Recommendations for treatment with

Prescriber Guide

This Guide provides you important information on EYLEA® 40 mg/ml solution for injection (2 mg aflibercept dose) and EYLEA® 114.3 mg/ml solution for injection (8 mg aflibercept dose), the medication itself and how to correctly administer it to your patients.

Please provide your patients with the link to the EYLEA® patient guide https://www.edumaterial.bayer.com.mt including its audio version (read out of the patient guide) and the Patient Information Leaflet.

Prescriber guide approved by Malta Medicines Authority in April 2024

INTRAVITREAL INJECTION PROCEDURE VIDEO

EYLEA 40 MG/ML SOLUTION FOR INJECTION (2 MG DOSE)
(PRE-FILLED SYRINGE)

AND

EYLEA 114.3 MG/ML SOLUTION FOR INJECTION (8 MG DOSE)
(VIAL)

PLEASE SCAN:

Note: The video for Retinopathy of Prematurity (ROP)
starts at approximately 11.26 minutes.)

OR VISIT:

https://www.edumaterial.bayer.com.mt/mt-eylea-pg

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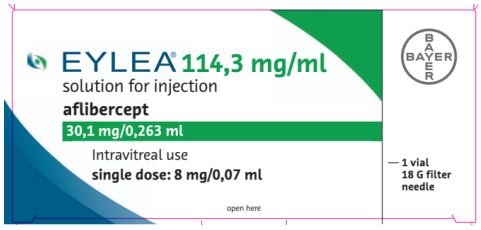
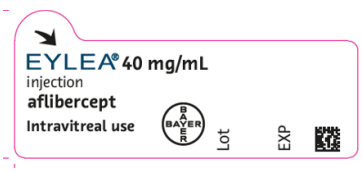
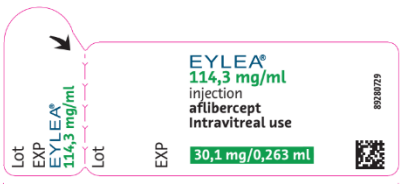
KEY SUMMARY FOR EYLEA

DIFFERENCES BETWEEN EYLEA 40 MG/ML SOLUTION FOR INJECTION (2 MG DOSE) AND EYLEA 114.3 MG/ML SOLUTION FOR INJECTION (8 MG DOSE)

	EYLEA 40 MG/ML	EYLEA 114.3 MG/ML
APPROVED INDICATIONS IN ADULTS*	wAMD, DME, BRVO, CRVO, mCNV	wAMD, DME
DOSE PER INJECTION	2 MG	8 MG
INJECTION VOLUME	0.05 ML	0.07 ML
PRESENTATION	PRE-FILLED SYRINGE AND VIAL	VIAL
PACKAGING		
VIAL		
LABEL ON VIAL		

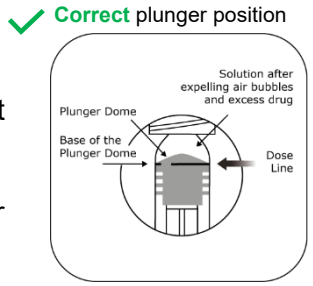
*For the use of Eylea 40 mg/ml in the treatment of Retinopathy of Prematurity, please refer to the Prescriber Guide for Retinopathy of Prematurity Indication section of this document.

Contraindications

- Hypersensitivity to aflibercept or to any of the excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC)
- Active or suspected ocular or periocular infection
- Active severe intraocular inflammation

Key instructions for use

- The vials and the 40 mg /ml (2 mg dose) EYLEA solution for injection pre-filled syringe contain more than the recommended dose of EYLEA**. Do not inject the entire volume.**
- Ensure proper aseptic technique including broad-spectrum microbicide to minimise the risk of intraocular infection
- For the intravitreal injection, a **30 G x ½ inch injection needle** should be used



- **Pre-filled syringe:** EYLEA 40 mg/ml solution for injection (2 mg dose)
  - Expel excess volume and air bubbles from the pre-filled syringe and adjust the base of the plunger dome **(NOT the tip)** to the dose line before injection
  - Push the plunger slowly and with constant pressure, and do not administer any residual volume remaining in the syringe after injection

Selected instructions for storage and handling

- **Store EYLEA in the refrigerator** (2°C to 8°C)
- EYLEA is **not licensed for multi-dose**, further compounding or vial splitting. Use of more than one injection from the vial or the pre-filled syringe **can lead to contamination and subsequent infection**

Special warnings and precautions for use

In all cases, instruct patients to immediately report signs and symptoms of adverse events

Adverse event/risk	Measures to minimize risk
Intraocular inflammation including endophthalmitis	Use proper aseptic technique when preparing the injection and during the injection itself Use recommended antiseptic agents Monitor patient after the injection
Transient IOP* increase	Properly prime the syringe by removing excess volume and air bubbles from the syringe before administration Monitor patient's vision and IOP after the injection
Medication error	Properly prime the syringe by removing excess volume and air bubbles from the syringe before administration Monitor patient's vision and IOP after the injection
Retinal pigment epithelial tear	Monitor patient after the injection
Cataract	Measure for correct site of injection, use correct injection technique
Off-label use/misuse	Use medication only for treatment of approved indications and use approved dose
Embryo-fetotoxicity	Instruct patient to use effective contraception during treatment: For at least 3 months after last intravitreal injection of EYLEA 40 mg/ml (2 mg dose) For at least 4 months after last intravitreal injection of EYLEA114.3 mg/ml (8 mg dose) EYLEA 40 mg/ml (2 mg dose) and EYLEA 114.3 mg/ml (8 mg dose) should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.
Exposure during breastfeeding	Eylea is not recommended in patients who are breastfeeding

*Intraocular pressure increase

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**
- Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay

GENERAL INFORMATION

You must explain to the patient the implications of anti-VEGF treatment. The patient guide is a tool that will help you to communicate to your patient about the disease and treatment. This guide is available upon request to Bayer and you should distribute it to your patients. It is available as a booklet and as an audio guide option for your patients. It contains information on the signs and symptoms of adverse reactions and when they should seek immediate medical attention.

The Summary of Product Characteristics, or SmPC, describes the properties of EYLEA and the approved indications for use. It is an important source of information for healthcare professionals on how to use EYLEA safely and effectively. It is located at https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf. Refer to the approved SmPC for EYLEA for complete information on posology and dosing recommendations for EYLEA 40 mg/ml solution for injection (2 mg dose) and Eylea 114.3 mg/ml solution for injection (8 mg dose).

ABOUT EYLEA

EYLEA is for intravitreal injection only. It must only be administered by a qualified physician experienced in administering intravitreal injections and familiar with the handling of the vial/pre-filled syringe

	EYLEA 40 mg/ml	**EYLEA 114.3 mg/ml**
Presentation	Pre-filled syringe and vial	Vial
Approved indications in adult (18 years and older) patients		
Neovascular (wet) AMD	Yes	Yes
Visual impairment due to diabetic macular oedema (DME)	Yes	Yes
Visual impairment due to macular oedema secondary to retinal vein occlusion (RVO), branch (BRVO) or central (CRVO)	Yes	No
Visual impairment due to myopic choroidal neovascularisation (mCNV)	Yes	No
Recommended dose	2 mg	8 mg
Volume to inject	50 microliters or 0.05 ml	70 microliters or 0.07 ml
Posology for approved indications	The posology recommendations for wAMD, RVO, DME and mCNV are different to each other Refer to the SmPC for complete information on posology and dosing for EYLEA 40 mg/ml and for EYLEA 114.3 mg/ml	

IMPORTANT SAFETY INFORMATION ABOUT EYLEA

Contraindications
EYLEA is contraindicated in the following:

- Hypersensitivity to aflibercept or to any of the excipients listed in section 6.1 of 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.

