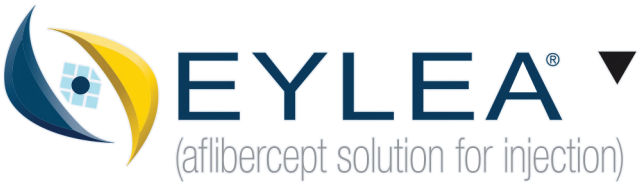
Recommendations for treatment with



PRESCRIBER GUIDE

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

Version 1.0, 14 July 2016

Intravitreal Injection Procedure Video

CONTENT PAGE

EYLEA® ▼
(aflibercept solution for injection)

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Version 1.0, 14 July 2016

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 retinal vein occlusion (branch RVO or central RVO)
- visual impairment due to diabetic macular oedema (DME)
- visual impairment due to myopic choroidalneovascularisation (myopic CNV)

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 discolourationor 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
- EYLEA is not licensed for multi-dose, further compounding or vial splitting. Use of more than one injection from the pre-filled syringe or the vial can lead to contamination and subsequent infection.

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

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 EYLEAmay 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, RVO, DME and myopic CNVare 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, and based on visual and/or anatomic outcomes, the treatment interval may be extended, such as with treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections.

Macular oedema secondary to RVO (branch RVO or central RVO)

- After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.

- If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.

- Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed.

- Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

- The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.

- Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Diabetic macular oedema

- EYLEA treatment is initiated 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 months of treatment with EYLEA, and based on visual and/or anatomic outcomes, the treatment interval may be extended, such as with treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

The schedule for monitoring should therefore be determined by the treating physician may be more frequent than the schedule of injections.
If visual and/or anatomic outcomes indicate that the patient is not benefiting from continued treatment,EYLEA should be discontinued.

Myopic choroidal neovascularisation

- The recommended dose for Eylea is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres.

- Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease.
- The schedule for monitoring should be determined by the treating physician.
- The interval between two doses should not be shorter than one month.

Contraindications

- 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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intravitreal injection-related reactions

Intravitreal injections, including those with Eylea, 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 Eylea. 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.

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. There are limited data on safety in the treatment of patients with CRVO, BRVO, DME or myopic CNV with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.

Other

As with other intravitreal anti-VEGF treatments for AMD, CRVO, BRVO, DME and myopic CNV other considerations apply includes:

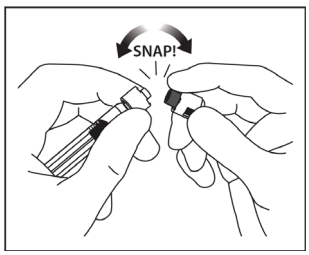
- Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of EYLEA.

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
- The pre-filled syringe and the vial are for single use only. EYLEA is not licensed for multi-dose, further compounding or vial splitting. Use of more than one injection from the pre-filled syringe or the vial can lead to contamination and subsequent infection.
- Surgical hand disinfection, sterile gloves, a sterile drape, and a sterilised eyelid speculum (or equivalent) are recommended
- For the intravitreal injection, a 30 G x ½ inch injection needle should be used

Pre-filled syringe:



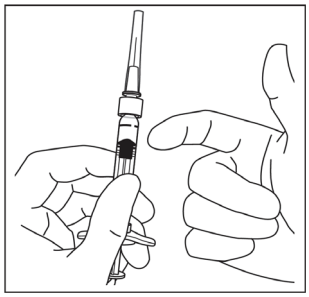
1. When ready to administer EYLEA, open the carton and remove the sterilized blister. Carefully peel open the blister, ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

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

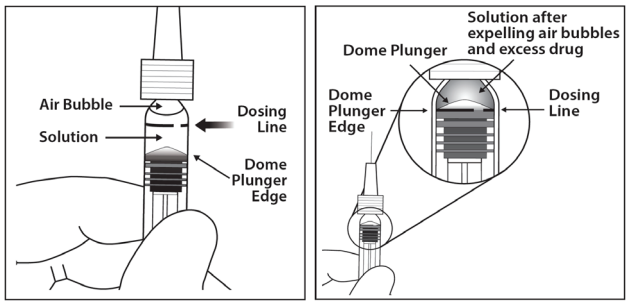
3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger. Please note: You should snap off (do not turn or twist) the syringe cap.

