EYLEA 40 mg/ml, solution for injection in prefilled syringe
B/1 (CIP: 34009 267 835 0 1)

EYLEA 40 mg/ml, solution for injection in a vial
One disposable vial of 100 µl (CIP: 34009 267 836 7 9)

Applicant: BAYER HEALTHCARE SAS

<table>
<thead>
<tr>
<th>INN</th>
<th>aflibercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2011)</td>
<td>S01LA05 (ocular antineovascularisation agent)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Extension of indication</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>“EYLEA is indicated for adults for the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).”</td>
</tr>
<tr>
<td>Actual benefit</td>
<td>Substantial.</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Improvement in actual benefit</td>
<td>EYLEA does not provide any improvement in actual benefit (level V, non-existent) compared with LUCENTIS for adults in the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>EYLEA is a first-line treatment.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation

Initial Marketing Authorisation: 22 November 2012 (centralised procedure)
Change: 26 August 2013 (extension of indication to the treatment in adults of visual impairment due to macular oedema secondary to central retinal vein occlusion).
RMP: commitment by the company to carry out an efficacy study in AMD.

Prescribing and dispensing conditions /special status

List I
Prescription restricted to ophthalmology specialists
Exception drug status

ATC Classification

2014: Sensory organs
S Ophthalmologicals
S01 Ocular vascular disorder agents
S01LA Antineovascularisation agents
S01LA05 aflibercept

02 BACKGROUND

EYLEA was initially granted Marketing Authorisation for adults for the treatment of neovascular (wet) age-related macular degeneration. This indication was assessed by the Transparency Committee on 3 April 2013; the Committee considered that, in this indication, the actual benefit of EYLEA was substantial, and that it did not provide any improvement in actual benefit compared with LUCENTIS.
The company is applying for inclusion on the National Health Insurance and hospital use lists for EYLEA in the extension of indication to the treatment in adults of visual impairment due to macular oedema secondary to central retinal vein occlusion.

03 THERAPEUTIC INDICATIONS

“EYLEA is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration.

EYLEA is indicated for adults for the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).”

04 DOSAGE

“Eylea is for intravitreal injection only.
Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.

[...]
**Macular oedema secondary to CRVO**

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

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

If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended.

Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered.

If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate.

Usually, monitoring should be done at the injection visits. If the interval between 2 injections is longer than 1 month, the monitoring schedule should be determined by the treating physician based on the patient's response, through to completion of therapy. These monitoring visits may be more frequent than the schedule of injections.”

---

**05 THERAPEUTIC NEED**

A distinction can be made between two main forms of retinal vein occlusion: an ischaemic form with poor visual prognosis and a form (termed oedematous) with good perfusion and a better prognosis.

The objective of treating oedematous retinal vein occlusion is to facilitate the restoration of normal retinal vein circulation, avoid progression to an ischaemic form leading to an irreversible loss of vision, and to prevent or treat macular complications, in particular cystoid macular oedema.

The objective of treating mixed or ischaemic venous occlusion is to prevent or treat neovascular complications.

OZURDEX (dexamethasone intravitreal implant) and LUCENTIS (ranibizumab intravitreal injection) are the first-line treatments for visual impairment due to macular oedema secondary to branch or central retinal vein occlusion. In the absence of data directly comparing LUCENTIS and OZURDEX, the choice of one or the other of these medicinal products should be made on the basis of their individual efficacy, the characteristics of the patient, the contraindications, the potential adverse effects and the monitoring constraints. Consequently, the age of the patient, his or her ability to travel to receive monthly injections in the case of LUCENTIS, the presence of the crystalline lens and the existence of glaucoma due to the increased risk of ocular hypertension and of cataract with OZURDEX, are important criteria to be taken into account when starting one or the other of these treatments.

It is recommended that fluorescein angiography should be performed before starting treatment in order to rule out ischaemic forms that are not indications for LUCENTIS. Since progression of the oedematous form to the ischaemic form is possible under treatment, it is recommended that this should be monitored.

