HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

4 December 2013

LUCENTIS 10 mg/mL, solution for injection

Vial of 0.23 mL (CIP: 34009 378 101 5 9)

Applicant: Novartis Pharma S.A.S.

INN	ranibizumab
ATC code (2013)	S01LA04 (ocular anti-neovascularisation agent)
Reason for the review	**Extension of indication**
List concerned	**National Health Insurance** (Social Security Code L.162-17) **Inclusion for hospital use** (Public Health Code L.5123-2)
Indications concerned	**"The treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia."**

Actual Benefit	**Substantial actual benefit**
Improvement in Actual Benefit	**LUCENTIS 10 mg/mL, solution for injection provides a moderate improvement in actual benefit (level III) in terms of efficacy in comparison with VISUDYNE in the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia.**
Therapeutic use	**1st line treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date of Marketing Authorisation (centralised procedure): 22 January 2007 Amendment to Marketing Authorisation: - 19 December 2007 (change in packaging) - 6 January 2011 (extension of indication to treatment of visual impairment due to diabetic macular oedema) - 27 May 2011 (extension of indication to treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion) - 8 July 2013 (extension of indication to treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia) Risk management plan
Prescribing and dispensing conditions / special status	List I Prescription-only medicine restricted to ophthalmologists Exception drug status

ATC Classification	2013	
	S	Sensory organs
	S01	Ophthalmologicals
	S01L	Ocular vascular disorder agents
	S01LA	Antineovascularisation agents
	S01LA04	ranibizumab

02 BACKGROUND

An application has been made for inclusion of LUCENTIS on the list of medicines refundable by National Health Insurance and medicines approved for hospital use in the extension of indication to treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

03 THERAPEUTIC INDICATIONS

"LUCENTIS is indicated in adults for:
- The treatment of neovascular (wet) age-related macular degeneration (AMD).
- The treatment of visual impairment due to diabetic macular oedema (DME).
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).
- **The treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)."**

04 DOSAGE

"LUCENTIS must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Posology for the treatment of wet AMD
The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL.
Treatment is given monthly and continued until maximum visual acuity is achieved i.e. the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment.
Thereafter patients should be monitored monthly for visual acuity.
Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month.

Posology for the treatment of visual impairment due to either DME or macular oedema secondary to RVO
The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL.
Treatment is given monthly and continued until maximum visual acuity is achieved i.e. the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended.
Thereafter patients should be monitored monthly for visual acuity.
Treatment is resumed when monitoring indicates loss of visual acuity due to DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month.

LUCENTIS and laser photocoagulation in DME and in macular oedema secondary to BRVO
There is some experience of Lucentis administered concomitantly with laser photocoagulation (see section 5.1). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. LUCENTIS can be administered in patients who have received previous laser photocoagulation.

Posology for the treatment of visual impairment due to CNV secondary to PM
Treatment is initiated with a single injection.
If monitoring reveals signs of disease activity, e.g. reduced visual acuity and/or signs of lesion activity, further treatment is recommended.
Monitoring for disease activity may include clinical examination, optical coherence tomography (OCT) or fluorescein angiography (FA).
While many patients may only need one or two injections during the first year, some patients may need more frequent treatment (see section 5.1[1]).
Therefore, monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician.
The interval between two doses should not be shorter than one month.

LUCENTIS and VISUDYNE photodynamic therapy in CNV secondary to PM
There is no experience of concomitant administration of LUCENTIS and VISUDYNE.

[1]Of the SPC.

Special populations
Hepatic impairment
LUCENTIS has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population.

Renal impairment
Dose adjustment is not needed in patients with renal impairment (see section 5.2[1]).

Elderly
No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME."

05 THERAPEUTIC NEED

In 5% of cases, pathologic myopia is complicated by choroidal neovascularisation (CNV), which results in progressive and irreversible loss of visual acuity, particularly central vision, leading to blindness. This complication occurs as readily in young patients as in elderly patients. Pathologic myopia is the leading cause of choroidal neovascularisation in patients aged under 50 years. Subfoveal CNV, the most common form, is associated with a poor prognosis.
Photodynamic therapy using verteporfin (VISUDYNE) as a photosensitiser is currently the only treatment for subfoveal CNV secondary to pathologic myopia. VISUDYNE only maintains visual acuity.

In the case of extrafoveal CNV, laser photocoagulation (direct destruction) may be considered but its results are disappointing in the long term because of the relapse rate (up to 72%) and the extension of photocoagulation scarring towards the fovea.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

VISUDYNE 15 mg, powder for solution for infusion (NOVARTIS) is the only comparator for LUCENTIS.
In its opinion of 20 November 2002 (inclusion), the Committee considered that this proprietary medicinal product provided a substantial (level I) improvement in actual benefit in patients with subfoveal choroidal neovascularisation due to pathologic myopia.
In its opinion of 17 October 2012 (renewal of listing), the Committee considered that the actual benefit of VISUDYNE remained substantial.

06.2 Other health technologies

Laser photocoagulation (extrafoveal forms only).

