For more information about EYLEA®,
visit www.EYLEA.com

EYLEA®
(aflibercept solution for injection)

Bayer Pharma AG, D-13342 Berlin, Germany

www.bayerhealthcare.com
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Intravitreal injections
Recommendations for treatment with

EYLEA®
(aflibercept solution for injection)

PRESCRIBER GUIDE

For further information and additional details on EYLEA®,
please see the Summary of Product Characteristics (SmPC).

FOR POSITION OF DVD HUB
ONLY---DOES NOT PRINT

Intravitreal Injection Procedure Video

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APPROPRIATE LOCAL SAFETY INFORMATION

Any suspected adverse drug reactions can be reported via the national Adverse Drug Reactions (ADRs) reporting system.

Report forms can be downloaded from
www.medicinesauthority.gov.mt and posted to:
The Medicines Authority
Post-Licensing Directrorate,
203, Level 3, Rue D'Argens,
Gzira GZR 1368, MALTA,
or sent by email to postlicensing.medicinesauthority@gov.mt

Or

Alfred Gera & Sons Ltd,
Triq il-Masgar,
Qormi QRM 3217,
MALTA,
or at:
pv@alfredgera.com
Tel: + 356 21446205

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GENERAL INFORMATION

Before the start of treatment with EYLEA®, a patient information booklet, including an audio CD and the Patient Information Leaflet, must be provided to each patient who is prescribed EYLEA.
The physician is responsible for providing the patient with these materials.
In addition, the implications of anti-VEGF treatment should be explained.
Specifically, any signs and symptoms of serious adverse events and when to seek medical attention should be discussed with the patient.

Therapeutic indications

EYLEA is indicated for adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD)
- visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)
- visual impairment due to diabetic macular oedema (DME)

Product information

- EYLEA 40 mg/ml solution for injection
- EYLEA is for intravitreal injection only. It must only be administered by a qualified physician experienced in administering intravitreal injections
- The solution is a clear, colourless to pale yellow, and iso-osmotic solution
- The solution should be inspected visually for any foreign particulate matter and/or discoloration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product
- The pre-filled syringe and the vial are for single use only

Qualitative and quantitative composition

- One pre-filled syringe contains 90 microlitres, equivalent to 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept. The pre-filled syringe contains more than the recommended dose of 2 mg. The extractable volume of the syringe (90 microlitres) is not to be used in total. The excess volume should be expelled before injecting.
- One vial contains an extractable volume of 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept. The vial contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microlitres) is not to be used in total. The excess volume should be expelled before injecting.
- Injecting the entire volume of the vial or the pre-filled syringe could result in overdose. To expel excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres; ie, 2 mg aflibercept).

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- Vitreous detachment
  Patients may experience sudden flashes of light and a sudden appearance/increase in the number of vitreous floaters.
- Retinal tear
- Retinal degeneration
- Retinal detachment
  Patients may experience sudden flashes of light, a sudden appearance or an increase of the number of vitreous floaters, a curtain over a portion of their visual field, and vision changes.
- Tear or detachment of the retinal pigment epithelium
- In the wet AMd phase 3 studies, there was an increased incidence of conjunctival haemorrhage in patients receiving antithrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and EYLEA®.
- Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of ATEs following intravitreal use of VEGF inhibitors.
- As with all therapeutic proteins, there is a potential for immunogenicity with EYLEA.

Make sure that, in any case of any adverse event that concerns your patient, your patient has immediate access to an ophthalmologist.

Appropriate management of ALL adverse events, including those associated with the intravitreal injection, should be carried out according to clinical practice and/or following standardised guidelines.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions. See page 14 of this Prescriber Guide or section 4.8 of the Summary of Product Characteristics for how to report adverse events.

Overdose

In clinical trials, doses of up to 4 mg in monthly intervals have been used, and isolated cases of overdoses with 8 mg occurred.

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and, if deemed necessary by the treating physician, adequate treatment should be initiated.