Various medicinal products that have not been evaluated in clinical studies are used off-label via the systemic route.

Slow-release triamcinolone (KENACORT retard) has been used off-label as an intravitreal injection. Its formulation is not suitable for the intravitreal route and includes a preservative that exposes the patient to a risk of pseudo-endophthalmitis-type local reactions. Other complications are cataract, roughly constant after two injections, and ocular hypertension.
Other treatments are used:
- Grid laser photocoagulation in oedematous forms and panretinal laser photocoagulation in ischaemic forms that have been present for at least 3 months.
- Surgical treatment of macular oedema: vitrectomy, radial optic neurotomy, chorioretinal venous anastomosis, arteriovenous adventitial sheathotomy. These treatments have not been evaluated in a clinical study.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Same TC* Yes/No</th>
<th>Indication</th>
<th>Date of Opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursed Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>OZURDEX 700 µg Dexamethasone ALLERGAN France S.A.S.</td>
<td>No</td>
<td>Treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).</td>
<td>17/11/2010</td>
<td>Substantial</td>
<td>IAB IV in the management of the treatment of macular oedema and oedema following either branch retinal vein occlusion or central retinal vein occlusion</td>
<td>Yes</td>
</tr>
<tr>
<td>LUCENTIS Ranibizumab Novartis Pharma S.A.S.</td>
<td>Yes</td>
<td>The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).</td>
<td>18/01/2012</td>
<td>Substantial</td>
<td>IAB IV compared with OZURDEX in the treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*therapeutic category

06.2 Other health technologies

Not applicable.

**Conclusion**

OZURDEX and LUCENTIS are the relevant comparators for EYLEA. LUCENTIS, which is in the same therapeutic category as EYLEA (anti-VEGF), is the more relevant comparator.
<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Population(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>YES</td>
<td>MA population or restricted</td>
</tr>
<tr>
<td>Italy</td>
<td>Assessment in progress</td>
<td>MA population</td>
</tr>
<tr>
<td>Germany</td>
<td>YES (26/08/2013)</td>
<td></td>
</tr>
<tr>
<td>England/Scotland</td>
<td>YES (approval by NICE)</td>
<td></td>
</tr>
</tbody>
</table>

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The dossier is based on two randomised, double-blind, phase III studies that compared intravitreal aflibercept injections with sham intravitreal injections:
- Study 14130 (Galileo)\(^1,2\)
- Study VGFT-OD-0819 (Copernicus)\(^3,4\)

EYLEA has not been compared with LUCENTIS or OZURDEX in a clinical study because the studies were set up and patients were included (July and October 2009) before the MA for retinal venous occlusions was granted to LUCENTIS (27 May 2011) or OZURDEX (27 July 2010). One indirect comparative study of these three proprietary medicinal products using the network meta-analysis method was provided.

8.1.1 The GALILEO and COPERNICUS clinical studies

The GALILEO and COPERNICUS clinical studies have a common phase from 0 to 24 weeks (evaluation of the primary efficacy endpoint); after that the study procedures differed. From 24 to 48 weeks, the patients in the sham injection group could be treated with aflibercept if they satisfied the retreatment criteria or with monthly sham injections if the retreatment criteria were not satisfied. After 52 weeks, the studies were followed by an open phase in which all the patients were treated with aflibercept if they satisfied the retreatment criteria or with monthly sham injections if the retreatment criteria were not satisfied.

The retreatment criteria were as follows:

---


Retreatment following deterioration:
- Increase of more than 50 µm in central retinal thickness compared with the lowest value previously measured by OCT,
- New or persistent cystic retinal changes or persistent diffuse subretinal fluid or oedema ≥ 250 µm in the central macular region,
- Loss of ≥ 5 letters on the ETDRS scale compared with the best previous score together with an increase in central renal thickness measured by OCT of any size

Retreatment following improvement: improvement in visual acuity of ≥ 5 letters since the most recent visit.

