HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

3 April 2013

EYLEA 40 mg/ml, solution for injection in a 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)

BAYER SANTE

INN	Aflibercept
ATC code (2011)	S01LA05 (ocular anti-neovascularisation agent)
Reason for request	**Inclusion**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital Use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"EYLEA is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)"**

Actual Benefit	**Substantial actual benefit**
Improvement in Actual Benefit	**EYLEA 40 mg/ml, solution for injection in a prefilled syringe and solution for injection in a vial, does not provide an improvement in actual benefit (IAB V) compared with LUCENTIS 10 mg/ml, solution for injection.**
Therapeutic use	**EYLEA 40 mg/ml is a first-line treatment for exsudative retrofoveolar AMD in the same way as LUCENTIS 10 mg/ml.**
Recommendations	**Exception drug status** **EYLEA will need to be reassessed taking account of the results of the clinical study requested by the EMA to assess the effectiveness of a fixed administration regimen every 2 months compared with the PRN regimen based on retreatment criteria of visual acuity and the anatomical appearance of the retina after the first year of treatment.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

MA (procedure)	22 November 2012 (centralised procedure) RMP: laboratory commitment to carry out an efficacy study
Prescribing and dispensing conditions/special status	List I Prescription restricted to ophthalmology specialists

ATC Classification	2011:	
	S	Sensory organs
	S01	Ophthalmologicals
	S01L	AMD medicines
	S01LA	Ocular anti-neovascularisation agents
	S01LA05	aflibercept

02 BACKGROUND

The active substance in EYLEA, aflibercept, is a recombinant fusion protein. It differs from the anti-VEGF which are currently available by blocking all the isoforms of VEGF-A and a related molecule, the presence of placental growth factor (PIGF), and in that it has a longer duration of action.

The dosage regimen recommended in the LUCENTIS MA is therefore three initial monthly injections followed by PRN injections based on the visual acuity results. The EYLEA dosage regimen is set for the first 12 months of treatment with three initial monthly injections followed by injections every 2 months, not taking account of change in visual acuity. After this 12 month period, the interval between two injections is governed by the visual acuity results and the results of anatomical investigations.
Follow-up visits are organised every 2 months for the first year of treatment and the visit frequency in the 2nd year is determined by the doctor administering treatment. Follow-up visits are monthly for LUCENTIS.

03 INDICATION(S) CONCERNED

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

04 DOSAGE

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

Posology
The recommended dose for Eylea is 2 mg of aflibercept, equivalent to 50 microlitres.
Eylea treatment is initiated with one injection per month for three consecutive doses followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

Special populations

Hepatic and/or renal impairment
No specific studies in patients with hepatic or renal impairment were conducted with Eylea.
Available data do not suggest a need for a dose adjustment with Eylea in these patients.
Elderly population:
No special considerations are needed.

Paediatric population
Safety and efficacy have not been established in children and adolescents. There is no relevant use of Eylea in the paediatric population in the indication wet AMD. ”

05 THERAPEUTIC NEED

Laser photocoagulation to treat exsudative forms of AMD is only used in extrafoveolar forms of the disease. If retrofoveolar neovascularisation is present, laser photocoagulation is not possible and other treatments may be used.

According to the latest HAS guidelines (June 2012[1]), as soon as a diagnosis of exsudative AMD with retrofoveolar choroidal neovascularisation is made, it is recommended that treatment be started as soon as possible (< 10 days) with an intravitreal anti-VEGF regardless of the initial level of visual acuity.

Dynamic phototherapy (DPT) with a verteporfin (VISUDYNE) is no longer the first-line treatment for wet AMD with predominantly visual retrofoveolar choroidal neovascularisation. It can be used in the presence of a contraindication or failure to respond to anti-VEGF and in some clinical forms in combination with anti-VEGF (for example, polypoid vasculopathy). VISUDYNE is no longer indicated in exsudative AMD with occult choroidal neovascularisation.

Pegaptanib (MACUGEN) and ranibizumab (LUCENTIS) are the two leading anti-VEGF which have Marketing Authorisation for the indication “treatment of neovascular (wet, exsudative) AMD”. Bevacizumab (AVASTIN) is used off label from its MA.
Pegaptanib and ranibizumab have not been compared in a clinical study. However, the efficacy of ranibizumab in terms of the percentage of patients with a gain in visual acuity of ≥15 letters appears greater than pegaptanib, which is very little prescribed in practice.