- **Always use proper aseptic injection techniques** when administering EYLEA
- **Monitor patients following injections as per local practice** to permit early treatment if an infection occurs
- **Instruct patients to immediately report any signs and symptoms** suggestive of endophthalmitis or any of the adverse reactions mentioned above

The pre-filled syringe and the vial contain more than the recommended dose of 2 mg or 8 mg aflibercept (equivalent to 0.05 ml/0.07 ml). Expel the excess volume and air bubbles from the syringe prior to injection.

- Administer the recommended dose and do not inject any residual volume, as increased injection volume can lead to clinically relevant intraocular pressure elevation

Increase in intraocular pressure
Transient increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including injections with EYLEA.

- **Monitor your patient after the injection procedure** and take special precaution in patients with poorly controlled glaucoma (do not inject EYLEA while the intraocular pressure is ≥30 mm Hg)
- Refer to the post-injection care section for further instructions

Immunogenicity
EYLEA is a therapeutic protein and has potential for immunogenicity.

- **Instruct patients to report any signs or symptoms of intraocular inflammation** (e.g. pain, photophobia or redness), which may be attributable to hypersensitivity
- Refer to the post-injection care section for further instructions

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.

- Exercise caution when treating patients with CRVO, BRVO, DME or mCNV, and wAMD with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 6 months as there are limited data on safety of EYLEA in these groups

Special populations

The following recommendations are made:

- **Women of childbearing potential**
  Use effective contraception during treatment and **for at least 3 months** after the last intravitreal injection of EYLEA 40 mg/ml (2 mg dose).
  Use effective contraception during treatment and for at least 4 months after the last intravitreal injection of EYLEA 114.3 mg/ml (8 mg dose).

- **Pregnancy**
  EYLEA 2 mg and EYLEA 8 mg should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

- **Breast-feeding**
  Based on very limited human data, aflibercept may be excreted in human milk at low levels. Aflibercept is a large protein molecule and the amount of medication absorbed by the infant is expected to be minimal. The effects of aflibercept on a breast-fed newborn/infant is unknown. As a precautionary measure, breast-feeding is not recommended during the use of Eylea.

Post-injection care
Immediately after intravitreal injection:

- Evaluate the patient's vision (hand movement or finger counting)

- Monitor the patient for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or conducting a tonometry test. Sterile equipment for paracentesis should be readily available if anterior chamber paracentesis needs to be done.

- Instruct the patient to report any signs and symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

- Instruct the patient to report any signs or symptoms after the injection that get worse over time.

Adverse Drug Reactions

Adverse drug reactions are the same for EYLEA 40 mg/ml (2 mg dose) and EYLEA 114.3 mg/ml (8 mg dose).

Key signs and symptoms of adverse reactions include:

Transient increased intraocular pressure	Patients may experience vision changes such as temporary vision loss, eye pain, halos around lights, red eye, nausea and vomiting
Tear of the retinal pigment epithelium	Patients may experience acute decrease in (central) vision, blind spot (central scotoma), and distorted vision with deviation of either vertical or horizontal lines (metamorphopsia)
Tear or detachment of the retina	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
Intraocular inflammation including 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
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

See section 4.8 of the SmPC for full list of potential adverse reactions.

Management of adverse reactions

In case of any adverse reactions that concern your patient, your patient must have immediate access to an ophthalmologist.

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

Healthcare Professionals are asked to report any suspected adverse reactions.
See section 4.8 of the SmPC for how to report suspected adverse reactions.

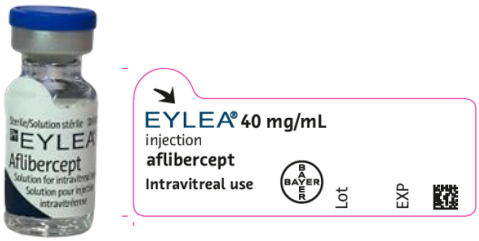
STORAGE AND HANDLING OF EYLEA

The solution is clear and colourless to pale yellow. It is an iso-osmotic solution.
Inspect the solution visually before use for any foreign particulate matter and/or unusual colour (the solution can be pale yellow, which is normal**) or any variation in physical appearance. If any of these are observed, discard the product.**

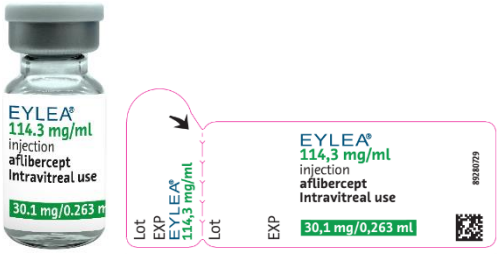
The EYLEA 40 mg/ml (2 mg dose) vial looks different to the EYLEA 114.3 mg/ml (8 mg dose) vial to allow for easy identification. Please take this into consideration when selecting the product to be injected to the patient (please see pictures below).

Do not split a vial/pre-filled syringe into more than one dose. Each vial/pre-filled syringe is for single eye use only. Extraction of multiple doses from a single vial/pre-filled syringe may increase the risk of contamination and subsequent infection in the patient.

Each EYLEA 40 mg/ml solution for injection in a pre-filled syringe (2 mg dose) contains **more than the recommended 0.05 ml dose of aflibercept. The excess volume and any air bubbles in the syringe must be expelled before injecting the patient with the recommended dose.**



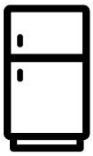
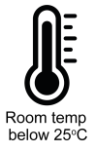
Each EYLEA 40 mg/ml solution for injection in a vial (2 mg dose) **contains more than the recommended 0.05 ml dose of aflibercept. The excess volume and any air bubbles in the disposable syringe must be discarded before injecting the patient with the recommended dose.**



Each EYLEA 114.3 mg/ml solution for injection in a vial (8 mg dose) **contains more than the recommended 0.07 ml dose of EYLEA. The excess volume and any air bubbles in the disposable syringe must be discarded before injecting the patient with the recommended dose.**

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

Special precautions for storage

	Store in a refrigerator (2–8°C).
	Do not freeze.
	Keep the pre-filled syringe in its blister and in the outer carton in order to protect it from light. Keep the vial in the outer carton in order to protect it from light.
	Prior to use EYLEA 40 mg/ml (2 mg dose), the unopened vial or blister of EYLEA may be kept at room temperature (below 25°C) for up to 24 hours.

The inside of the sealed EYLEA 40 mg/ml (2 mg dose) solution for injection in a pre-filled syringe blister packaging is sterile. Do not open the pre-filled syringe blister outside the clean administration room.

After opening the blister or vial, proceed under aseptic conditions.