### GALILEO study

<table>
<thead>
<tr>
<th>Principal study objective</th>
<th>Comparison of intravitreal aflibercept injections with sham intravitreal injections in relation to the improvement in the best corrected visual acuity (BCVA) after 6 months of treatment in patients with macular oedema secondary to a central retinal vein occlusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Comparative randomised double-blind study versus sham intravitreal injections (placebo).</td>
</tr>
</tbody>
</table>
| Inclusion criteria        | ▪ Age ≥ 18 years  
  ▪ Macular oedema with involvement of the centre of the macula  
  ▪ Retinal thickness ≥ 250 µm in the central region of the macula measured by optical coherence tomography (OCT) at inclusion BCVA score in the study eye between 20/40 and 20/230 |
| Non-inclusion criteria    | ▪ The following ocular or periocular diseases: myopia (-8 dioptres), uncontrolled glaucoma, aphakia, history or presence of age-related macular oedema or diabetic macular oedema, iris neovascularisation, vitreous haemorrhage, tractional retinal detachment, preretinal fibrosis with involvement of the macula, structural changes to the centre of the macula or vitreomacular traction or epiretinal membranes precluding an improvement in visual acuity, autoimmune uveitis, bilateral central retinal vein occlusion, visual impairment due to another disease.  
  ▪ History of the following treatments: laser treatment, cataract treatment, vitreoretinal surgery, filtering surgery, sheathotomy, peri- or intraocular corticosteroid treatment, anti-VEGF treatment or any other treatment for macular oedema, including treatments under development.  
  ▪ Systemic diseases: uncontrolled arterial hypertension or diabetes, history of stroke or myocardial infarction in the last 6 months, renal failure treated with dialysis or awaiting transplantation. |
| Treatment groups          | ▪ Aflibercept 2 mg by intravitreal injections  
  ▪ Sham intravitreal injections |

#### Course of the study

**Weeks 0 to 52:**  
- **Aflibercept:** one injection every 4 weeks until week 20 (6 injections) followed by monthly evaluations from week 24 to week 48 with retreatment according to pre-established criteria. If the criteria are not satisfied, monthly sham injections.  
- **Sham injections:** one sham injection every 4 weeks until week 20 (6 injections).  

**Weeks 24 to 48:** monthly evaluations and continuation of treatment with monthly sham injections.

**Weeks 52 to 76:** open phase in which all patients who satisfy the retreatment criteria can be treated with aflibercept 2 mg. The patients are evaluated every 8 weeks. If any of the criteria are not satisfied, monthly treatment with sham injections.

**Primary efficacy endpoint**  
- Percentage of patients with a gain of ≥ 15 letters (ETDRS scale at a distance of 4 m) in visual acuity from baseline.  
  - At the end of the study, all patients who have received at least one injection of aflibercept or placebo are evaluated with the ETDRS visual acuity test at a distance of 4 m.
Results of the GALILEO study:

A total of 177 patients underwent randomisation, 106 in the aflibercept group and 71 in the sham injection group. The proportion of patients who completed the first 24 weeks of the study was 78.9% in the sham injection group and 90.6% in the aflibercept group. The proportion of patients who completed the first 52 weeks of the study was 73.2% in the sham injection group and 85.8% in the aflibercept group.

The main reasons for premature discontinuation of the study at 24 weeks were:
- sham injections: lack of efficacy (7.0%), adverse event (5.6%), withdrawal of consent (4.2%)
- aflibercept: protocol deviation (4.7%), withdrawal of consent (2.8%).

The characteristics of the patients included in the groups were comparable. The patients had a mean age of 64 years and slightly more than half (57%) were men.

Most of the patients (83%) had a BCVA < 20/200 (≥ 35 letters read) and 17% had a BCVA ≤ 20/200 (≤ 34 letters read). The mean retinal thickness was 665.49 ± 231.00 µm. The time since diagnosis was ≤ 2 months in 46.2% of cases and > 2 months in 52.6% of cases.

