear:* Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating Lucentis therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. *Rhegmatogenous retinal detachment or macular holes:* Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. *Systemic effects following intravitreal use:* Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. *Women of childbearing potential/contraception in females:* Women of childbearing potential should use effective contraception during treatment. *Pregnancy:* For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child. *Breast-feeding:* It is unknown whether Lucentis is excreted in human milk. Breast-feeding is not recommended during the use of Lucentis. *Effects on ability to drive and use machines:* The Lucentis treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see section 4.8). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

INTERACTIONS: No formal interaction studies have been performed.

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, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia. 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+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 may be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Malta Medicines Authority, Sir Temi Zammit Buildings, Malta Lifeciences 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 □□r□□□s □□□□□ □□r□s□□t□t□□□ □ □□□□ M□t□ □□ □□□□□□ □□ 21222□□2□□□ □□□ □□ 22□□□21□ □r □□ □□□ □□□□□ drug□s□□□t□□□ □t□□ □□□□rt□s□□□□