INSTRUCTIONS FOR USE OF EYLEA

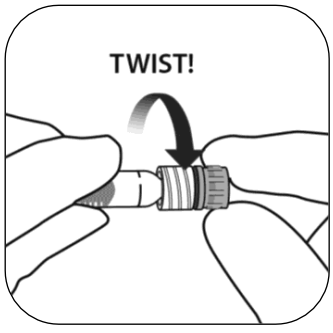
General preparation for injection

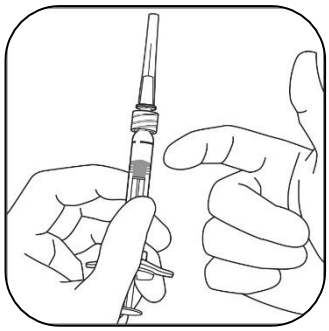
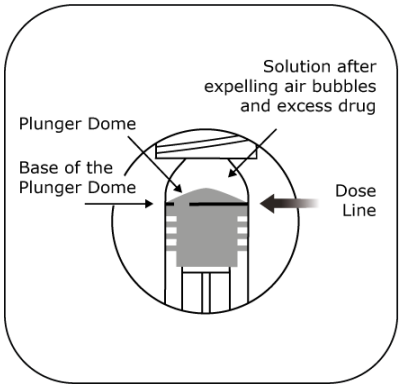
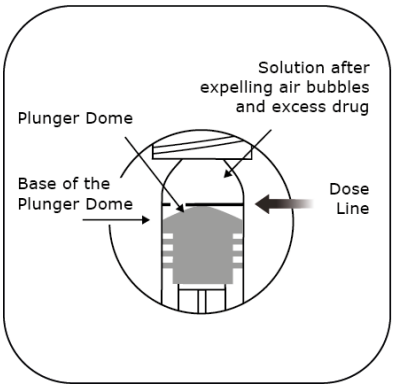
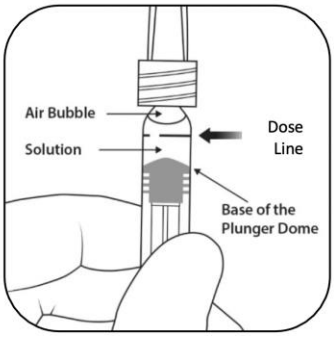
- Intravitreal injections must be carried out according to medical standards and applicable guidelines by **a qualified physician experienced in administering intravitreal injections and familiar with the handling** of the vial/pre-filled syringe
- Surgical hand disinfection, aseptic gloves, a sterile 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 40 mg/ml (2 mg dose), solution for injection

Note: the EYLEA pre-filled syringe is a glass syringe with a rubber plunger that requires slightly more force to depress compared with plastic syringes (such as those used with the vial presentation). **Become familiarised with this syringe before using it on patients.**

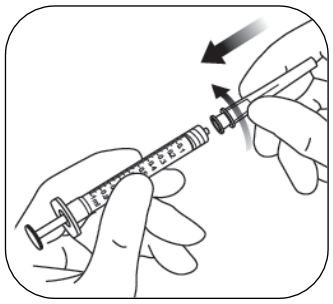
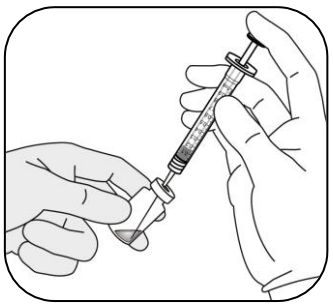
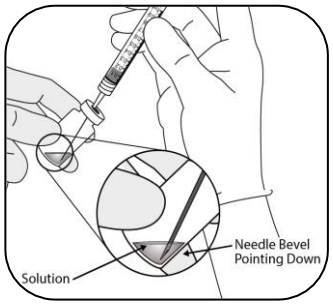
The pre-filled syringe and contents must be inspected before using. Do not use the pre-filled syringe if any part is damaged or loose. Do not use it if the syringe cap is detached from the Luer Lock. Look for any particulate matter and/or unusual colour or any variation in physical appearance. If any of these are observed, discard the product.

1	<u>Prepare the pre-filled syringe for administration</u> It is important to prepare the pre-filled syringe using aseptic technique. An assistant should carry out the following steps: Remove the carton containing the pre-filled syringe from the refrigerator. Open the carton and remove the blister containing the syringe. The blister must not be placed on an aseptic surface because the outside surface of the blister is not sterile. The inside of the sealed blister and the pre-filled syringe are sterile. Carefully peel open the blister. **Aseptic technique must be used once the blister is opened.** The qualified physician carries out the remainder of the steps with sterile technique including the use of aseptic gloves (white gloves in pictures) when handling: with two fingers, remove the pre-filled syringe from the blister, visually inspect the syringe and place the syringe in an aseptic tray until ready for assembly.
2	<u>Remove the syringe cap</u> Hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger. **Twist off – do not snap off – the syringe cap.** 
3	**Do not pull back the plunger.** This may compromise the sterility of the product.

4	<u>Attach the needle</u> Using aseptic technique, **firmly twist the 30 G x ½ inch injection needle onto the Luer-lock syringe tip.**	
5	<u>Check for bubbles</u> Holding the syringe with the needle pointing upwards, **check the solution for bubbles. If bubbles are present, gently tap the syringe with your finger until the bubbles rise to the top.**	
6	<u>Eliminate air bubbles and excess drug</u> **Correct handling of the prefilled syringe is important in order to avoid the risk of medication errors. This includes removal of the excess volume and air bubbles, in order to avoid overdosing.** Remove the air bubbles and excess drug from the syringe by slowly depressing the plunger rod to align the base of the plunger dome (not the tip of the dome) with the dose line on the syringe. Remember that the feel with this syringe is different from disposable syringes. The remaining volume after aligning to the dose line ensures an injection volume of 0.05 ml. **Accurate positioning of the plunger is critical. Incorrect plunger positioning can lead to delivering more or less than the labelled dose.** ✓ **Correct** plunger position  ✗ **Incorrect** plunger position  	

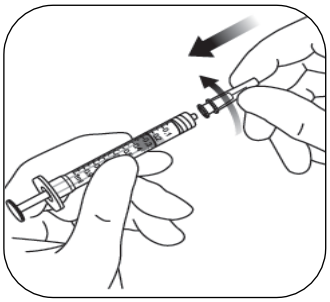
7	Inject EYLEA **Inject the solution into the eye carefully with constant pressure on the plunger. Do not apply additional pressure once the plunger has reached the bottom of the syringe.** **Do not administer any residual solution observed in the syringe**.
8	**Dispose of any unused medicinal product or waste material in accordance with local regulations.**

Vial 40 mg/ml (2mg dose) and 114.3 mg/ml (8mg dose) solution for injection

1	<u>Inspect the vial, and remove the vial cap</u> It is important to prepare the syringe with EYLEA from the vial, using aseptic technique. Note in the pictures that darker/grey gloves are not aseptic and white gloves are aseptic. An assistant should carry out the following steps (assistant is shown with darker/grey gloves in the images): Remove the carton containing the vial from the refrigerator. Open the carton and remove the vial. **Check the carton, the vial and label to ensure the correct EYLEA solution is chosen.** The vial should not be placed on an aseptic surface because the outside surface of the vial is not sterile. The inside of the vial is sterile. Visually inspect the vial and contents. Remove the plastic cap and disinfect the outer part of the rubber vial stopper.	
2	<u>Attach the filter needle</u> The qualified physician should carry out the remaining steps using aseptic technique, including the use of aseptic gloves: Using aseptic technique, screw on the 18 G, 5-micron filter needle supplied in the carton to a 1 ml sterile Luer-lock syringe.	
3	<u>Insert needle into vial</u> Insert the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the needle tip touches the bottom or bottom edge of the vial.	
4	<u>Draw up the solution</u> 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 in the liquid. Continue to tilt the vial during withdrawal, keeping the bevel of the filter needle submerged in the liquid. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.	
5	<u>Remove the filter needle</u> Unscrew and properly dispose the filter needle. **Do not use the filter needle for intravitreal injection.**	

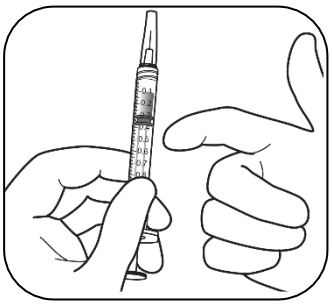
6 Attach the injection needle

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



7 Check for air bubbles

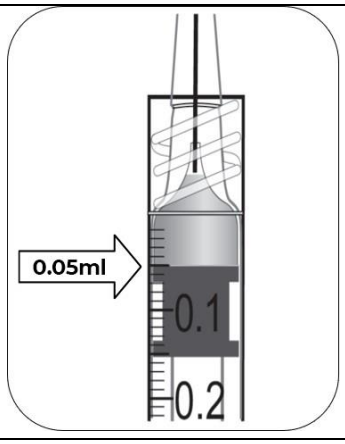
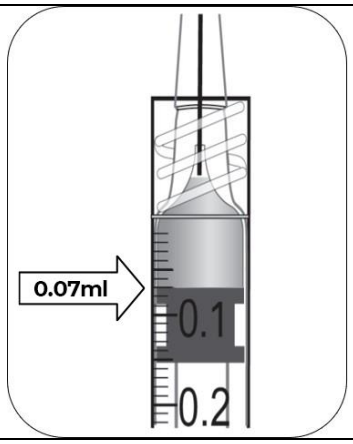
Holding the syringe with the needle pointing upwards, visually inspect the contents of the syringe. **Check the solution for bubbles. If bubbles are present, gently tap the syringe with your finger until the bubbles rise to the top.**

