SUMMARY

aflibercept

EYLEA 40 mg/mL,

solution for injection in pre-filled syringe

Indication extension

Original French opinion adopted by the Transparency Committee on 19 July 2023

The legally binding text is the original French opinion version

Transparency Committee's conclusions

Clinical Benefit

- Retinopathy of prematurity (ROP) is a retinal vascular development abnormality that affects preterm infants. In the majority of cases, ROP regresses spontaneously. However, it can progress to forms with retinal scarring, causing irreversible visual impairment or even blindness.
- This proprietary medicinal product is a curative treatment.
- The efficacy/adverse effects ratio is low given the absence of formal demonstration of its non-inferiority compared to laser photocoagulation despite high response probabilities similar to those of the laser photocoagulation group (85% vs 82%) as well as uncertainties concerning its long-term efficacy and safety.
- In 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, EYLEA (aflibercept) is an alternative to laser therapy in the following situations only:
  - in highly active forms of the disease (aggressive posterior ROP),
  - in the event of extensive zone I disease,
  - if it is impossible to perform laser therapy or general anaesthesia.

Public health benefit

Considering:

- the seriousness of the disease, which, in its most severe forms, can cause irreversible visual impairment or even lead to blindness,
- the rarity of the disease,
- the partially met medical need,

- the partial response to the identified need:
  - high response probability, similar to that obtained with laser photocoagulation, without demonstration of the non-inferiority of aflibercept to laser photocoagulation,
  - the lack of a demonstrated additional impact on quality of life,
  - a potential additional impact compared to laser photocoagulation on the organisation of care and the patient's care pathway, with intravitreal injection of aflibercept being easier to implement since it is possible to administer the injection at the patient's bedside, without the need to move them to the operating theatre or an expert centre, and under much shorter and less deep general anaesthesia or even local anaesthesia. In addition, its administration remains possible in cases where laser photocoagulation is impossible, particularly in preterm infants who are too unstable to undergo general anaesthesia or in the event of poor visualisation of the eye fundus (intravitreal haemorrhage, corneal or lens opacity),

EYLEA (aflibercept) is unlikely to have an additional impact on public health.

In the treatment of retinopathy of prematurity with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease:

Considering all these elements, the Committee deems that the clinical benefit of EYLEA 40 mg/mL (aflibercept) solution for injection in pre-filled syringe in the treatment of retinopathy of prematurity is:

- **low only in the following situations:**
  - **in highly active forms of the disease (aggressive posterior ROP),**
  - **in the event of extensive zone I disease,**
  - **if it is impossible to perform laser therapy or general anaesthesia,**
- **insufficient to justify its public funding cover in all other clinical situations of the MA.**

The Committee issues a favourable opinion for inclusion of EYLEA 40 mg/mL (aflibercept) solution for injection in pre-filled syringe in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of retinopathy of prematurity in the following situations only:

- **in highly active forms of the disease (aggressive posterior ROP),**
- **in the event of extensive zone I disease,**
- **if it is impossible to perform laser therapy or general anaesthesia.**

The Committee issues an unfavourable opinion:

- **for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other clinical situations of the MA;**
- **for inclusion in the retail formulary list of reimbursed proprietary medicinal products approved for use in the entire MA indication.**

Clinical Added Value

Considering:

- the results of the FIREFLEYE study demonstrating high response percentages (absence of active ROP and unfavourable structural outcomes) at week 24 with aflibercept and similar to those

in the laser photocoagulation group (85.5% versus 82.1%), in 121 preterm infants with retinopathy;

- the results of the FIREFLEYE NEXT extension study in infants at 2 years of age, demonstrating maintenance of the clinical response in the aflibercept and laser groups;
- the medical need partially met by laser photocoagulation, which can sometimes be difficult to perform (in the operating theatre, under general anaesthesia that can sometimes last several hours and by a trained ophthalmologist) or even impossible (particularly in preterm infants who are too unstable to undergo general anaesthesia or in the event of poor visualisation of the eye fundus) and is associated with short and long-term complications impairing vision (reduction in peripheral field of vision, myopia and strabismus);
- the advantages of anti-VEGF injection compared to laser photocoagulation since it is possible to administer the injection at the patient's bedside, under shorter and less deep anaesthesia, without the need to move them to the operating theatre or an expert centre;

but considering:

- the lack of formal demonstration of the non-inferiority of aflibercept compared to laser photocoagulation in the FIREFLEYE study;
- as well as in the BUTERFLEYE study conducted in the USA, with an assessment at week 52 with the same primary efficacy endpoint;
- that only the "summary of evidence" study, the aim of which was to compare the efficacy results observed with aflibercept in the FIREFLEYE study with those in the laser photocoagulation group, increasing the number of patients in the latter group by adding the results of two historic studies, suggests this non-inferiority;
- uncertainties concerning the long-term efficacy (risk of late recurrence) and safety (consequences of systemic absorption of anti-VEGF therapies in a vulnerable population, particularly on psychomotor development) and the absence of data beyond the age of 2 years;

the Committee deems that EYLEA 40 mg/mL (aflibercept) solution for injection in pre-filled syringe provides no clinical added value (CAV V) in the current care pathway for retinopathy of prematurity.