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. 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.

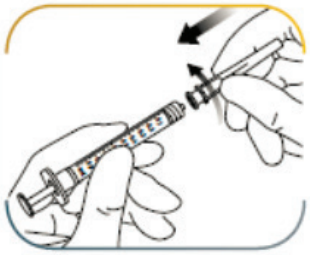


7. To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres). The excess volume needs to be expelled before injecting EYLEA to avoid overdose.

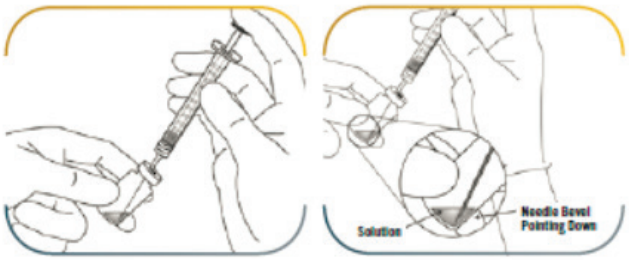
8. The pre-filled syringe is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Vial:

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



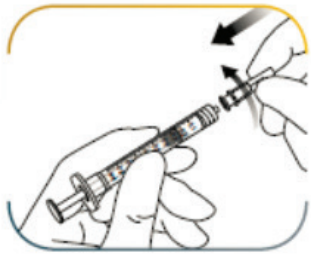
2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1-ml sterile Luer-lock syringe.
3. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.



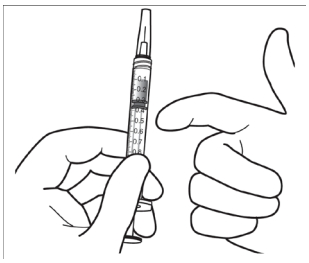
4. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To avoid the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial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

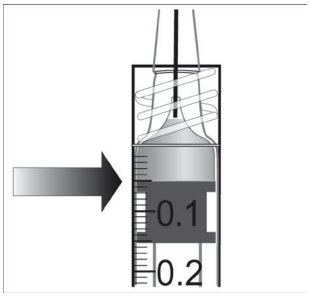
6. Remove the filter needle and properly dispose of it. Note: filter needle is not to be used for intravitreal injection

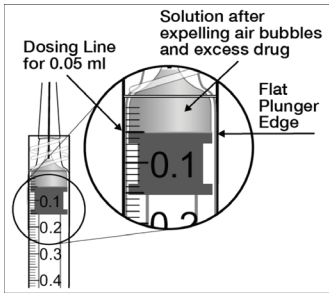


7. Using aseptic technique, firmly twist a 30 G x ½ - inch injection needle to the Luer-lock syringe tip.



8. 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





9. Eliminate all bubbles and expel excess medicinal product 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.

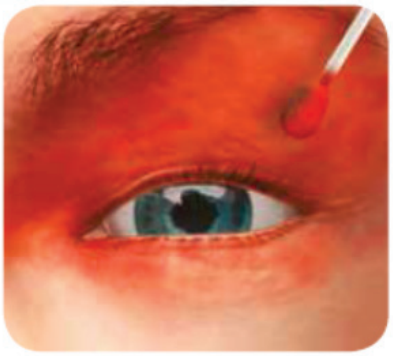
10. The vial is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

INJECTION PROCEDURE

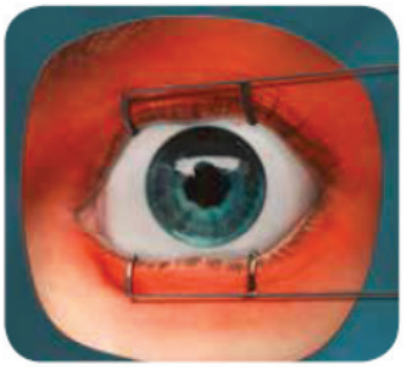
For use of topical antibiotics please refer to local or national clinical guidelines.