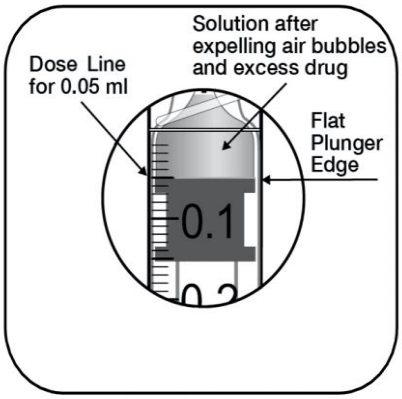
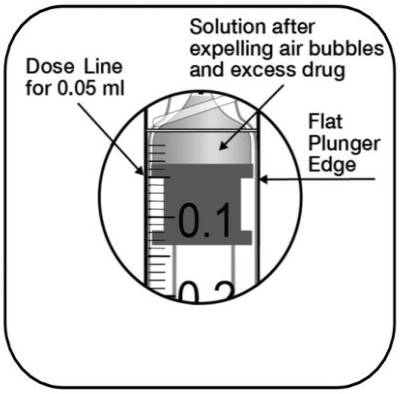


8 Eliminate air bubbles and excess drug

Correct handling of the filled syringe is important in order to avoid the risk of medication errors. This includes removal of the excess volume and air bubbles, in order to avoid overdosing.

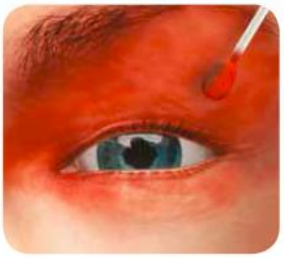
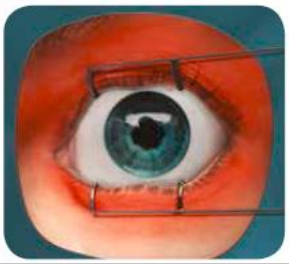
Attention! The EYLEA 2 mg dose uses 0.05 ml volume of EYLEA 40 mg/ml solution. The EYLEA 8 mg dose uses 0.07 ml volume of EYLEA 114.3 mg/ml solution.

EYLEA 2 mg dose	EYLEA 8 mg dose
Use 0.05 ml volume of EYLEA 40 mg/ml solution	Use 0.07 ml of EYLEA 114.3 mg/ml solution
Eliminate all air bubbles and expel excess drug by slowly depressing the plunger rod to align the flat plunger edge with the **0.05 ml line on the syringe for the 40 mg/ml mg vial.**	Eliminate all air bubbles and expel excess drug by slowly depressing the plunger rod to align the flat plunger edge with the **0.07 ml line on the syringe for the 114.3 mg/ml mg vial.**
	

	Accurate positioning of the plunger is critical. Incorrect plunger positioning can lead to delivering more or less than the recommended dose, refer to the example below for 0.05 ml volume and the same applies for 0.07 ml volume. ✓ **Correct** plunger position for 0.05 ml volume  ✗ **Incorrect** plunger position for 0.05 ml volume 
9	**Dispose of any unused medicinal product or waste material in accordance with local regulations.**

Injection procedure

For further information on intravitreal injection procedure, sterile techniques (including periocular and ocular disinfection) and anaesthesia, please refer to local and/or national clinical guidelines.

1	Administer topical anaesthesia.	
2	Apply disinfectant (e.g. 5% povidone iodine solution or equivalent) to the eyelids, eyelid margins and into the conjunctival sac. The disinfectant should be on the surface for the length of time recommended in local practice guidelines Eye dilation prior to the injection procedure is **not** necessary.	
3	A disinfectant (e.g. 10% povidone iodine solution or equivalent) should also be applied to the periocular skin, eyelids and eyelashes, avoiding extensive pressure to the periocular glands. The disinfectant should be on the surface for the length of time recommended in local practice guidelines	
4	Cover with sterile drape and insert sterile lid speculum. A second application of disinfectant, e.g., 5% povidone iodine solution, may be made to the conjunctival sac. Disinfectant should be on the surface for the length of time recommended in local practice guidelines	
5	Tell patient to look away from the injection site. Position the eye adequately. At an area of 3.5–4.0 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. Inject the recommended dose, with careful and constant pressure on the plunger. Do not apply additional pressure once the plunger has reached the bottom of the syringe. Do not inject any residual volume remaining in the syringe after the injection. Use a different scleral site for subsequent injections.	

OTHER SOURCES OF INFORMATION

https://www.edumaterial.bayer.com.mt

Local Safety Information

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt

Or

E: pv@alfredgera.com

For more information about EYLEA, visit https://ophthalmology.bayer.com

Recommendations for treatment with

EYLEA®
(aflibercept solution for injection)

Prescriber Guide for the Retinopathy of Prematurity Indication*

This Guide provides you with important information on EYLEA, the medication itself and how to correctly administer it to your patients.

Please provide the EYLEA parent/caregiver guide and the Patient Information Leaflet to the patient's parent/caregiver.

In this document, patient = preterm infant = premature baby.

*This indication is not approved in all regions, please refer to the local product information before prescribing.

KEY SUMMARY FOR EYLEA USE IN THE TREATMENT OF RETINOPATHY OF PREMATURITY

Indication in preterm infants

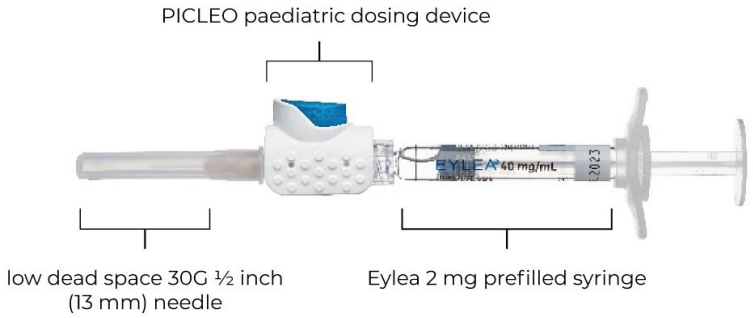
- Retinopathy of Prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.

Contraindications

- Hypersensitivity to aflibercept or to any of the excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC)
- Active or suspected ocular or periocular infection
- Active severe intraocular inflammation

Key instructions for use

- **The EYLEA 2 mg pre-filled syringe is used for the treatment of preterm infants with ROP, and it must be used in combination with the PICLEO® paediatric dosing device and a low dead space 30G ½ inch (13 mm) injection needle to ensure administration of the recommended dose.**



- Ensure that the procedure is carried out in a sterile environment and that proper aseptic technique is followed, including use of a broad-spectrum microbicide to minimise risk of intraocular infection. Ensure that the injection needle is inserted into the patient's eye such that damage to the lens and the retina is avoided. Refer to the instructions for use section in this guide.
- The EYLEA 2 mg pre-filled syringe is for single use in one eye only.
- The PICLEO paediatric dosing device is for single use in one eye only.
- For the intravitreal injection, **a low dead space 30G injection needle, ½ inch (13 mm) in length** must be used. A low dead space needle has a reduced excessive space in the needle hub. **The EYLEA 2 mg pre-filled syringe contains more than the recommended dose of 0.4 mg (equivalent to 0.01 mL dose of EYLEA). Do not inject the entire volume contained in the syringe.**
- **Carefully read the Instructions for Use included in the package of the PICLEO paediatric dosing device, including the Important Information section. Also read the sections in this prescriber guide for instructions on proper storage, handling and use.**

Selected instructions for storage and handling for EYLEA

- **Store EYLEA in the refrigerator (**2°C to 8°C); it may be kept at room temperature (below 25°C) in the unopened blister in the carton for up to 24 hours.
- EYLEA is **not licensed for multi-dose**, further compounding or splitting. Use of more than one injection from the pre-filled syringe **can lead to contamination and subsequent infection.**

Special warnings and precautions for use

In all cases, observe your patients immediately for any signs and symptoms of adverse reactions, and instruct the parent/caregiver to also be watchful for the signs and report without delay.