Primary efficacy endpoint:
At 24 weeks, the percentage of patients with a gain of ≥ 15 letters was greater under aflibercept (60.2%) than with the sham injections (22.1%), which is a difference of 38.3% (adjusted difference 38.3%; 95% CI = [24.4; 52.1]; p < 0.0001).

Secondary endpoints:
- Change in BCVA at 24 weeks:
  At 24 weeks, the adjusted mean change in BCVA was greater under aflibercept (+17.7 letters) than with placebo (+0.3 letters), which is a significant difference of 14.7 letters (p < 0.0001).
- Change in central retinal thickness at 24 weeks:
At 24 weeks, the adjusted mean retinal thickness had decreased more under aflibercept (-447.97 µm) than with the sham injections (-208.55 µm), which is a difference of -239.42 µm (p < 0.0001).

- Percentage of patients developing neovascularisation:
  In the course of 24 weeks of treatment, 3 patients in each group developed neovascularisation in the anterior segment; that is, 2.9% of the patients treated with aflibercept and 4.4% of the patients treated with sham injections. No significant difference between the two groups was demonstrated.

Other endpoints (exploratory analyses):

- **Analysis at week 52:**
  - The percentage of patients with a gain of ≥ 15 letters was 60.2% in the patients treated with aflibercept and 25.1% in the patients treated with sham injections then aflibercept.
  - The adjusted mean change in BCVA was +18.1 letters under aflibercept and +4.9 letters with sham injections (p < 0.0001).

- **Analysis at week 76:**
  A total of 50 patients in the sham injection/aflibercept group and 102 patients in the aflibercept group continued the study after 52 weeks.
  The percentage of patients with a gain of BCVA ≥ 15 letters was 57.3% in the aflibercept group and 29.4% in the group treated with sham injections then aflibercept.
  The mean change in adjusted BCVA was +15.0 letters in the aflibercept group and +7.4 letters in the group treated with sham injections then aflibercept.

**Results of the COPERNICUS study:**

A total of 189 patients were randomised, 115 to the aflibercept group and 74 to the sham injection group.
The proportion of patients who completed the first 24 weeks of the study was 81.1% in the sham injection group and 95.7% in the aflibercept group.
The proportion of patients who completed the first 52 weeks of the study was 77% in the sham injection/aflibercept group and 93.0% in the aflibercept group.

The main reasons for premature discontinuation of the study up to 24 weeks were:
- sham injections: lack of efficacy (5.4%), adverse event (4.1%), death (2.7%), and lost to follow up (2.7%)
- aflibercept: withdrawal of consent (2.6%)

The characteristics of the patients included in the groups were comparable.
The patients had a mean age of 66 years and slightly more than half (57%) were men.

Most of the patients (75.4%) had a BCVA < 20/200 (≥ 35 letters read) and 24.6% had a BCVA ≤ 20/200 (≤ 34 letters read). The mean retinal thickness was 665.8 ± 239.82 µm. The time since diagnosis was ≤ 2 months in 62.0% of cases and > 2 months in 37.4% of cases.
Primary efficacy endpoint:
At 24 weeks, the percentage of patients with a gain of ≥ 15 letters was greater under aflibercept (56.1%) than with the sham injections (12.3%), which is a difference of 43.8% (adjusted difference 44.8%; 95% CI = [33.0; 56.6]; p < 0.0001).

Secondary endpoints:
- Change in BCVA at 24 weeks:
  At 24 weeks, the adjusted mean change in the BCVA was +16.36 letters under aflibercept and -5.3 letters under placebo, which is a significant difference of +21.70 letters (p < 0.0001).
- Change in central retinal thickness at 24 weeks:
  At 24 weeks, the adjusted mean retinal thickness had decreased more under aflibercept (-487.1 µm) than with the sham injections (-175.2 µm), which is a difference of -319.9 µm (p < 0.0001).
- Percentage of patients developing neovascularisation:
  In the course of 24 weeks of treatment, 5 patients in the sham injection group (6.8%) versus no patients in the aflibercept group developed neovascularisation in the anterior segment (p < 0.006).
- Change in the NEI VFQ-25 score at 24 weeks:
  At inclusion, the NEI VFQ-25 score was 77.8 in the aflibercept group and 78.0 in the sham injection group. A greater improvement in the score was observed in the aflibercept group (+8.80 points) than in the sham injection group (+2.54 points; p = 0.0001); however, the minimum clinically relevant difference is not known.