The HAS recommends that one injection of ranibizumab be given monthly for 3 consecutive months (interval between two injections ≥ 4 weeks) supplemented by a follow-up phase in which it is recommended to perform every 4 weeks:
- measurement of visual acuity by ETDRS;
- fundoscopy and/or retinographs;
- optical coherence tomography.

Fluorescein angiography may be performed if necessary.

After the first three injections, repeated injection of ranibizumab is recommended in the following situations:
- persistent signs of neovascular activity with or without a fall in visual acuity;
- the lesion continues to respond to repeated treatments;
- no contraindication to continue the treatment.

A further injection may be offered during this process in the absence of signs of neovascular activity if previous attempts to discontinue the treatment or extend the reinjection intervals have resulted in neovascular recurrence.

[1] Age-related macular degeneration (AMD): diagnostic and therapeutic management. HAS (June 2012) http://www.has-sante.fr/portail/jcms/c_1311607/diagnostic-et-prise-en-charge-de-la-dmla

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicines

INN	Identical pharmacotherapeutic class	Name (Company)	Indication	Date of opinion	AB	IAB	Reimbursement
ranibizumab	Yes	LUCENTIS (Novartis Pharma)	Treatment of neovascular (wet) age-related macular degeneration (AMD) in adults	21/11/2012	Substantial	In light of the data submitted, the Committee deems that the substantial improvement in actual benefit (IAB II) of LUCENTIS 10 mg/ml is maintained for the management of patients suffering from exsudative AMD with subfoveal choroidal neovascularisation.	Yes
pegaptanib	Yes	MACUGEN (Pfizer)	Treatment of neovascular (wet) age-related macular degeneration (AMD) in adults	29/11/2006	Substantial	(IAB V) compared with VISUDYNE in the indications common to both proprietary medicinal products. (IAB III) for the management of patients suffering from subfoveal AMD in whom VISUDYNE is not indicated, particularly in scarcely visible choroidal neovascularisation.	Yes
verteporfin	No L01XD02 (photosensitizing agent for photodynamic therapy)	VISUDYNE (Novartis S.A.S.)	▪ Treatment of adult patients suffering from exsudative (wet) age-related macular degeneration (AMD) with predominantly visible subfoveal choroidal neovascularisation (CNV) ▪ Treatment of adult patients with subfoveal choroidal neovascularisation secondary to pathological myopia.	03/10/2012 (re-registration)	Substantial Substantial	▪ No change in IAB: The improvement in actual benefit is substantial (level I). (opinion of 11/10/200) ▪ No change in IAB: The improvement in actual benefit is substantial (level I). (opinion of 20/11/2002)	Yes Yes

06.2 Other health technologies

Not applicable.

Conclusion

The most relevant comparator for EYLEA is LUCENTIS, an anti-VEGF medicinal product for intravitreal injection.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSED	
	YES/NO If no, why	Population(s) MA population or restricted
United States	yes	Treatment of neovascular (wet) age-related macular degeneration (AMD) in adults
Australia	yes	
Japan	yes	
Switzerland	yes	
Germany	yes	
United Kingdom	yes	

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The efficacy evaluation of aflibercept in the treatment of exsudative AMD is based on 2 non-inferiority pivotal studies (VIEW 1 and VIEW-2) against ranibizumab 0.5 mg by monthly intravitreal injections. Both of these studies followed the same protocol. Aflibercept, administered as intravitreal injections, was evaluated in three different dosage regimens:

- 2.0 mg every 4 weeks
- 0.5 mg every 4 weeks
- 2.0 mg every 8 weeks after an induction period involving one monthly injection for 3 consecutive months (regimen validated by the MA), one sham injection being given in the 4th week.

Only results for the dosage confirmed in the MA will be described.

The dosage of ranibizumab used in these studies was the same as in the MA, MARINA and ANCHOR pivotal studies whereas the current LUCENTIS SPC recommends three consecutive monthly injections followed by a PRN regimen with monthly follow-up of patients' visual acuity.

