Bayer (Pty) Ltd	Approved date: 06 February 2020

SCHEDULING STATUS: S4

1. PROPRIETARY NAME AND DOSAGE FORM:

EYLEA, Solution for Injection

2. Qualitative and quantitative composition

One milliliter solution for injection contains 40 mg aflibercept.
Each pre-filled syringe contains an extractable volume of 90 microlitres, equivalent to 3.6 mg aflibercept.
Each single dose vial contains an extractable volume of 100 microlitres, equivalent to 4.0 mg aflibercept.

This product contains less than 1 mmol sodium (23 mg) per dose, i.e essentially "sodium-free".

Contains sugar: sucrose
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

EYLEA, Solution for Injection

EYLEA is a sterile, clear, and colourless to pale yellow solution for injection which has no visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

EYLEA is indicated for the treatment of

- neovascular (wet) age-related macular degeneration (AMD).
- macular oedema following central retinal vein occlusion (CRVO)
- macular oedema secondary to branch retinal vein occlusion (BRVO)
- diabetic macular oedema (DME)
- myopic choroidal neovascularisation (myopic CNV)

4.2 Posology and method of administration

EYLEA is for intravitreal injection. It must only be administered by a doctor experienced in administering intravitreal injections.

Posology:
Neovascular (wet) age-related macular degeneration (wet AMD)

The recommended dose for EYLEA is 2 mg aflibercept (equivalent to 50 microliters solution for injection).
EYLEA treatment is initiated with one injection per month (every 4 weeks) for three consecutive doses, followed by one injection every 2 months. (every 8 weeks)

Based on the medical practitioner's judgement of visual and/or anatomic outcomes the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals are gradually increased to maintain stable visual and/ or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

There is no requirement for monitoring between injections. Based on the medical practitioner´s judgement the schedule of monitoring visits may be more frequent than the injections visits.

Treatment intervals greater than 4 months (16 weeks) between injections have not been studied.

Macular oedema following central retinal vein occlusion (CRVO)

The recommended dose for EYLEA is 2 mg aflibercept (equivalent to 50 microliters solution for injection).
After the initial injection, treatment is given monthly (every 4 weeks) until visual and/ or anatomic outcomes are stable. Three or more consecutive, monthly (every 4 weeks) injections may be needed. The interval between two doses should not be shorter than one month (4 weeks).
Treatment should be continued and the interval may be extended based on visual and/or anatomic outcomes (treat and extend regimen).

Macular oedema secondary to branch retinal vein occlusion (BRVO)

The recommended dose for EYLEA is 2 mg (equivalent to 50 microliters).

After the initial injection, treatment is given monthly (every 4 weeks) until visual and/ or anatomic outcomes are stable. Three or more consecutive, monthly (every 4 weeks) injections may be needed. Treatment should be continued and the interval may be extended based on visual and or anatomic outcomes (treat and extend regimen).

Diabetic macular oedema (DME)

The recommended dose for EYLEA is 2 mg (equivalent to 50 microliters) administered by intravitreal injection monthly (every 4 weeks) for the first 5 consecutive doses, followed by one injection every 2 months (every 8 weeks).

Myopic choroidal neovascularization (myopic CNV)

The recommended dose for EYLEA is a single intravitreal injection of 2 mg (equivalent to 50 microliters). Additional doses should be administered only if visual and anatomic outcomes indicate that the disease persists. In a clinical trial with EYLEA the median injection number was 2,0.

Monitoring Schedule

Monitoring should be done during treatment interval extension through to completion of therapy. The monitoring schedule should be determined by the treating doctor based on the individual patient's response and may be more frequent than the schedule of injections.

Method of administration

Each pre-filled syringe or vial should only be used for the treatment of a single eye and is for single use in one eye only. Extraction of multiple doses from a single vial or pre-filled syringe may increase the risk of contamination and subsequent infection.

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a doctor experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including a topical broad spectrum microbiocide (e.g., povidone iodine), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

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, a sterile paracentesis should be available.

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.

After injection any unused product must be discarded.

Instructions for use / handling

The pre-filled syringe and the vial are for single use only.