Other endpoints (exploratory analyses):
- Analysis at week 52:
  - The percentage of patients with a gain of ≥ 15 letters was 60.2% under aflibercept and 25.1% with the sham injections, which is a difference of 27.8%, p = 0.0004);
  - The adjusted mean change in BCVA was +18.1 letters under aflibercept and +4.9 letters with the sham injections (p < 0.0001).
- Analysis at week 100:
  A total of 68 patients in the sham injection group and 103 patients in the aflibercept group continued the study after 52 weeks.
  - The percentage of patients with a gain of ≥ 15 letters was 49.1% in the patients treated with aflibercept and 23.3% in the patients treated with sham injections then aflibercept.
  - The adjusted mean change in BCVA was +16.2 letters under aflibercept and +3.8 letters with the sham injections (p < 0.0001).

Combined analysis of the GALILEO and COPERNICUS studies:
The total number of patients randomised in the two studies was 366, and the full analysis set was 306 patients.

The characteristics of the patients included in the groups were comparable. The patients had a mean age of 64 years and slightly more than half (57%) were men.

Most of the patients (82.4%) had a BCVA < 20/200 (≥ 35 letters read) and 17.6% had a BCVA ≤ 20/200 (≤ 34 letters read). The mean retinal thickness was 665.7 ± 235.2 µm. The time since diagnosis was ≤ 2 months in 57.5% of cases and > 2 months in 41.6% of cases. The mean total NEI VFQ-25 score was 78.55.

Primary efficacy endpoint:
At 24 weeks, the percentage of patients with a gain of ≥ 15 letters was greater under aflibercept (60.4%) than with the sham injections (17.0%), which is an adjusted difference of 43.6%; 95% CI = [34.6; 52.6]; p < 0.0001).
Secondary endpoints:

- Change in BCVA at 24 weeks:
  At 24 weeks, the adjusted mean change in the BCVA was +17.66 letter under aflibercept and -0.49 letters under the placebo, which is a significant adjusted difference of +18.6 letters (p < 0.0001).

- Change in central retinal thickness at 24 weeks:
  At 24 weeks, the adjusted mean retinal thickness had decreased more under aflibercept (-453.06 µm) than with the sham injections (-157.22 µm), which is an adjusted difference of -277.7 µm (p < 0.0001).

- Percentage of patients developing neovascularisation:
  In the course of 24 weeks of treatment, 8 patients in the sham injection group (5.7%) versus 3 patients in the aflibercept group (1.4%) developed neovascularisation in the anterior segment (p = 0.250).

- Change in the NEI VFQ-25 score at 24 weeks:
  A greater improvement in the score was observed in the aflibercept group (+7.31 points) than in the sham injection group (+2.22 points; p < 0.0001).

Analysis at week 52 (exploratory analysis):
- The proportion of patients who had a gain of ≥ 15 letters was 58.5% under aflibercept, 30.1% in patients treated with sham injections than aflibercept and 32.4% in patients only treated with sham injections.
- The proportion of patients who had a gain of ≥ 30 letters was 18.5% under aflibercept, 1.4% in patients treated with sham injections than aflibercept and 7.35% in patients only treated with sham injections.

8.1.2 Indirect comparative study

The objective of this indirect comparative study was to compare aflibercept with ranibizumab and to dexamethasone as an intravitreal implant in patients with macular oedema secondary to CRVO.

This comparison was carried out using the network meta-analysis method with two approaches, firstly the Bucher method and secondly the Bayesian method.