	Joint protocol for the VIEW-1 and VIEW-2 studies
Primary objective of the study	To demonstrate non-inferiority of aflibercept compared with ranibizumab in the treatment of retrofoveal exsudative AMD including juxtafoveal choroidal neovascular lesions (CNV)
Method	Double blind, randomised, comparative study.
Inclusion criteria	▪ age ≥ 50 years old ▪ Active primary retrofoveolar CNV secondary to AMD including juxtafoveal lesions affecting the fovea, demonstrated on fluorescein angiography (FA) ▪ CNV over at least 50% of the total surface of the lesion. ▪ visual acuity in the eye being studied of between 20/40 and 20/320 (73 letter score at 25 on the ETDRS scale) ▪ agreement to follow the study design and visits ▪ ability to read.
The non-inclusion criteria included	▪ previous treatment for CNV secondary to AMD (excluding micronutrients or dietary measures) ▪ previous treatment with the anti-VEGF being studied or one under investigation (not approved by the FDA) in the treated eye. In the untreated eye, treatment with an anti-VEGF under investigation was permitted until 3 months before the study and treatment with an approved anti-VEGF was permitted during the study ▪ ocular or systemic treatment with a study substance during the 3 months before the 1st day of the study ▪ use of long-acting or systemic or intraocular corticosteroids during the 6 months before the 1st day of the study.
Treatment groups	▪ aflibercept 2.0 mg every 4 weeks (2 mg/4 w) ▪ aflibercept 0.5 mg every 4 weeks (0.5 mg/4 w) ▪ **aflibercept 2.0 mg every 8 weeks** after an induction period involving one monthly injection for 3 consecutive months (regimen validated by the MA, with one sham injection on the 4th week (2.0 mg/8 w) ▪ **ranibizumab** 0.5 mg every 4 weeks (0.5 mg/4 w) Intravitreal administration
The study process	Initial 52-week phase: the patients were treated by the administration regimens shown above. Monthly follow-up visits.

	44-week follow-up phase: patients were given the same treatment dose but at variable intervals of between 4 and 12 weeks. Monthly follow-up visits Retreatment according to predetermined criteria: ▪ increase in central retinal thickness ≥100 µm compared with the lowest value measured previously by OCT or ▪ ≥ 5 letter loss on the ETDRS scale compared with the best previous score with recurrent fluid confirmed by OCT or ▪ development or persistence of fluid confirmed by OCT or ▪ appearance of new visible neovascularisation or ▪ appearance or persistence of fluid on fluorescein angiography or ▪ new macular haemorrhage or ▪ 12 week interval since the previous intravitreal therapy.
Primary efficacy endpoint	**Percentage of patients who maintained their vision at 52 weeks, i.e. a loss of vision of <15 letters on measurement of best corrected visual acuity (BCVA) compared with baseline. Visual acuity was measured on the ETDRS scale[2] at an initial distance of 4 metres.**
The secondary endpoints included:	▪ change in BCVA at 52 weeks measured on the ETDRS scale, ▪ percentage of patients who gained at least 15 letters at 52 weeks, ▪ quality of life measured by the change in the NEI-VFQ-25 score[3]at 52 weeks.
Calculation of the number of people required	The sample size was calculated from the following assumptions: ▪ 90% of patients treated at a dose of 0.5 mg of ranibizumab would maintain their vision (defined as loss of less than 15 letters compared with baseline), ▪ 90% of patients treated with aflibercept would also maintain their vision; ▪ using a non-inferiority threshold of 10%. In order to achieve a power of 90% to demonstrate non-inferiority with an alpha risk of 0.049, 191 patients were required per group. Assuming a drop-out rate of 30% (this high rate was chosen because of the large number of available treatments), 300 patients were required for each treatment arm in the study.
Statistical analysis	Primary efficacy endpoint: Non-inferiority analysis on the PP population[4] using a predefined sequential analysis: 2 mg/4 w compared with ranibizumab, then 0.5 mg/4 w compared with ranibizumab then 2.0 mg/8 w compared with ranibizumab. The sequential analysis was continued for as long as aflibercept was shown to be non-inferior in the previous sequence. Aflibercept was deemed to be non-inferior to ranibizumab if the upper limit of the confidence interval (CI) of the (ranibizumab – aflibercept) difference was <10%, a negative difference being in favour of aflibercept. The EMA set a non-inferiority threshold of 7% in the combined analysis of the two studies. A patient was deemed to be a "non-responder" if he/she stopped the study because of treatment failure before week 36. Secondary endpoints: If aflibercept was shown to be non-inferior for the three administration regimens the

[2] The ETDRS scale is a geometric (logarithmic) progression of letter size from line to line, each line containing 5 letters. The patient reads all of the letters beginning with the top line. The examiner then scores visual acuity letter by letter rather than line by line. This scale includes five letters on each line. A three line progression through the ETDRS tables represents a doubling of visual angle.