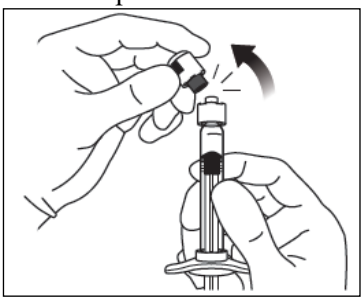
Prior to administration visually inspect the solution for injection. Do not use the vial or pre-filled syringe if particulates, cloudiness, or discolouration are visible.

Prior to usage, the unopened vial or blister pack of EYLEA may be stored at room temperature (25 °C) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.

For the intravitreal injection a 30 G x ½ inch (12.7 mm) injection needle should be used.

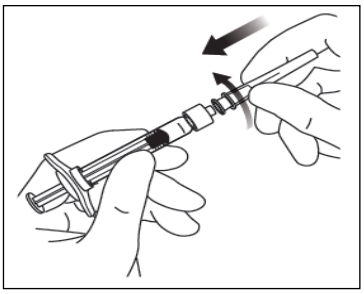
Pre-filled syringe:

1. When ready to administer EYLEA, open the carton and remove the sterilised blister pack. Carefully peel open the blister pack 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 sterilised blister pack.
3. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and fore finger. Please note: Snap off (do not turn or twist), the syringe cap.

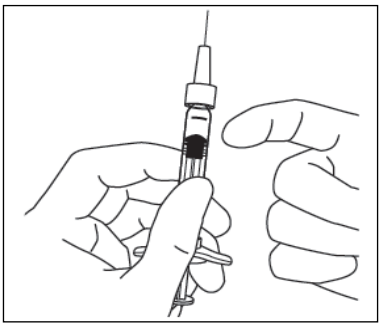


4. To avoid compromising the sterility of the product, do not pull back on the plunger.

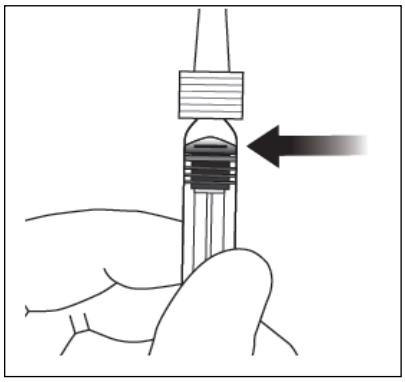
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

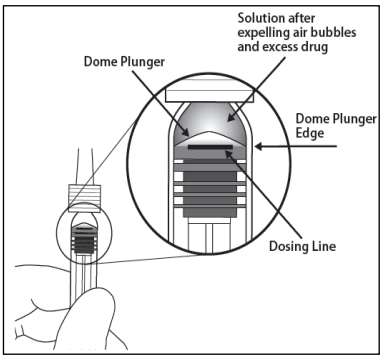


6. Remove the plastic needle shield.
7. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



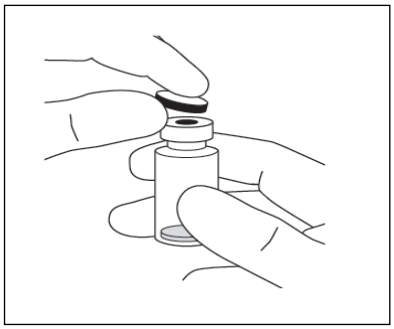
8. To eliminate all bubbles and to expel excess drug, slowly depress the plunger to align the cylindrical base of the dome tip with the black dosing line on the syringe (equivalent to 50 microliters).



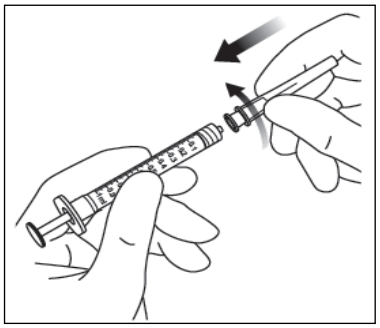


Vials:

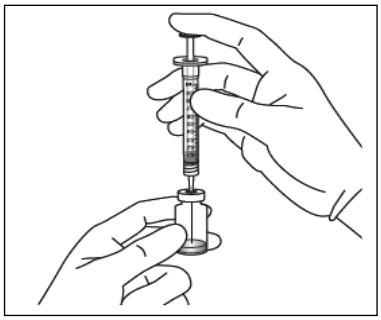
1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.