Four randomised, double-blind, phase III superiority studies versus placebo were included in the analysis:
- the GALILEO and COPERNICUS studies for aflibercept
- the CRUISE study for ranibizumab
- the GENEVA 008 and GENEVA 009 studies for dexamethasone. Because these studies included patients with either a central retinal vein occlusion (CRVO) or a branch retinal vein occlusion (BRVO), the results of the comparisons with dexamethasone will not be described.

The results were analysed after 6 months in terms of a gain of visual acuity of ≥ 15 letters.

Bucher method:
Comparison of aflibercept with ranibizumab: OD = 1.53; 95% CI = [0.71; 3.32]

Bayesian random effect method:
Comparison of aflibercept with ranibizumab: OD = 1.56; 95% CI = [0.11; 23.30]

Conclusion: The results obtained by the two approaches are consistent and do not demonstrate a significant difference between aflibercept and ranibizumab.
08.2 Safety/Adverse effects

8.2.1 Data from clinical studies

Combined analysis of the GALILEO and COPERNICUS studies

The ocular adverse events were due to the injection (increase in intraocular pressure, conjunctival haemorrhage, eye pain) or due to disease progression (macular oedema, reduction in visual acuity).

In the course of the first 24 weeks, the most common ocular adverse events were: eye pain (12.8%), conjunctival haemorrhage (11.9%), and increase in intraocular pressure (7.8%), retinal exudates (6.9%), vascular disorders in the optic disc (6.0%) or the retina (5.5%) and vitreous floaters (5.0%). Eye pain is the only adverse event that is more frequent in the aflibercept group than in the sham injection group with a difference ≥ 5%.

The adverse events observed more often in the sham injection group than in the aflibercept group were events associated with the disease: reduction in visual acuity (14.1%) and macular oedema (8.5%).

From week 24 to week 52, the frequency of cystoid macular oedema, macular oedema, vitreous detachment and reduction of visual acuity was greater in the aflibercept group than in the other two treatment groups (sham injections and sham injections followed by aflibercept).

The frequency of conjunctival haemorrhages and retinal pigment epitheliopathies was higher in the sham injection/aflibercept group than in the other two groups.

The frequency of increased lacrimation, macular cysts, vascular disorders in the optic disc, retinal degeneration and retinal haemorrhages was higher in the sham injection group than in the other two groups.

Retinal fibrosis and exudate, a complication of CRVO, was observed more often in the sham injection/aflibercept group than in the aflibercept group.

Non-ocular adverse events were observed at comparable frequencies in the different treatment groups. The most common were nasopharyngitis, hypertension and headaches.

The safety profile did not change when treatment was continued for 100 weeks.

8.2.2 SPC data

The SPC states that the serious adverse events that occurred as a result or the injection procedure following three intravitreal injections of aflibercept out of 2728 injections in patients treated for macular oedema secondary to CRVO were: one endophthalmitis, one cataract and one vitreous detachment.

The most frequent adverse effects (in at least 5% of patients) cited are: conjunctival haemorrhage (15.8%), increase in intraocular pressure (12.9%), eye pain (12.6%), vitreous detachment (6.9%), vitreous floaters (5.7%), increased lacrimation (5.0%) and ocular hyperaemia (5.0%).

In addition, particular attention is devoted to the precautions for use common to all intravitreal anti-VEGFs (see SPC, section 4.4: Special warnings and precautions for use).

08.3 Summary & discussion

Two randomised double-blind studies compared intravitreal aflibercept injections with sham intravitreal injections in relation to the improvement in the best corrected visual acuity (BCVA) after 6 months of treatment in patients with macular oedema secondary to a central retinal vein
occlusion (with a visual acuity score between 20/40 and 20/320 and a central retinal thickness \( \geq 250 \mu m \)).