[3] NEI-VFQ-25: score calculated based on the answers to 25 questions and ranging from "0: worst vision" to "100: perfect vision"

[4] *Per population protocol* : this includes all patients in the FAS[5] population who received at least nine doses of treatment (a sham injection is deemed to be a dose) and had at least nine visits during the initial phase with the exception of major breaches of protocol; this population includes treatment failures (defined by a fall in BCVA of at least 15 letters compared with baseline during two consecutive assessments carried out 4 weeks apart) occurring during the initial phase of the study.

	comparison was continued for the secondary endpoints. The secondary endpoints were analysed on the FAS population[5] according to the paired frequencies to test superiority of aflibercept against ranibizumab. The sequential analysis was continued for as long as aflibercept was shown to be superior in the previous sequence. Aflibercept was deemed to be superior to ranibizumab if the CI of the difference was negative.

Results of the VIEW-1 study

The numbers in the different study populations are shown in table 1.
A minimum of 300 patients were randomised into each group.

Table 1: populations in the VIEW-1 study.

n (%)	**ranibizumab 0.5 mg/4 w**	**Aflibercept**			Total
		2.0 mg /4 w	0.5mg /4 w	**2.0 mg /8 w**	
Patients randomised	**306 (100.0)**	304 (100.0)	304 (100.0)	**303 (100.0)**	1,217
FAS population	**304 (99.3)**	304 (100.0)	301 (99.0)	**301 (99.3)**	1,210
PP population	**269 (87.9)**	285 (93.8)	270 (88.8)	**265 (87.5)**	1,089

FAS: *Full analysis set*; PP: *Per Protocol*

The majority of patients (n = 1130, 92.9%) completed the first study phase of 52 weeks. 92% of these 1,130 patients entered the second phase. During the two phases a total of 179/1217 dropped out of the study early mostly on the patient's decision (60/1217, 4.9%) and because of an adverse event (38/1217, 3.1%). The death rate was 22/1217 (1.8%) throughout the study.

Patient characteristics were comparable between the groups.
Most patients were at least 75 years old (71.8%). There were more women than men (58.8%).
Mean patient's visual acuity was 55 letters with a median of 57 letters (ETDRS).
The lesions were occult (38.3%), partially visible (34.1%) or classical (26.5%). The total lesion surface area was 6.95 mm^2 and the surface area involving choroidal neovascularisation (CNV) was 6.6 mm^2.
Mean retinal thickness was 266.6 µm.

Mean NEI VFQ-25 quality of life scale at inclusion was 70.7 points.

[5] *Full Analysis Set*: this includes all patients randomised who received at least one treatment dose and had at least one assessment of their BCVA.

- **52-week results**

Primary endpoint (PP population):

The percentages of patients with a fall in BCVA of < 15 letters after treatment for 52 weeks were 94.4% in the ranibizumab 0.5 mg/4 w group and 95.1% in the aflibercept 2.0 mg/8 w group, i.e. a (ranibizumab – aflibercept) difference of -0.7% with a 95% CI of [-4.5; 3.1].

The upper limit of the 95% confidence interval of the difference between the treatments was below the non-inferiority threshold of 10% and aflibercept 2.0 mg/4 w was therefore demonstrated to be non inferior to ranibizumab 0.5 mg/4 w.

Secondary endpoints:

No statistically significant difference between aflibercept 2.0 mg/8 w and ranibizumab 0.5 mg/4 w:

- Change in BCVA at 52 weeks. +7.9 compared with +8.1 letters
- Percentage of patients with a gain in BCVA of ≥ 15 letters at 52 weeks: 30.6% compared with 30.9%
- Change in the NEI VFQ-25 quality of life score compared with baseline: +5.1 compared with +4.9 points compared with baseline of 69.6 in the aflibercept 2.0 mg/8 w group and 71.8 in the ranibizumab group.

- **96-week results:**

The efficacy of both aflibercept and ranibizumab was maintained up to 96 weeks for all criteria (see table 2).