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

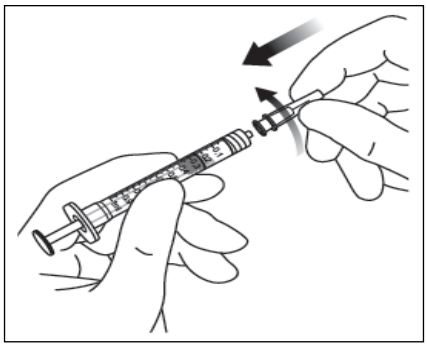


3. Push the filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.
4. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.



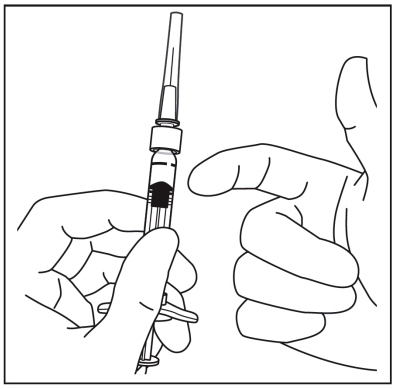
5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
6. Remove the filter needle and properly dispose of it.
   Note: Filter needle is not to be used for intravitreal injection.

7. Using aseptic technique, firmly twist a 30 G x ½ inch (12.7 mm) injection needle to the Luer-lock syringe tip.

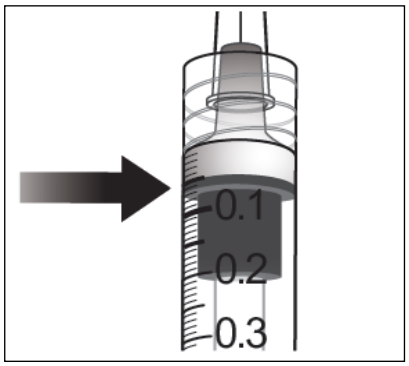


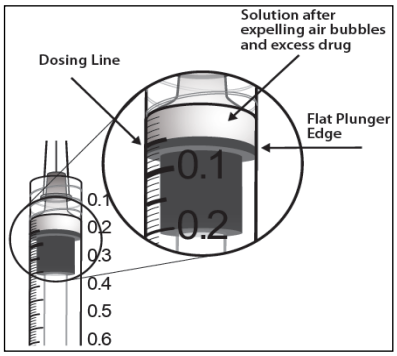
8. When ready to administer EYLEA, remove the plastic needle shield.

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.





4.3 Contraindications:

- Known hypersensitivity to aflibercept or to any of the excipients of EYLEA.
- Ocular or periocular infection
- Active severe intraocular inflammation
- Pregnancy and mothers who are breastfeeding their infants (see "section 4.6")

4.4 Special warnings and precautions for use

Endophthalmitis
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis (see "Section 4.8"). 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 should be managed appropriately.

Increase in intraocular pressure
Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, with EYLEA (see "Section 4.8"). Special care is needed in patients with poorly controlled glaucoma. In all cases both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Arterial thromboembolic events:
There is a potential risk of arterial thromboembolic events (ATEs), including stroke and myocardial infarction following the intravitreal use of VEGF inhibitors including EYLEA.

A low incidence rate of arterial thromboembolic events was observed in the EYLEA clinical trials, which ranged from 0 % - 6.4 % of Eylea treated patients in the pivotal phase III studies. ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause).

Immunogenicity:
There is a potential for immunogenicity with EYLEA.

Additional information on special populations

Patients with hepatic and/or renal impairment:
No specific studies in patients with hepatic and/or renal impairment were conducted with EYLEA. Available data do not suggest a need for a dose adjustment with EYLEA in these patients.

Elderly:
No special considerations are needed.

Information about excipients:

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take EYLEA

4.5 Interactions with other medicines and other forms of interactions

No formal drug interaction studies have been performed with EYLEA.

4.6 Fertility, pregnancy and lactation

EYLEA should not be used during pregnancy (see section 4.3).
Studies in animals have shown reproductive toxicity after systemic exposure to aflibercept using intravenous or subcutaneous routes of administration.