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ADVERSE DRUG REACTIONS

- Blurred vision
- Eye pain
- Abnormal sensation in the eye
- Foreign body sensation in eyes
- Increased lacrimation
- Conjunctival or ocular hyperaemia
- Conjunctival/injection-site haemorrhage

  Patients may experience bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye.
- Pain or irritation of the injection site
- Punctate keratitis
- Abrasion or erosion or epithelium defect of the cornea

  Patients may experience pain, redness, increased lacrimation, photophobia, and vision changes.
- Eyelid irritation or oedema
- Corneal oedema

  Patients may experience halos around lights, photophobia, and vision changes.
- Transient increased intraocular pressure

  Patients may experience halos around lights, red eye, nausea and vomiting, and vision changes.
- Anterior chamber flare
- Hypopyon
- Iritis or iridocyclitis or vitritis or uveitis

  Patients may experience eye pain, photophobia, redness, or vision changes.
- Endophthalmitis

  Patients may experience eye pain or increased discomfort, worsening eye redness, photophobia or sensitivity to light, swelling, and vision changes, such as a sudden decrease in vision or blurring of vision.
- Hypersensitivity

  Patients may experience pain, photophobia or redness.
- Cataract (traumatic, nuclear, subcapsular, cortical) or lenticular opacities

  Patients may experience less vivid lines and shapes, shadows, and colour vision than before, and vision changes.
- Vitreous floaters or haemorrhage

For further information and additional details on EYLEA®, please see the Summary of Product Characteristics (SmPC).

Special precautions for storage

- Store in a refrigerator (2°C to 8°C)
- Do not freeze
- Keep the pre-filled syringe in its blister and in the outer carton in order to protect from light
- Keep the vial in the outer carton in order to protect from light
- Prior to usage, the unopened vial or blister of EYLEA® may be kept at room temperature (below 25°C) for up to 24 hours. Do not open the sterile, pre-filled blister outside the clean administration room. After opening the blister or vial, proceed under aseptic conditions

Dosing recommendations

- The recommended dose for EYLEA is 2 mg aflibercept, equivalent to 50 microlitres
- Please note that the dosing recommendations for wAMD, CRVO and DME are different to each other and are as described below:

wet AMD

- EYLEA treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections
- After the first 12 months of treatment with EYLEA, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections

Macular Oedema secondary to CRVO

- After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.
- If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended.
- Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered.
- If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate.
- Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

Diabetic Macular Oedema

- EYLEA treatment is intiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.
- After the first 12 vmonths of treatment with EYLEA, the treatment interval may be extended based on visual and anatmoic outcomes. The schedule for monitoring should be determined by the treating physician.
- If visual and anatomic outvomes indicate that the patient is not benefiting from continued treatment, EYLEA should be discontinued.

Contraindications

- Known hypersensitivity to aflibercept or to any of the excipients listed in section 6.1 in the SmPC
- Active or suspected ocular or periocular infection
- Active severe intraocular inflammation

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SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Endophthalmitis

Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis. Proper aseptic injection technique must always be used when administering EYLEA®. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay, and these should be managed according to clinical practice.

Increase in intraocular pressure

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with EYLEA. Special precaution is needed in patients with poorly controlled glaucoma (do not inject EYLEA while the intraocular pressure is ≥30 mm Hg). In all cases, both intraocular pressure and the perfusion of the optic nerve head must, therefore, be monitored and managed according to clinical practice.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with EYLEA. Patients should be instructed to report any signs or symptoms of intraocular inflammation, (eg, pain, photophobia, or redness), which may be a clinical sign attributable to hypersensitivity.

Systemic effects

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, and there is a theoretical risk that these may relate to VEGF inhibition.

AFTER INJECTION

- Evaluate vision immediately after injection (hand movement or finger counting)
- Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available
- Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (eg, eye pain, redness of the eye, photophobia, blurring of vision) without delay
- Application of antibiotic eye drops after intravitreal injections should be according to local ophthalmologic society guidelines. Please take this into consideration

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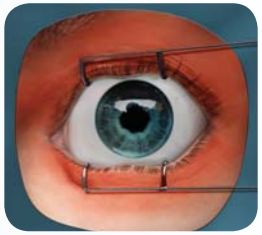
INJECTION PROCEDURE

For use of topical antibiotics please refer to local or national clinical guidelines.

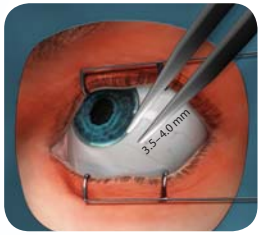
1 Administer topical anaesthesia.

2 Instill disinfectant (ie, 5% povidone iodine solution) according to manufacturer's guidance.

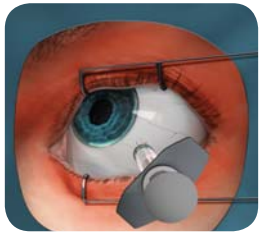
3 A disinfectant (eg, 10% povidone iodine solution or equivalent) may also be applied to the periocular skin, eyelids, and eyelashes, avoiding extensive pressure to eye glands.