Table 2: Results of the VIEW-1 study at 96 weeks

Endpoints:	**Ranibizumab 0.5 mg/4 w** n=304	**Aflibercept 2.0 mg/8 w** n=301
% of patients who lost < 15 letters (LOCF)	89.8	91.4
Mean change in BCVA (letters)	+7.3	+7.1
% of patients with gain of ≥ 15 letters:	30.6	32.9
Change in NEI VFQ-25 score	+4.2	+5.3

Results of the VIEW-2 study:

The numbers in the different study populations are shown in table 3.
A minimum of 300 patients were randomised into each group.

Table 3: populations in the VIEW-2 study

n (%)	**ranibizumab 0.5 mg/4 w**	aflibercept			Total
		2.0 mg /4 w	0.5mg /4 w	**2.0 mg /8 w**	
Patients randomised	**303 (100)**	313 (100)	311 (100)	**313 (100)**	1240 (100)
FAS population	**291 (96.0)**	309 (98.7)	296 (95.2)	**306 (97.8)**	1202 (96.9)
PP population	**269 (88.8)**	274 (87.5)	268 (86.2)	**270 (86.3)**	1081 (87.2)

FAS: *Full analysis set*; PP: *Per Protocol*

The majority of patients (n = 1115, 89.9%) completed the first 52-week phase of the study and entered the second phase. During the two phases, a total of 215/1240 dropped out of the study mostly on the patient's decision (77/1240, 6.2%) and for an adverse event (50/1240, 2.0%). The death rate was 20/1240 (1.6 %) throughout the study.

Patient characteristics were comparable between the groups.

Most patients were at least 75 years old. There were more women than men (55.5 %).
Mean patient visual acuity was 52.4 letters with a median of 55 letters (ETDRS).
The lesions were occult (38.4%), partially visible (35.4%), classical (25.8%) or uncategorised (0.4 %). The total lesion surface area was 8.29 mm^2 and the surface area involving choroidal neovascularisation (CNV) was 7.84 mm^2.
Mean retinal thickness was 332.5 µm.

Mean NEI VFQ-25 quality of life scale at inclusion was 70.7 points.

- **52-week results**

Primary endpoint (PP population):

The percentages of patients with a fall in BCVA of < 15 letters after treatment for 52 weeks were 94.4% in the ranibizumab 0.5 mg/4 w group and 95.6% in the aflibercept 2.0 mg/8 w group, i.e. a (ranibizumab – aflibercept) difference of -1,13% with a 95% CI of [-4.81; 2.55].

The upper limit of the 95% confidence interval of the difference between the treatments was below the non-inferiority threshold of 10% and aflibercept 2.0 mg/8 w was therefore demonstrated to be non inferior to ranibizumab 0.5 mg/4 w .

Secondary endpoints:

No statistically significant difference between aflibercept 2.0 mg/8 w and ranibizumab 0.5 mg/4 w:
- Change in BCVA at 52 weeks. +8.9 compared with +9.4 letters
- Percentage of patients with a gain in BCVA of ≥ 15 letters at 52 weeks: 31.4 % compared with 34.0 %
- Change in the NEI VFQ-25 quality of life score compared with baseline: +4.9 compared with +6.3 points, compared with 73.70 in the aflibercept 2.0 mg/8 w group and 72.9 in the ranibizumab 0.5 mg/4 w group.

- **96-week results:**

The efficacy of both aflibercept and ranibizumab was maintained up to 96 weeks for all criteria (see table 4).

Table 4: Results of the VIEW-2 at 96 weeks

Primary endpoint (mean values)	**Ranibizumab 0.5 mg/4 w** n=291	**Aflibercept 2.0 mg/8 w** n=306
% of patients who lost < 15 letters (LOCF)	93.5	91.5
Mean change in BCVA (letters)	+8.5	+8.1
% of patients with gain of ≥ 15 letters:	32.7	34.0
Change in NEI VFQ-25 score	+6.3	+5.3

Combined results of the VIEW-1 and VIEW-2 studies:
The randomised population included a total of 2457 patients, the PP population included 2170 patients and the FAS population included 2412 patients.
The demographic features of patients who were randomised were very slightly different between these two studies.
Patients in the VIEW2 study were approximately 5 years younger (73 compared with 78 years old in the VIEW1 study), had slightly larger lesions (8 mm^2 compared with 6.9 mm^2), slightly poorer visual acuity (52 letters compared with 54 letters) and slighter thicker retinas (322 µm compared with 266 µm). Fewer had a past history of hypertension (57% compared with 71%) although more had a past history of myocardial infarction (88% compared with 76%).