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

Lactation
EYLEA must not be used by mothers who are breast-feeding their infants

4.7 Effects on ability to drive or use machines

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. They should not drive or use machinery until visual function has recovered sufficiently.

4.8 Undesirable effects

A total of 3 102 patients treated with EYLEA constituted the safety population in the eight phase III studies. Among those, 2 501patients were treated with the recommended dose of 2 mg.

Serious adverse reactions related to the injection procedure endophthalmitis, retinal detachment, traumatic cataract, cataract, vitreous detachment and increased intraocular pressure have occurred.
The most frequently observed adverse reactions (in at least 5 % of patients treated with EYLEA) were conjunctival haemorrhage, eye pain, cataract, increased cataract intraocular pressure, vitreous detachment, and vitreous floaters.
The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000).
Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

All treatment-emergent adverse drug reactions reported in patients in phase III studies

System Organ Class	Very common	Common	Uncommon	Rare
Eye disorders	Conjunctival haemorrhage, Eye pain, Visual acuity reduced.	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Cataract, Cortical cataract, Nuclear cataract, Subcapsular cataract, Corneal erosion, Corneal abrasion, Increased intraocular pressure, Blurred vision, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes,	Endophthalmitis**, Retinal detachment, Retinal tear, Uveitis, Iritis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Anterior chamber flare, Corneal oedema	Traumatic cataract, Vitritis, Hypopyon, Blindness.

System Organ Class	Very common	Common	Uncommon	Rare
		Increased lacrimation, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia, Retinal degeneration, Vitrous haemorrhage		

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
** Culture positive and culture negative endophthalmitis

Post-marketing Experiences
During the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/ anaphylactoid reactions.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents.
ATC code: S01LA05
Aflibercept is a recombinant fusion protein consisting of portions of human Vascular Endothelial Growth Factor (VEGF) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.
Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells, by recombinant DNA technology.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with a higher affinity than their natural receptors, and thereby it inhibits the binding and activation of these cognate VEGF receptors.

5.2 Pharmacokinetic properties

Absorption / Distribution
Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only "free aflibercept" is able to bind endogenous VEGF.

In a pharmacokinetic substudy, the maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 microgram/ml (range 0 to 0.054) within 1 to 3 days after a 2

mg intravitreal injection and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.
It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than a 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF. Therefore, systemic pharmacodynamic effects are unlikely.

Elimination
Free aflibercept binds VEGF to form a stable, inert complex. Free and bound aflibercept are expected to be cleared by proteolytic catabolism.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polysorbate 20,
sodium phosphate monobasic monohydrate,
sodium phosphate dibasic heptahydrate,
sodium chloride,
sucrose – 50 mg/ml,
water for injection.
This product contains less than 1 mmol sodium (23 mg) per dose, i.e essentially “sodium-free”.
Contains sugar: sucrose

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a refrigerator (2°C to 8°C).
Do not freeze. Any unused or excess solution should be discarded in accordance with local requirements.
Keep the pre-filled syringe in its blister pack and in the outer carton in order to protect from light.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container
Pre-filled syringes:
Each carton includes a sealed blister pack with a sterile 1 ml colourless pre-filled type I glass syringe, containing an extractable volume of 90 microlitre solution for injection, sealed with bromobutyl gray fluoropolymer elastomeric plunger stopper siliconised with silicone oil and a tamper-evident bromobutyl gray elastomeric tip cap that is part of a closure system with Luer lock adaptor. The syringe has a pre-attached plunger rod and a finger plate.

Vials:
Each carton includes a type I; 2 ml colourless glass vial containing an extractable volume of 100 microlitre solution for injection with butyl gray fluoropolymer coated elastomeric rubber stopper with an aluminium crimp seal with a coloured polypropylene button, and an 18 G filter needle.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicines and other handling of the product
Not Applicable

7.HOLDER OF CERTIFICATE OF REGISTRATIONS

Bayer (Pty) Ltd
(Reg No: 1968/011192/07)
27 Wrench Road
Isando,1609

8.REGISTRATION NUMBER:

A 46/15.4/0841

9.DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 29 July 2016

10. DATE OF REVISION OF THE TEXT

06 February 2020