1. Administer topical anaesthesia.

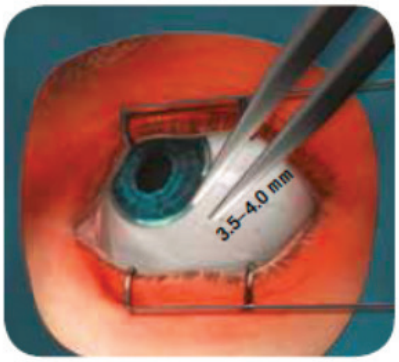
2. Instill disinfectant (eg, 5% povidone iodine solution or equivalent) applied to eyelids, eyelid margins and into the conjunctival sac.



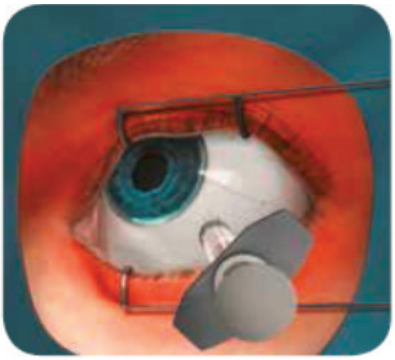
3. A disinfectant (eg, 10% povidone iodine solution or equivalent) may also be applied to the periocular skin, eyelids, and eyelashes, avoiding extensive pressure to eye glands.



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 area3.5 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 theglobe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.

Other sources of information include:

- Intravitreal guidelines and techniques ONE® Network. The ophthalmic news and education network. American Acaedmy of Ophthalmology. http://one.aao.org/focalpointssnippetdetail.aspx?id=f759cd36-2047-4608-a78c-9bbd42fa7cac. Last accessed 14 July 2016.
- Guidelines for Intravitreal Injections Procedure 2009. The Royal College of Ophthalmologists. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2015/01/2009-SCI-012_Guidelines_for_Intravitreal_Injections_Procedure_1.pdf. Last accessed 14 July 2016.
- Age-Related Macular Degeneration: Guidelines for Management, September 2013. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf. Last accessed 14 July 2016.
- Jaissle GB et al. Recommendation for the implementation of intravitreal injections--statement of the German Retina Society, the German Society of Ophthalmology (DOG) and the German Professional Association of Ophthalmologists (BVA). KlinMonblAugenheilkd. 2005 May;222(5):390-5. Article in German.
- SociétéFançaised'Ophtalmologie. Guidelines for intravitreal injections. KorobelnikJF et al. Recommendations - Guidelines for intravitreal injections. Journal françaisd'ophtalmologie (2009) 32, e1—e2.
- Intravitreal Injection Procedure Video

AFTER THE 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 eyedrops after intravitreal injections should be according to local or national clinical guidelines.

ADVERSE DRUG REACTIONS

See section 4.8 of the Summary of Product Characteristics for full list of undesirable effects

- 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.

- Transient increased intraocular pressure

Patients may experience halos around lights, red eye, nausea and vomiting, and vision changes.

- 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.

- Tear or detachment of the retinal pigment epithelium

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.

Management of injection related adverse events:

In any case of an adverse event that concerns your patient, your patient must have 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 section 4.8 of the Summary of Product Characteristics for how to report adverse events.

APPROPRIATE LOCAL SAFETY INFORMATION

Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from: www.medicinesauthority.gov.mt/adrportal

and sent to:

E: postlicensing.medicinesauthority@gov.mt

Or

E: pv@alfredgera.com

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

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www.pharma.bayer.com

Date of Preparation July 2016
MT.PH.SM.Eylea.2016.0001