The results of the combined analysis were similar to those of the two studies in isolation for the primary endpoint and for the secondary endpoints at 52 and 96 weeks.

08.2 Safety/Adverse effects

- **Data from clinical studies**

VIEW-1 study

The average number of IVT per patient during the 96 weeks of the study were:
- 16.0 in the ranibizumab group
- 16.3 in the aflibercept 2.0 mg/4 w group
- 16.1 in the aflibercept 0.5 mg/4 w group
- 11.3 in the aflibercept 2.0 mg/8 w group

The adverse event rate was 6.3% in the ranibizumab group and 3.3% in the aflibercept 2.0 mg/8 w group.

The most common ocular adverse events related to treatment were:
- vitreous floaters: 0.7% in the aflibercept 2.0 mg/8 w group compared with 2.0% in the ranibizumab group.
- rise in intraocular pressure: 0.7 % compared with 1.3 %
- reduced visual acuity: 0.3 % compared with 0.3 %

The most common ocular adverse events related to the injection were:
- conjunctival haemorrhage: 44.9 % compared with 47.0 %
- eye pain: 6.6 % compared with 9.2 %
- foreign body sensation: 5.0 % compared with 3.0 %
- rise in intraocular pressure: 4.3 % compared with 5.6 %
- vitreous floaters 4.0 % compared with 7.6 %
- pain at the injection site 4.0 % compared with 4.9 %

Cases of endophthalmitis were reported in both groups: four cases (4/911, 0.4%) of endophthalmitis with aflibercept (all doses combined) and five cases (5/304, 1.6%) with ranibizumab.

The non-ocular adverse events related to treatment were:
- aflibercept 2.0 mg/8 w (1%) CVA (n = 1), proteinuria (n = 1)
- ranibizumab (0,7 %) : proteinuria (n = 1), dizziness (n =1)

No deaths attributable to treatment were reported during the study

VIEW-2 study

The average number of IVT per patient during the 96 weeks of the study were:
- 16.8 in the ranibizumab group
- 15.7 in the aflibercept 2.0 mg/4 w group
- 16.3 in the aflibercept 0.5 mg/4 w group
- 11.1 in the aflibercept 2.0 mg/8 w group.

The adverse event rate was 6.3% in the ranibizumab group and 3.3% in the aflibercept 2.0 mg/8 w group.

The main ocular adverse events related to treatment were:
- pigmented epithelial tear: 1.3 % in the aflibercept 2.0 mg/8 w group compared with 0.3 % in the ranibizumab group.
- macular degeneration: 1.0 % compared with 0.3 %

- reduced visual acuity: 1.0 % compared with 1.4 %
- cataract: 1.0 % compared with 0.0 %
- eye pain: 1.0% compared with 1.7%

The most common ocular adverse events related to the injection were:
- conjunctival haemorrhage: 9.4 % compared with 9.3 %
- eye pain: 7.2 % compared with 8.6 %
- rise in intraocular pressure: 5.9 % compared with 6.2 %
- pain at the injection site 3.3 % compared with 2.7 %
- haemorrhage at the injection site: 2.0 % compared with 2.1 %
- vitreous floaters 2.0 % compared with 3.4 %

The most common non-ocular adverse events related to treatment were:
- aflibercept 2.0 mg/8 w (3.9%): hypertension (n = 3), CVA (n = 2), ischaemic accident (n = 1), epistaxis (n = 1), allergic cough (n = 1)
- ranibizumab (2.7%): hypertension (n = 1), drowsiness (n= 1), rosacea (n = 1).

Two deaths were deemed to be related to the treatment: 1 ischaemic accident in the aflibercept 2.0 mg/8 w group and one CVA in the ranibizumab group.

- **Data from the SPC**

In summarising the two VIEW-1 and VIEW-2 studies, the SPC states that:

"The most common adverse reactions (in at least 5% of patients treated with EYLEA) were conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%) and increased intra-ocular pressure (7.2%).
Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with EYLEA and included endophthalmitis, traumatic cataract and transient increased intraocular pressure. "

In addition, particular attention is drawn to the risks of non-ocular adverse reactions due to the systemic effects of the anti-VEGF:

"Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by the Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke or vascular death (including deaths of unknown cause). The incidence in the phase 3 wet AMD studies (VIEW1 and VIEW2) during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with EYLEA compared with 3.2% (19 out of 595) in patients treated with ranibizumab. "