4 Cover with sterile drape and insert sterile lid speculum.



5 Tell your patient to look away from the injection site. Position the eye adequately. At an area 3.5 to 4.0 mm posterior to the limbus, mark an injection site.



6 Insert the injection needle into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.

For further information on the intravitreal injection procedure, please see:

- Evolving guidelines for intravitreous injections. Aiello LP, Brucker AJ, Chang S, et al. Retina. 2004;24(5 Suppl):S3-S19.
- Guidelines for Intravitreal Injections Procedure 2009. The Royal College of Ophthalmologists. Available at: http://www.rcophth.ac.uk/page.asp?section=451. Accessed October 23, 2013.
- Age-Related Macular Degeneration: Guidelines for Management, September 2013. Available at: http://www.rcophth.ac.uk/page.asp?section=451. Accessed October 23, 2013.
- Guidelines for intravitreal injections. Korobelnik JF, Weber M, Cohen SY, et al. J Fr Ophtalmol. 2009;32(4):288-289.
- Intravitreal Injection Procedure Video (page 2)

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Other

As with other intravitreal anti-VEGF treatments for AMD, CRVO and DME the following also applies:

- The safety and efficacy of EYLEA® therapy administered to both eyes concurrently have not been systematically studied
- 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 EYLEA therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears
- Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes
- In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired
- 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
  - A subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50% of the total lesion area
- The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery
- EYLEA should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus.
- Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept
- There is limited experience with treatment of patients with ischaemic, chronic CRVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, the treatment is not recommended.

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INSTRUCTIONS FOR USE / HANDLING

Injection preparation

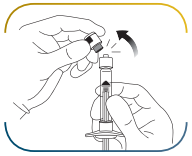
- Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections
- In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (eg, povidone iodine applied to the periocular skin, eyelid, and ocular surface), have to be ensured
- Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended
- For the intravitreal injection, a 30 G x ½ inch injection needle should be used

Pre-filled syringe:

1 When ready to administer EYLEA®, open the carton and remove the sterilized blister. Carefully peel open the blister, ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2 Using aseptic technique, remove the syringe from the sterilized blister.

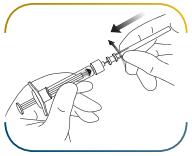
3 To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger.



Please note: Snap off (do not turn or twist) the syringe cap.

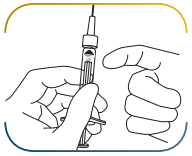
4 To avoid compromising the sterility of the product, do not pull back on the plunger.

5 Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

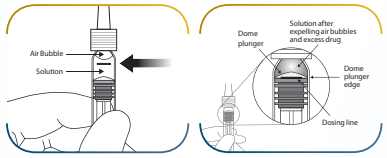


6 Remove the plastic needle shield.

7 Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



8 To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres). The excess volume needs to be expelled before injecting EYLEA to avoid overdose.



9 The pre-filled syringe is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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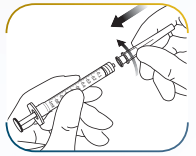
Vial:

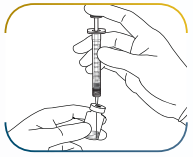
1 Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

2 Attach the 18 G, 5-micron filter needle supplied in the carton to a 1-ml sterile Luer-lock syringe.



3 Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom edge of the vial.

4 Using aseptic technique withdraw all of the Eylea® vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.

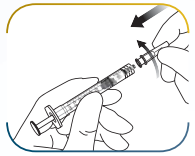


5 Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

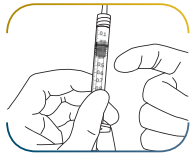
6 Remove the filter needle and properly dispose of it. Note: filter needle is not to be used for intravitreal injection.

7 Using aseptic technique, firmly twist a 30 G x ½-inch injection needle to the Luer-lock syringe tip.

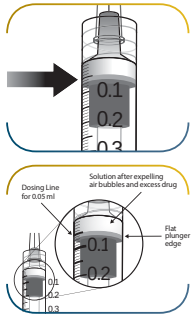
8 When ready to administer EYLEA, remove the plastic needle shield.



9 Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



10 Eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 ml on the syringe. The excess volume needs to be expelled before injecting EYLEA to avoid overdose.



11 The vials are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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