The studies had a common randomised double-blind phase from week 0 to week 24 (evaluation of the primary efficacy endpoint) during which the patients received monthly injections; after that the study procedures differed. In the first study, from 24 to 48 weeks, the patients treated with aflibercept received further treatment if they satisfied the retreatment criteria and the patients on sham injections continued the monthly injections. In the second study, from 24 to 48 weeks, the patients in the sham injection group were treated with aflibercept if they satisfied the retreatment criteria or by monthly sham injections if the retreatment criteria were not satisfied. After 52 weeks, the studies were followed by an open phase in which all the patients were treated with aflibercept if they satisfied the retreatment criteria or by monthly sham injections if the retreatment criteria were not satisfied.

The results of the two studies were similar. The combined analysis of the two studies showed that the percentage of patients with a gain of \( \geq 15 \) letters after 24 weeks (primary efficacy endpoint) was greater under aflibercept (60.4%) than with the sham injections (17.0%), which is an adjusted difference of 43.6%; 95% CI = [34.6; 52.6]; \( p < 0.0001 \). The adjusted mean change in the BCVA was +17.66 letters under aflibercept and -0.49 letters under placebo, which is a significant adjusted difference of +18.6 letters (\( p < 0.0001 \)).

After 52 weeks, the proportion of patients who had a gain of \( \geq 15 \) letters was 58.5% under aflibercept, 30.1% in patients treated with sham injections than aflibercept and 32.4% in patients only treated with sham injections. This results suggests that, following a delay in the start of treatment, it is not possible to catch up with the level of efficacy achieved in patients put on aflibercept at the start of the study.

The data from the open phase of the studies suggests that the efficacy of aflibercept is maintained for more than 52 weeks, with a proportion of patients with a gain in BCVA \( \geq 15 \) letters of 57.3% after 76 weeks (60.2% after 52 weeks) in the first study and 49.1% after 100 weeks (56.1%) in the second study.

The most commonly observed adverse effects (in at least 5% of patients) under aflibercept were ocular and mainly due to the injection procedure: conjunctival haemorrhage (15.8%), increase in intraocular pressure (12.9%), eye pain (12.6%), vitreous detachment (6.9%), vitreous floaters (5.7%), increased lacrimation (5.0%) and ocular hyperaemia (5.0%). The non-ocular adverse effects were mainly nasopharyngitis, hypertension and headaches. The safety profile of aflibercept in the treatment of visual impairment due to macular oedema secondary to CRVO is similar to that observed in the treatment of AMD.

There are no studies comparing aflibercept with ranibizumab because they were under development at the same time. For the record (see the opinion of 18 January 2012), the efficacy of ranibizumab was evaluated in a randomised double-blind study versus intravitreal injections in patients with visual impairment due to macular oedema secondary to CRVO with the same characteristics as those in the study relating to aflibercept (visual acuity score between 20/40 and 20/320 and central retinal thickness \( \geq 250 \mu m \)). The mean change in BCVA after 24 weeks by comparison with the baseline value (primary efficacy endpoint) was greater under ranibizumab than with the sham injections (+14.9 letters versus +0.8 letters, or a difference of +13.8 letters; \( p < 0.0001 \)). The data suggest that an improvement compared with the baseline value is maintained for 52 weeks (+12.9 letters) in patients treated with ranibizumab throughout the study.

An indirect comparative study between aflibercept and ranibizumab was carried out using two approaches, the Bayesian random effect method and the Bucher method. The results of the indirect comparison, which are consistent between the two methods of calculation, did not demonstrate a statistically significant difference between aflibercept and ranibizumab in terms of a gain in visual acuity of \( \geq 15 \) letters after 6 months.
08.4 Planned studies

No studies are planned in the indication visual impairment due to macular oedema secondary to CRVO.

09 THERAPEUTIC USE

Like OZURDEX (dexamethasone intravitreal implant) and LUCENTIS (ranibizumab intravitreal injection), EYLEA is a first-line treatment for visual impairment due to macular oedema secondary to central retinal vein occlusion. In the absence of data directly comparing between EYLEA, LUCENTIS and OZURDEX, the choice of one or other of these medicinal products should be made on the basis of their individual efficacy, the characteristics of the patient, the contraindications, the potential adverse effects and the monitoring constraints. Consequently, the age of the patient, his or her ability to travel to receive monthly injections in the case of EYLEA and LUCENTIS, the presence of the crystalline lens and the existence of glaucoma due to the increased risk of ocular hypertension and of cataract with OZURDEX, are important criteria to be taken into account when starting one or other of these treatments.