Adverse reaction/risk	Measures to minimise risk
Intraocular inflammation including endophthalmitis	Use proper aseptic technique when preparing the injection and during the injection itself. Use recommended antiseptic agents such as antibiotic ointment and/or drops. Monitor patients frequently post-injection and instruct the parent/caregiver to also monitor.
Transient IOP increase	The EYLEA 2 mg pre-filled syringe must be used in combination with the PICLEO paediatric dosing device, for the treatment of ROP in pre-term infants. Monitor IOP and optic nerve perfusion immediately after the injection.
Medication error	The EYLEA 2 mg pre-filled syringe must be used in combination with the PICLEO paediatric dosing device, for the treatment of ROP in pre-term infants. Air bubbles must be removed before use from the PICLEO paediatric dosing device + EYLEA 2 mg pre-filled syringe + low dead space 30G ½ inch (13 mm) injection needle assembly to avoid the possibility of underdosing.
Cataract	Measure for correct site of injection, use correct injection technique.
Off-label use/misuse	Use EYLEA 2 mg pre-filled syringe only in combination with the PICLEO paediatric dosing device and a low dead space injection needle for treatment of retinopathy of prematurity. Use medication only for treatment of retinopathy of prematurity and use approved dose (0.4 mg, equivalent to 0.01 mL).

After the injection

- **Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure**
- In the days following the intravitreal injection, patients should be observed for any symptoms suggestive of endophthalmitis (e.g., redness/irritation of the eye, ocular discharge, lid swelling, photophobia)

Parents and caregivers should also be instructed to observe and to report any signs suggestive of endophthalmitis without delay.

GENERAL INFORMATION

You must explain to the parent/caregiver of your patient the implications of anti-VEGF treatment. The parent/caregiver guide is a tool that will help you to communicate to the parents/caregivers of your patient about the disease and treatment. This guide is a booklet and is available from Bayer upon request. You should distribute it to the parents/caregivers of your patients. It contains information on the signs and symptoms of adverse reactions and when the parent/caregiver of the patient should seek immediate medical attention for the patient.

ABOUT EYLEA

- EYLEA is a 40 mg/mL solution of aflibercept for intravitreal injection, in a pre-filled syringe
- **EYLEA is for intravitreal injection only.** It must only be administered by a qualified physician experienced in administering intravitreal injections and familiar with the handling of the EYLEA 2 mg pre-filled syringe and with the PICLEO paediatric dosing device.
- Other than for the treatment of ROP in preterm infants, EYLEA is also approved for use in adults for the treatment of specific adult retinal diseases. For more information, please consult the EYLEA Prescriber Guide for use in adults. Please also refer to the approved Summary of Product Characteristics (SmPC) for EYLEA prefilled syringe for complete information.
- The SmPC is a document that describes the properties of EYLEA and the approved conditions of use. It is an important source of information for healthcare professionals on how to use EYLEA safely and effectively. It is located at https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf.

EYLEA is indicated in preterm infants for the treatment of:

- Retinopathy of Prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.

Dosing recommendations for retinopathy of prematurity:

- The recommended dose for EYLEA for the treatment of ROP is 0.4 mg aflibercept, equivalent to 0.01 mL. **Note that the recommended dose for the treatment of ROP patients is lower than the dose used to treat adult patients for other approved EYLEA indications.** For this reason the PICLEO paediatric dosing device must be used with the EYLEA prefilled syringe and a low dead space needle to ensure administration of the correct dose to the patient. A low dead space needle has a reduced excessive space in the needle hub.

IMPORTANT SAFETY INFORMATION ABOUT EYLEA

The safety of EYLEA for the treatment of ROP was evaluated in a 6-month phase III study, which included 75 pre-term infants treated with aflibercept 0.4 mg at baseline. The long-term safety profile in pre-term infants has not been established.

Contraindications
EYLEA is contraindicated in the following:

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

Special warnings and precautions for use

Increase in intraocular pressure

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including injections with EYLEA.

- **Immediately following the intravitreal injection, monitor your patient for elevation in intraocular pressure and have sterile equipment available in case a paracentesis is required**

Refer to the post-injection care section for further instruction

Further 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.

- **Always use proper aseptic injection techniques** when administering EYLEA
- **Monitor patients during the week following injection** to permit early treatment if an infection occurs
- **Closely observe your patients for any signs and symptoms** suggestive of endophthalmitis or any of the adverse reactions mentioned below. Instruct the parent/caregiver to also closely observe the patient for the signs and symptoms noted below, and to report without delay
- **The pre-filled syringe contains more than the recommended dose of 0.4 mg aflibercept (equivalent to 0.01 mL). For the treatment of ROP in pre-term infants, the pre-filled syringe must be used in combination with the PICLEO paediatric dosing device and a low dead space needle to avoid administration of a higher than recommended volume that could result in increased intraocular pressure**
- Carefully read the instructions for use (IFU) included in the package of the PICLEO paediatric dosing device

Intraocular inflammation/Endophthalmitis

- **Observe your patients for any signs or symptoms of intraocular inflammation** (e.g., redness/irritation of the eye, ocular discharge, lid swelling, photophobia) that may be attributable to infection. Instruct the parent/caregiver to also observe the patient for these signs and symptoms and to report without delay
- Refer to the post-injection care section for further instructions

Immunogenicity

EYLEA is a therapeutic protein and has potential for immunogenicity.

- **Observe your patients for any signs or symptoms of intraocular inflammation** (e.g., redness/irritation of the eye, ocular discharge, lid swelling) that may be attributable to hypersensitivity. Instruct the parent/caregiver to also observe the patient for these signs and symptoms and to report without delay.
- Refer to the post-injection care section for further instructions

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.

Post-injection care
Immediately after intravitreal injection:

- Immediately monitor the patient for elevation in intraocular pressure. Appropriate monitoring may consist of fundus examination including a check for perfusion of the central retinal artery, or conducting a tonometry test. Sterile equipment for paracentesis should be readily available if anterior chamber paracentesis needs to be done.

After intravitreal injection:

- Observe your patient for any signs and symptoms suggestive of endophthalmitis (e.g., redness of the eye, photophobia, irritation of the eye, ocular discharge, lid swelling) without delay.

- Observe your patient for any signs or symptoms after the injection that get worse over time and instruct the parent/caregiver to do the same, and to report any observed signs and symptoms without delay.

Adverse Drug Reactions

Adverse reactions reported in more than one patient treated with aflibercept 0.4 mg were retinal detachment, conjunctival haemorrhage, injection site haemorrhage, intraocular pressure increased, eyelid oedema and retinal haemorrhage. Additionally, adverse reactions established for adult indications are considered applicable to preterm infants with ROP, though not all were observed in the phase III paediatric study.

Key signs and symptoms of intravitreal injection-related adverse reactions include:

Transient increased intraocular pressure	Pre-term infant may experience cloudy anterior segment of eyeball (corneal oedema), rock-hard eyeball, red eye, paroxysmal crying, nausea and vomiting.
Tear or detachment of the retina	Pre-term infant may experience white pupil (leukocoria), newly observed crossed eyes (strabismus) and vision changes.
Intraocular inflammation including endophthalmitis	Pre-term infant may experience eye pain or increased discomfort, worsening eye redness, sensitivity to light (photophobia), lid swelling, paroxysmal crying and ocular discharge.
Cataract (traumatic)	Pre-term infant may experience white pupil, loss of red reflex, and vision changes.