08.3 Summary & discussion

Aflibercept has been compared with ranibizumab in two double-blind, randomised, non-inferiority studies in patients suffering from retrofoveolar exsudative AMD.
The protocols for these studies were similar. Patients were randomised to receive:

- aflibercept according to three different dosage regimens, including the regimen in the MA, i.e. an induction phase of three monthly intravitreal injections of 2 mg for 3 months followed by one injection every 8 weeks for 52 weeks and then at variable intervals of between 4 and 12 weeks for 44 weeks.
- Ranibizumab 0.5 mg monthly injections for 52 weeks then for 44 weeks at variable intervals of between 4 and 12 weeks based on predetermined criteria of visual acuity, fluorescein angiography and OCT.

The two studies showed aflibercept to be non-inferior (when given according to the MA regimen) compared with ranibizumab in terms of the percentage of patients who lost <15 letters (ETDRS) at 52 weeks (10% non-inferiority threshold).

- First study: 95.1% for ranibizumab compared with 94.4% with aflibercept, i.e a difference of -0.7%, 95% CI = [-4.5; 3.1];
- 2nd study: 94.4% with ranibizumab compared with 95.6% with aflibercept, i.e. a difference of -1.13%, 95% CI = [-4.81; 2.55].

No significant difference was found between the treatments for the secondary endpoints measured at 52 weeks: change in visual acuity, percentage of patients who gained at least 15 letters (in the region of 30% in both studies) and quality of life measured on the NEI-VFQ-25 scale.

After 44 weeks of additional administration at variable intervals, both treatments continued to be effective in terms of the percentage of patients who lost < 15 letters, gained ≥ 15 letters, mean change in visual acuity and quality of life (NEI VFQ-25).

The safety profile of aflibercept was similar to that of ranibizumab in both studies.
The most common adverse effects related to the treatment or injection were conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%) and increased intraocular pressure (7.2%).
Four cases (0.4%) of endophthalmitis were reported with aflibercept (all doses combined) and five cases with ranibizumab (1.6%).
The non-ocular adverse events related to treatment were relatively uncommon and included cardiovascular events (first study: one CVA with aflibercept, second study: three cases of hypertension, two CVAs and one ischaemic accident with aflibercept 2 mg every 8 weeks compared with one case of hypertension with ranibizumab).

The efficacy and safety profiles of aflibercept (2 mg administered according to the MA dosage regimen) are similar to those of ranibizumab (0.5 mg as monthly injections for 52 weeks then at variable intervals for 44 weeks).
It should be noted that the dosage regimen for ranibizumab in these studies was not the one now recommended in its MA (monthly injections until the visual acuity remains stable in three consecutive monthly assessments and then retreatment on the same basis if visual acuity falls).
In the second part of the study, however, which included injections at variable intervals depending on patient follow-up criteria (visual acuity, fluorescein angiography, OCT), the proportion of patients who maintained their visual acuity remained stable with both aflibercept and ranibizumab.
There are no data to assess the merits of a fixed administration regimen compared with a PRN regimen after the first year of aflibercept treatment.

08.4 Study programme

In order to assess the utility of a fixed regimen compared with the PRN regimen, the company has made a commitment to the EMA to carry out a post-marketing efficacy study comparing the dosage regimen with routine injections every 2 months with a retreatment regimen based on visual acuity and anatomical criteria after the first year of treatment.
EYLEA will need to be reassessed by the Transparency Committee following the results of the clinical study requested by the EMA.

09 THERAPEUTIC USE

EYLEA is a first-line treatment in the same way as LUCENTIS for the treatment of retrofoveolar exsudative AMD.

The SPC describes injections every 2 months for 1 year and then retreatment based on visual and anatomical criteria after an induction phase of three monthly injections.

During the first year, follow-up investigations should be carried out every 2 months before each injection.
From the second year, if the interval between injections is greater than 2 months, the follow-up visits may be closer to each other.

According to the HAS guidelines on the diagnostic and therapeutic management of AMD (2012)[1], follow-up visits must include measurement of visual acuity, fundoscopy and OCT and if necessary, fluorescein angiography.