It is recommended that fluorescein angiography should be performed before starting treatment in order to rule out ischaemic forms that are not indications for anti-VEGF treatment. Since progression of the oedematous form to the ischaemic form is possible under treatment, it is recommended that this should be monitored.

No data evaluating the benefits of using a second anti-VEGF in the event of failure of the first anti-VEGF are available.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- Central retinal vein occlusion is an eye disease affecting the retina and, at its centre, the macula responsible for high-resolution vision. It results in slow circulation, infiltrations and macular oedema giving rise to reduced visual acuity.
- The functional prognosis depends on the clinical form of retinal vein occlusion: a distinction can be made between two main forms: an ischaemic form with poor visual prognosis and a form (termed oedematous) with good perfusion and a better prognosis.
- These proprietary medicinal products are intended as symptomatic treatment.
- The efficacy/adverse effects ratio is high.
- These medicinal products are first-line therapies.
- There are treatment alternatives.

- **Public health benefit:**
  - Because of the small number of cases, the public health burden of retinal vein occlusions is low.
  - The reduction of visual impairment is a public health need (GTNDO [National Technical Group for the Definition of Public Health Objectives] priority).
  - On the basis of the available data, in the short term, the proprietary medicinal product EYLEA is expected to have a moderate impact on the morbidity associated with such pathologies, primarily in terms of maintaining visual acuity.
  - In the absence of available or relevant data, the impact of EYLEA on the quality of life and the organisation of care is not quantifiable.
  - It is debatable whether the study results can be extrapolated to practice, particularly because of the uncertainties relating to the form of management (in particular, in respect of the implementation of the recommended angiography before treatment), the optimal number of injections and the retreatment criteria.
  - The proprietary medicinal product EYLEA could provide a partial response to an identified public health need in the same way as LUCENTIS and OZURDEX. However, there are no data that demonstrate a supplementary impact of EYLEA in terms of morbidity in comparison with the available alternative forms of treatment.
  - Therefore, it is not expected that EYLEA will have an impact on public health.

Taking account of these points, the Transparency Committee considers that the actual benefit of EYLEA 40 mg/ml, solution for injection in prefilled syringe and injectable solution in a vial, is substantial for adults in the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication to “treatment for adults of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)” and at the dosages in the Marketing Authorisation.

- **Proposed reimbursement rate: 65%**
010.2 Improvement in actual benefit (IAB)

EYLEA does not provide any improvement in actual benefit (level V, non-existent) compared with LUCENTIS for adults in the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).

010.3 Target population

The target population of EYLEA is defined by adult patients with visual impairment due to macular oedema secondary to central retinal vein occlusion.

According to the data from the “Beaver Dam Eye Study”\(^6\)^,\(^7\) the annual incidence of CRVO is estimated at 0.03% in a population between 43 and 84 years of age. If these figures are related to the number of people in France aged 43 years and older, the number of patients affected by CRVO each year is estimated at 10,000.\(^8\)

In the “Beaver Dam Eye Study”,\(^2\) 7 incident cases of macular oedema were identified among the 18 cases of CRVO (39%).

Thus, on the basis of these data, the number of patients each year who develop macular oedema following retinal vein occlusion is estimated at about 3900. However, these data do not allow an estimation to be made regarding the number of patients for whom treatment with EYLEA would be justified (the possibility of spontaneous regression of the macular oedema or of progression to an ischaemic form cannot be addressed, the visual acuity endpoint needs to be taken into account).

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- **Packaging**
  Appropriate for the prescribing conditions.

- **Specific requests inherent to reimbursement**
  Exception drug status.

---


\(^8\) Number of people aged 43 and older in France on 1 January 2010: 29, 453, 771 (source: http://www.insee.fr).