See section 4.8 of the SmPC for a complete list of potential adverse reactions.

Management of intravitreal injection-related adverse events

In case of any adverse events, 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.

Healthcare Professionals are asked to report any suspected adverse reactions.
See section 4.8 of the SmPC for how to report suspected adverse reactions.

STORAGE AND HANDLING OF EYLEA

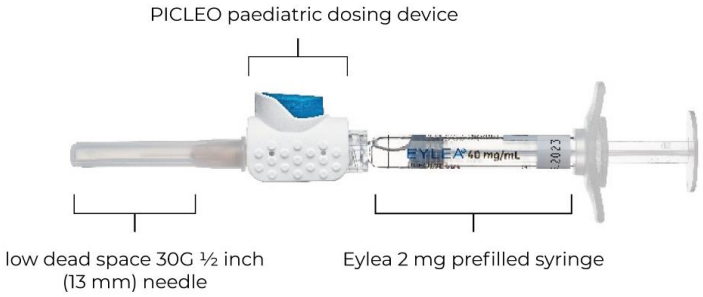
The EYLEA solution is isosmotic, and it is clear and colourless to pale yellow.

Inspect the solution visually before use, for any foreign particulate matter and/or unusual colour (the solution can be pale yellow, which is normal) or any variation in physical appearance. If any of these are observed, discard the product.

Inspect the syringe. If any part is damaged or loose, or if the syringe cap is detached from the Luer Lock, do not use.

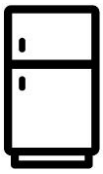
Do not split a pre-filled syringe into more than one dose. Each pre-filled syringe is for single use in one eye only. Extraction of multiple doses from a single pre-filled syringe may increase the risk of contamination and subsequent infection in the patient.

Each pre-filled syringe contains more than the recommended dose of 0.4 mg EYLEA (equivalent to 0.01 mL)



To ensure the administration of the recommended dose, the prefilled syringe must be used with the PICLEO paediatric dosing device and a low dead space 30G ½ inch (13 mm) needle. Please refer to the section "Important information about the PICLEO paediatric dosing device" in this guide

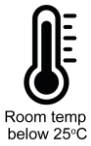
Special precautions for storage of the EYLEA pre-filled syringe



Store in the sealed blister in the outer carton in a refrigerator (2–8°C).

Do not freeze.

Keep the pre-filled syringe in its blister and in the outer carton in order to protect it from light.



Prior to use, the unopened blister of EYLEA in the outer carton may be kept at room temperature (below 25°C) for up to 24 hours.

The inside of the blister of the sealed pre-filled syringe packaging and the pre-filled syringe itself are sterile. Do not open the pre-filled syringe blister outside the clean administration room.

After opening the blister, proceed under aseptic conditions.

Storage and handling instructions for the PICLEO paediatric dosing device

Carefully read the instructions for use (IFU) included in the package of the PICLEO paediatric dosing device

Do not use the PICLEO device for more than one dose. The PICLEO paediatric dosing device is for single use in one eye only. Never re-use the device as it will malfunction, and contamination increases the risk to the patient of intraocular infection

It is recommended to store the PICLEO paediatric dosing device at room temperature.

Keep it within its original packaging. Keep it away from sunlight.

Do not open the sealed blister pack before time of use. Do not use beyond use-by date.

The inside of the blister of the sealed PICLEO paediatric dosing device packaging and the PICLEO paediatric dosing device itself are sterile. Do not open the PICLEO paediatric dosing device blister outside the clean administration room. After opening the blister, proceed under aseptic conditions.

INSTRUCTIONS FOR USE OF EYLEA FOR ROP

General preparation for injection

- Intravitreal injections in pre-term infants must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. **The physician must be trained to properly use the EYLEA 2 mg pre-filled syringe together with the PICLEO paediatric dosing device and low dead space injection needle. Training on assembly with the use of demonstration samples is required**
- **Ensure that you read the instructions for use provided with the PICLEO paediatric dosing device**

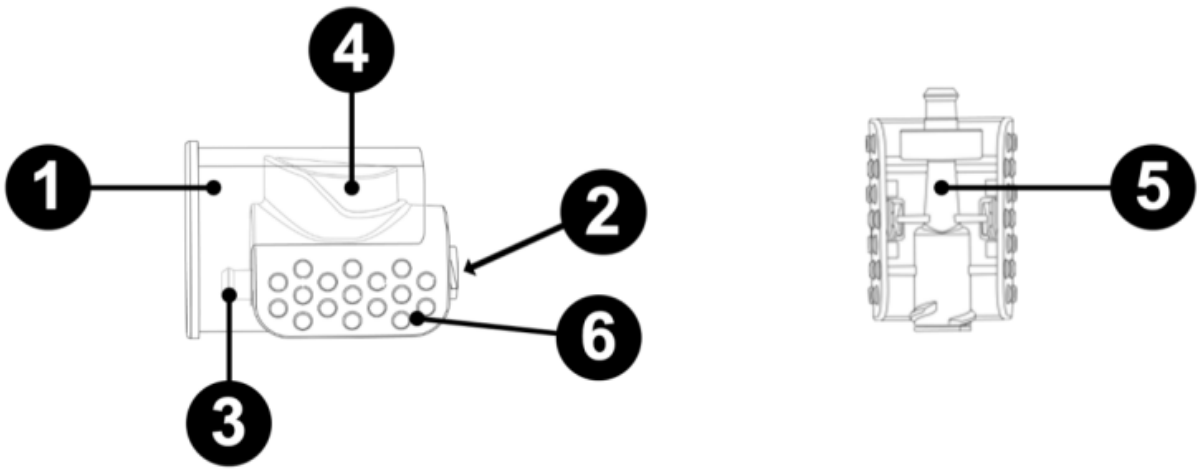
- Surgical hand disinfection, sterile gloves, a sterile drape and a sterilised eyelid speculum (or equivalent) are recommended
- For the intravitreal injection, a **30 G ½ inch (13 mm) low dead space injection needle** must be used. The following injection needles are recommended:
  TSK, 30G x ½" / 0.3 x 13 mm (Art. N. LDS-30013I-100)
  OcuJect - OcuSafe®, 30G x ½" / 0.3 x 13 mm (Art. N. PN0403-03)
  Any other combinations are not supported by the manufacturer of the device
- Check the expiration date of the EYLEA 2 mg pre-filled syringe and of the PICLEO paediatric dosing device. Do not use the pre-filled syringe or the paediatric dosing device if the packaging is damaged/open or if any parts of the products are broken or loose

Important information about the PICLEO paediatric dosing device

- Use the PICLEO paediatric dosing device only with the EYLEA 2 mg pre-filled syringe and a low dead space 30G ½ inch (13 mm) injection needle because it is designed for use only in combination with these two components. Use only a low dead space injection needle as use of other needles could lead to underdosing
- The PICLEO paediatric dosing device is provided sterile. Do not use if the packaging is damaged or has been tampered with
- Use aseptic technique when removing the PICLEO paediatric dosing device from its blister pack and for all subsequent steps to prevent contamination
- Assemble the syringe and injection needle firmly to the PICLEO paediatric dosing device to avoid leakage as well as accidental detachment
- Air bubbles must be removed from the syringe and device and the system must be primed. When using the PICLEO paediatric dosing device with the pre-filled syringe, it is not required to align the syringe plunger of the pre-filled syringe with the dosing line on the syringe when using the PICLEO paediatric dosing device
- Make sure not to touch the blue dose button of the PICLEO paediatric dosing device before the medicinal product administration. Should the dose button be inadvertently depressed during assembly, do not proceed and discard the device and the pre-filled syringe. Select a new PICLEO paediatric dosing device and follow assembly procedure steps using a new pre-filled syringe