The criteria for stopping treatment are:
- suspected or overt hypersensitivity reaction;
- best corrected visual acuity < 15 letters on the ETDRS scale in the treated eye in two consecutive visits attributable to the AMD;
- a fall in visual acuity of ≥ 30 letters compared with baseline visual acuity or the best recorded acuity since beginning treatment in the absence of a sub-retinal haematoma or pigmented epithelial tear;
- signs of morphological deterioration of the lesion despite optimal treatment.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all of the above information, and following the debate and vote, the Committee recommends:

010.1 Actual benefit

Age-related macular degeneration (AMD) is the leading cause of blindness in France in patients over 50 years old. The severe forms of AMD which are responsible for the largest number of cases of severe reduction in visual acuity include the exsudative or neovascular forms.
This proprietary medicinal product is intended as curative therapy for the consequences of the disease.
The efficacy/adverse effects ratio for this medicinal product is high.
This medicinal product is a first-line therapy for retrofoveolar exsudative AMD.
There are treatment alternatives.

◗ Public health benefit:

The public health burden of exsudative subfoveal AMD is moderate.
Improvement in the management of AMD is a public health need (GTNDO* priority).
In light of the available data (non-inferiority study against ranibizumab), the proprietary medicinal product EYLEA is not expected to have additional impact on the morbidity of patients treated, particularly on the change in their visual acuity. In addition, the impact of aflibercept on quality of life is at the limit of clinical relevance, with no additional impact compared with ranibizumab. There are inadequate data available to demonstrate the potential impact of EYLEA on organisation of care by reducing the number of injections as:

- the comparator, ranibizumab, was administered monthly, whereas the currently approved administration regimen is a PRN regimen (depending on visual and anatomical results).
- the utility of a fixed administration regimen during the first year of treatment compared with a PRN regimen has not been assessed and
- administration of EYLEA by a fixed regimen after the first year of treatment needs to be assessed (EMA request) compared with the currently approved PRN regimen.

In addition, it is debatable whether the study results can be extrapolated to practice, particularly because of questions over the optimal number of intravitreal injections, observing the visit frequency every 2 months and the retreatment criteria.
The proprietary medicinal product EYLEA does not provide an additional response to the identified public health need.
Overall, EYLEA is not expected to have a public health benefit in this indication.

Taking account of these points, the Committee considers that the actual benefit of EYLEA 40 mg/ml, solution for injection in a disposable vial and in a prefilled syringe is <u>substantial</u> for the treatment of retrofoveolar exsudative AMD.

The Committee recommends inclusion of EYLEA 40 mg/ml, solution for injection in a disposable vial and in a prefilled syringe on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use for the treatment of retrofoveolar exsudative AMD in adults at the dosages in the MA.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

EYLEA 40 mg/ml, solution for injection in a prefilled syringe and injectable solution in a vial, does not provide an improvement in actual benefit (IAB V) compared with LUCENTIS 10 mg/ml, injectable solution.

010.3 Target population

The target population for EYLEA is the population of patients suffering from retrofoveolar exsudative AMD.
The study by Korobelnik (2006)[6] estimated the annual incidence of eyes affected by treatable AMD in France through a Markov model developed specifically to take account of mortality, duration of treatment, average age at diagnosis and the likelihood of AMD developing in the second eye. The data used in the model were obtained from an exhaustive literature review. In order to estimate the annual incidence of AMD in the first eye, the results of the Rotterdam study (van Leeuwen R. et al., 2003) were used and then standardised for age (direct standardisation method from United Nations data).
Results were obtained using the following assumptions made after a literature review to form a basic scenario:

- mean duration of treatment: 2 years,
- mean age at diagnosis of the disease: 75 years old
- incidence of AMD in the second eye, 30% during the 5 years after the diagnosis in the first eye.

The results obtained from the model using the basic scenario indicate that the number of treatable eyes for retrofoveolar exsudative AMD in 2005 was between 37,000 and 39,000. The model plans for an increase of 2% annually until 2025.
On these bases and taking account of French demographics in 2012, the number of eyes treatable for retrofoveolar exsudative AMD in 2012 can be estimated as being between 41,700 and 44,800.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescription conditions.

◗ Specific requests inherent to reimbursement
Exception drug status

◗ Request for data
EYLEA will need to be reassessed taking account of the results of the clinical study requested by the EMA to evaluate the effectiveness of a fixed administration regimen every 2 months compared with the PRN regimen based on retreatment criteria of visual acuity and the anatomical appearance of the retina after the first year of treatment.

[6] Korobelnik JF et al. Estimating the yearly number of eyes with treatable neovascular aged-related macular degeneration using a direct standardization method and a Markov Model. IOVS 2006;47(10):4270-76.