Conclusion
VISUDYNE is the only clinically relevant comparator.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

To date, the extension of indication of LUCENTIS in the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia is not reimbursed in any country.
Reimbursement has been requested in the countries where LUCENTIS is already marketed: Germany, the United Kingdom, Italy and Spain.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

This assessment of ranibizumab's efficacy in the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia is based on a randomised, double-blind study that compared ranibizumab, administered according to two treatment regimens based on visual acuity or disease activity, to verteporfin over 12 months (the RADIANCE study).

Primary objective: To demonstrate the superiority of ranibizumab, administered according to two different treatment regimens, to verteporfin in terms of mean average best corrected visual acuity (BCVA) change from month 1 to month 3 compared to baseline in patients with visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

Method: A randomised, double-blind, double-dummy study (sham intravitreal injection and sham photodynamic therapy session) with a total duration of 12 months.

Study design:
On inclusion, patients were randomised into 3 treatment groups (2:2:1 randomisation):

- **"Ranibizumab/stabilisation":** Ranibizumab 0.5 mg administered according to visual acuity stabilisation criteria. Stabilisation was defined as no change in BCVA as compared with the two previous monthly visits.

  Patients received 2 successive injections on inclusion and at month 1, then:
  - treatment stopped when BCVA stabilisation criteria were met (month 2 at the earliest);
  - if BCVA deteriorated, monthly injections were resumed until stabilisation across 3 consecutive monthly evaluations.

  "Ranibizumab/activity": Ranibizumab 0.5 mg administered according to disease activity criteria. Disease activity was defined as a visual impairment attributable to intraretinal or subretinal fluid or active leakage secondary to pathologic myopia (OCT examination and/or fluorescein angiography).Patients received 1 injection on inclusion. At month 1, injections were suspended if no disease activity was detected. They were resumed as soon as the activity criteria were met and continued until this was no longer the case.

- **"Verteporfin PDT":** One session of photodynamic therapy with verteporfin on inclusion, then from 3 months, depending on disease activity patients could receive:
  - ranibizumab 0.5 mg, or

- verteporfin PDT, or
- a combination of ranibizumab + verteporfin PDT.

Treatment had to be suspended if disease activity criteria were not met, and resumed if they recurred.

One eye per patient was selected and treated.
Double blinding was maintained by using a placebo in each group (sham intravitreal injection or sham PDT) and visual acuity examinations and investigations for signs of disease activity were performed by an investigator who were masked to the treatment assignment; a separate investigator was responsible for deciding on treatment.

Inclusion criteria:

- Age ≥ 18 years
- Diagnosis of active CNV secondary to pathologic myopia confirmed by eye examination using the following criteria:
  - pathologic myopia (> -6D spherical equivalence)
  - ocular ultrasound or biometry showing anterior-posterior elongation ≥ 26 mm
  - presence of posterior changes compatible with pathologic myopia, visible on ophthalmoscopy and fundus photography
  - active leakage from CNV visible on fluorescein angiography
  - intraretinal or subretinal fluid or increase in central retinal thickness visible on OCT
- At least one of the following lesions in the eye studied:
  - subfoveal
  - juxtafoveal (< 200 µm from the centre) with involvement of the central macular area
  - extrafoveal (> 200 µm from the centre) with involvement of the central macular area
  - at the edge of the optic disc with involvement of the central macular area
- BCVA ≥ 24 and ≤ 78 letters (ETDRS), i.e. approximately 20/32 to 20/320, at a distance of 4 metres.
- Visual loss only due to the presence of any eligible types of CNV secondary to pathologic myopia based on clinical ocular findings, fluorescein angiography (FA), and optical coherence tomography (OCT) data.

Principal exclusion criteria:

- Confirmed hypertension with systolic pressure > 150 mmHg or diastolic pressure > 90 mmHg
- History of hypersensitivity to the products studied or to fluorescein
- History of a stroke
- The presence of choroidal neovascularisation due to any cause other than pathologic myopia
- Intraocular inflammation or active infection or active or suspected periocular infection in either eye at the time of recruitment
- Uncontrolled glaucoma in either eye at the time of selection (IOP ≥ 25 mmHg)
- Iris neovascularisation in either eye
- Amblyopia or ocular disease with a corrected visual acuity < 20/200 or amaurosis in the other eye
- **History of the following treatments:**
  - pan-retinal laser photocoagulation or focal/grid laser photocoagulation in the eye studied at any time
  - intraocular treatment with any vascular endothelial growth factor (VEGF) inhibitor or verteporfin in the eye studied
  - intravitreal corticosteroid treatment in the eye studied within 3 months of randomisation
  - intraocular surgery in the eye studied within 3 months of randomisation
- History or presence of porphyria (verteporfin contraindication)
- Pregnant or breastfeeding women and women of childbearing age

Primary efficacy endpoint: Analysis of superiority to verteporfin in terms of mean average BCVA change from month 1 to month 3 compared to baseline.