- Medicinal product will remain in syringe and PICLEO paediatric dosing device after correct dose administration. Do not administer this residual solution but discard it

- The PICLEO paediatric dosing device is for single use in one eye only. Never re-use the device as it will malfunction, and contamination increases the risk of intraocular infection



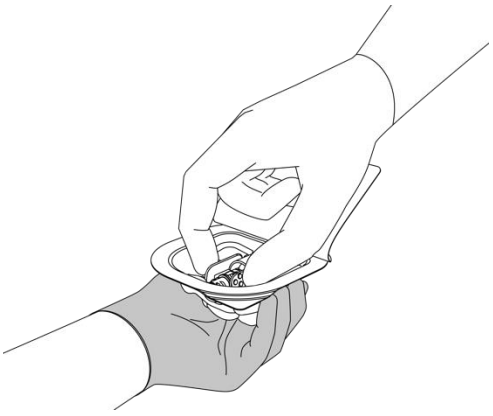
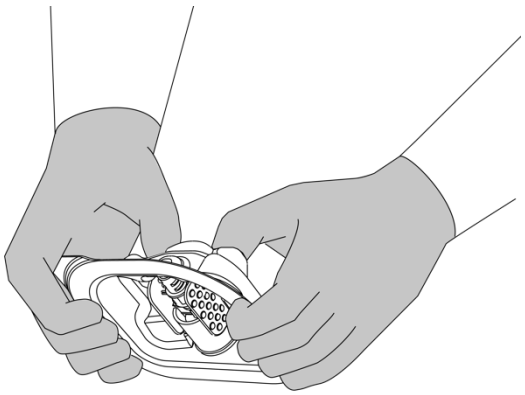
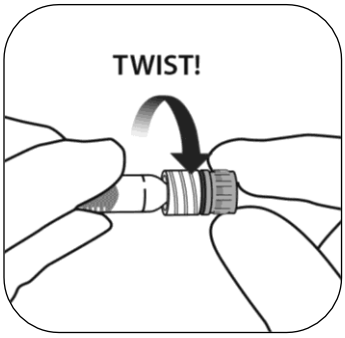
1. Cover
2. Connection for the syringe (female Luer Connector)
3. Connection for the needle (male Luer Connector)
4. Dose button
5. Viewing window
6. Grip area

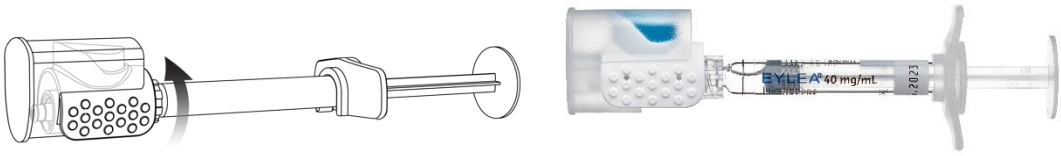
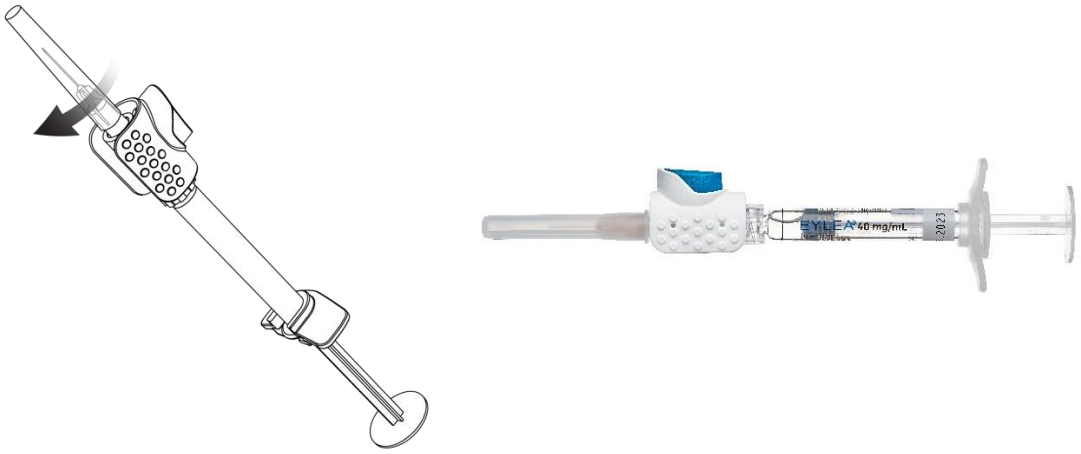
Pre-filled syringe

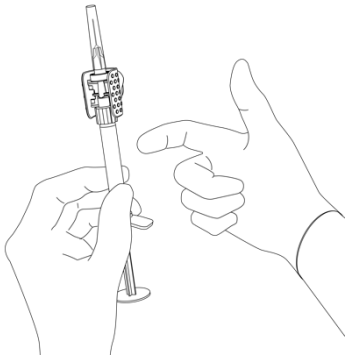
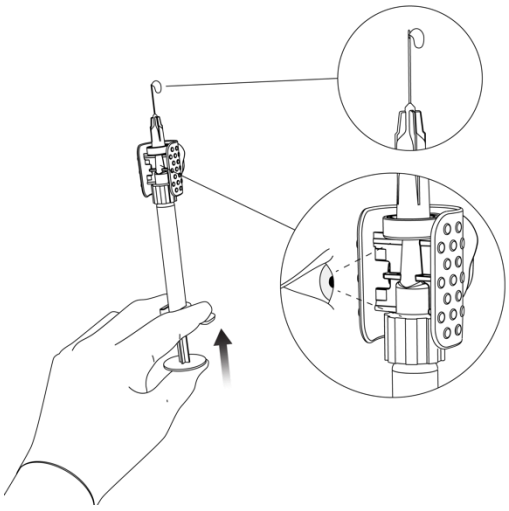
Note: the EYLEA 2 mg pre-filled syringe is a glass syringe with a rubber plunger that requires slightly more force to depress compared with plastic syringes. **Become familiarised with the features of this syringe before attaching it to the PICLEO paediatric dosing device.**

Preparation of administration

1	<u>Prepare the EYLEA 2 mg pre-filled syringe for attachment to the PICLEO paediatric dosing device</u> It is important to prepare the EYLEA 2 mg pre-filled syringe and the paediatric dosing device using aseptic technique. In the figures, the assistant is shown wearing darker gloves to indicate contact to non-sterile surface. The assistant should remove the carton containing the pre-filled syringe from the refrigerator. Note that the pre-filled syringe can be stored in the carton at room temperature for up to 24 hours. Open the carton and remove the blister containing the syringe. The blister must not be placed on a sterile surface because the outside surface of the blister is not sterile. The inside of the sealed blister and the pre-filled syringe are sterile. Carefully peel open the pre-filled syringe blister. **Aseptic technique must be used once the blister is opened.**

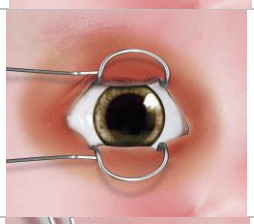
	The assistant should open the carton of the PICLEO paediatric dosing device and remove the sealed blister pack. Carefully peel open the device blister. **Aseptic technique must be used once the blister is opened. Note: The outside of the blister pack is non-sterile. The inside of the blister pack is sterile. Do not place the blister on a sterile surface.** The qualified physician carries out the remainder of the steps using aseptic technique including the use of sterile gloves.
2	<u>Prepare the PICLEO paediatric dosing device for administration</u> With two fingers, remove the pre-filled syringe from the blister. Visually inspect the syringe for loose or damaged parts and inspect the solution in the syringe for particulate matter and discolouration. Place the syringe in a sterile tray until ready for assembly. Using aseptic technique, carefully remove the PICLEO paediatric dosing device from its blister pack by taking it out with two fingers, while your assistant holds the blister from the outside, as shown in Figure a. Alternatively, your assistant can open the blister pack, and drop the PICLEO paediatric device onto a sterile surface as shown in Figure b. Only the inside of the blister pack and the enclosed PICLEO paediatric dosing device are sterile. To avoid contamination, do not touch the Luer Connectors. Figure a  Figure b 
3	<u>Attachment of the EYLEA 2 mg prefilled syringe to the device.</u> Remove the pre-filled syringe cap by holding the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and forefinger. **Twist off – do not snap off – the syringe cap.** 

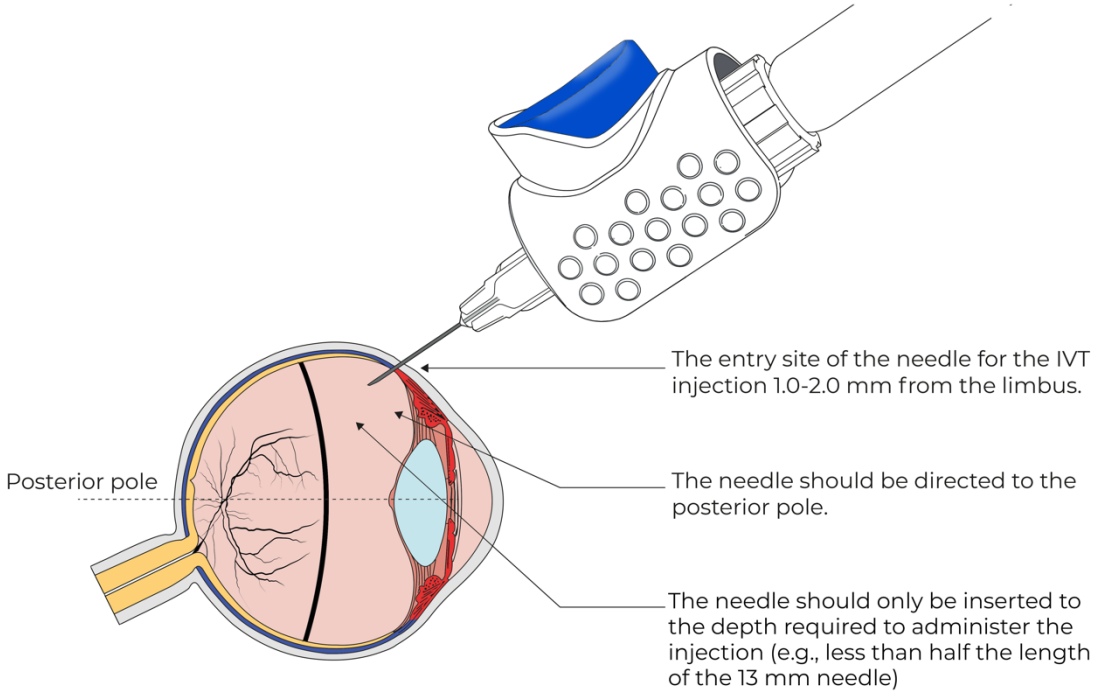
	Hold the PICLEO paediatric dosing device at the finger grips. Firmly twist the syringe onto the female Luer connector of the PICLEO paediatric dosing device. Make sure the connection is firm. 
4	<u>Attach the low dead space 30 G ½ inch (13 mm) injection needle to the PICLEO paediatric dosing device</u> Hold the Picleo paediatric dosing device at the grip area and carefully remove the cover from the PICLEO paediatric dosing device by pulling it straight off. **Do not touch the dose button when assembling. If it is pressed or partially pressed in error, it will not deliver the recommended dose**. If pressed, the system needs to be discarded and you need to start again with a new device and pre-filled syringe. Do not depress the syringe plunger rod when assembling.  Hold the PICLEO paediatric dosing device at the grip area and firmly twist the low dead space 30 G ½ inch (13 mm) length injection needle onto the male Luer connector of the PICLEO paediatric dosing device. The device has been validated with EYLEA 2 mg pre-filled syringe and the low dead space 30G ½ inch (13 mm) injection needle only. The EYLEA 2 mg pre-filled syringe and injection needle must be firmly attached to the PICLEO paediatric dosing device to avoid accidental detachment and to avoid leakage. 

5	Inspection and priming of the system Hold the EYLEA 2 mg pre-filled syringe with the injection needle pointing upwards and the viewing window of the PICLEO paediatric dosing device facing towards you. Inspect the medicinal product and the PICLEO paediatric dosing device for particles. Do not use if particulates are visible. Check the syringe for air bubbles. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top. Remove the cap from the needle. Prime the system by slowly depressing the plunger rod while observing through the viewing window. Eliminate air bubbles from the syringe and the PICLEO paediatric dosing device. The system is now ready for intravitreal injection. Caution: Aligning the syringe plunger with the dosing line on the syringe is not required. After air removal and priming, the PICLEO paediatric dosing device and injection needle contain the required volume. To avoid compromising the sterility of the medicinal product, do not pull-back the plunger.   
	The system is now ready for intravitreal injection. After injection, dispose of any unused medicinal product or waste material in accordance with local regulations.

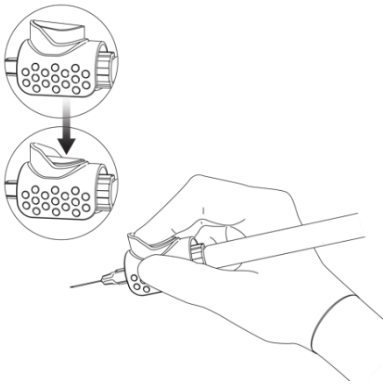
Injection procedure

For further information on intravitreal injection procedure, sterile techniques (including periocular and ocular disinfection) and anaesthesia, please refer to local and/or national clinical guidelines.

1	Administer topical anaesthesia.	
2	Apply disinfectant (e.g., povidone iodine solution or equivalent) to the periocular skin, eyelashes, eyelids, and into the conjunctival sac, avoiding extensive pressure to the periocular glands. The disinfectant should be on the surface according to local clinical guidelines.	 
3	Cover with sterile drape as needed and insert a sterile lid speculum to keep the eyelids open. Apply a second application of disinfectant (e.g., povidone iodine solution). The disinfectant should be on the ocular surface (conjunctival sac) in accordance with local clinical guidelines.	
4	Position the eye adequately. At an area of 1.0–2.0 mm posterior to the limbus, mark an injection site.	
5	Hold the PICLEO paediatric dosing device with needle and syringe assembly by the finger grips with the blue dosing button facing upward. The forefinger should be available to depress the dosing button. The injection needle should be angled and inserted such that damage to the lens and retina is avoided: Insert the injection needle into the vitreous cavity at the injection site, directed towards the posterior pole. The needle should only be introduced to the depth required to administer the injection, so less than half the length of the ½ inch (13 mm) needle.	



When ready, completely depress the dosing button on the PICLEO paediatric dosing device to administer the dose without moving the syringe or plunger. You will hear a click once the dose button has been fully depressed. This confirms that the dose has been delivered correctly.



Remove the injection needle with care and avoiding damage or contact with the lens.

Never administer the dose by depressing the syringe plunger rod as this may result in incorrect dosing.
Because only the medicinal product within the needle and PICLEO paediatric dosing device will be injected, residual medicinal product will remain in the syringe and the PICLEO paediatric dosing device. Do not administer any residual medicinal product. The PICLEO paediatric dosing device is for single use in one eye only. After injection, any unused medicinal product must be discarded. Avoid the needle touching the lens and damaging it.

Post-injection care information is found in the Important Safety Information About EYLEA section.

OTHER SOURCES OF INFORMATION

https://www.edumaterial.bayer.com.mt

Local Safety Information

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt

Or

E: pv@alfredgera.com

For more information about EYLEA, visit https://ophthalmology.bayer.com