Secondary endpoints included:

- Non-inferiority analysis in the intention-to-treat (ITT) population between the 2 ranibizumab re-treatment regimens, in terms of mean average BCVA change from month 1 to month 6 compared to baseline: ranibizumab/stabilisation was considered non-inferior to ranibizumab/activity if the upper limit of the 95% confidence interval for the difference between the treatments was below the non-inferiority margin (+5 letters). Analysis in the per-protocol population (PP), the more rigorous approach for a non-inferiority analysis, was treated as a sensitivity analysis.
- Mean change in BCVA over month 12 in comparison with baseline.
- Percentage of patients with a gain in BCVA of ≥ 15 letters or achieving ≥ 84 letters (ETDRS) at 3 months.
- Change in visual function at 3 months measured with the VFQ-25 score[2]

Results:

A total of 277 patients were randomised (2:2:1), comprising 106 in the ranibizumab/stabilisation group, 116 in the ranibizumab/activity group and 55 in the verteporfin group.

No patients withdrew from the study due to adverse effect. One patient in the ranibizumab/stabilisation group stopped the study early, on D38, due to a protocol deviation (blood pressure outside the inclusion values) and 2 patients left in month 3 of the study (1 patient was lost to follow-up, the other withdrew consent). In the verteporfin group, 2 patients who received ranibizumab before month 3 were maintained in the verteporfin group analysis.

Patient characteristics were comparable among the groups. Patients had a mean age of 55 years (19.9% were under 45). The mean BCVA at inclusion was 55.4 letters (54.7 to 55.8 letters across all 3 groups). The neovascularisation was subfoveal in 68.6% of patients, juxtafoveal in 23.8% and extrafoveal in 4.0% of patients. The mean axial length at inclusion was 29.1 mm. The refractive error was -13.7 D in the ranibizumab/stabilisation group, -11.6 D in the ranibizumab/activity group and -12.2 D in the verteporfin group.

During the first 3 months of the study, patients received an average of 2.5 injections in the ranibizumab/stabilisation group and 1.8 injections in the ranibizumab/activity group.
Over the 12-month period, patients in the ranibizumab/stabilisation group received 4.6 injections, patients in the ranibizumab/activity group received 3.5 injections and those in the verteporfin then ranibizumab group received 3.2 injections. Of the 53 patients who were treated with verteporfin at inclusion, 38 (71.7%) had at least one ranibizumab injection during the year and 15 (28.3%) did not.

In the verteporfin group, all patients had one treatment at inclusion. Re-treatments were administered in accordance with the protocol except for 2 cases. Of the 55 patients included, 2 received ranibizumab in the first 3 months (protocol deviation) and 38 received ranibizumab after 3 months. Fifteen patients were never treated with ranibizumab and 2 of these had a second verteporfin treatment. During the 12 months of the study, no patients were treated with combined verteporfin + ranibizumab.

Primary efficacy endpoint:

[2]VFQ-25: a composite score covering 12 areas: general health, ocular pain, activities related to near vision and distance vision, social functioning, wellbeing/distress, role limitations, dependency, driving, colour vision and peripheral vision. The total score ranges from 0 (worst visual function) to 100 (perfect visual function).

The mean averageBCVA change from month 1 to month 3 compared to baseline was +10.5 letters in the ranibizumab/stabilisation group, +10.6 letters in the ranibizumab/activity group and +2.2 letters in the verteporfin group.
Superiority to verteporfin was demonstrated for both ranibizumab groups (stabilisation and activity) ($p < 0.00001$; see Table 1).

Table 1: Mean average BCVA change (ETDRS) from month 1 to month 3 compared to baseline (ITT population[3])

	Ranibizumab		**Verteporfin PDT**
	Stabilisation N = 106	**Activity N = 116**	**N = 55**
Mean baseline BCVA	55.4 ± 13.4	55.8 ± 12.6	54.7 ± 13.8
Mean change in BCVA from M1 to M3	66.0 ± 13.0	66.4 ± 12.3	56.9 ± 14.5
Mean change in BCVA from baseline to M1 through M3 compared to baseline	10.5 ± 8.2*	10.6 ± 7.3*	2.2 ± 9.5

* $p < 0.00001$ versus verteporfin

Secondary endpoints:

- Non-inferiority analysis of the 2 ranibizumab re-treatment regimens in terms of mean average BCVA change from month 1 to month 6 compared to baseline:
ITT population:
The mean average BCVA change from month 1 to month 6 compared to baseline was +11.9 letters in the ranibizumab/stabilisation group and +11.7 letters in the ranibizumab/activity group, with a difference of -0.1 letters (95% CI = [-2.2; 2.0]). The upper limit of the 95% CI for the difference between the treatments was below the non-inferiority margin (+5 letters).

PP population[4]:
The mean average BCVA change from month 1 to month 6 compared to baseline was +12.1 letters in the ranibizumab/stabilisation group and +11.9 letters in the ranibizumab/activity group, i.e. a difference of -0.2 letters (95% CI = [-2.6; 2.1]). The upper limit of the 95% CI for the difference between the treatments was below the non-inferiority margin (+5 letters).

- Mean change in BCVA at 12 months compared to baseline
At 3 months, the mean change in BCVA compared to baseline was +12.1 letters in the ranibizumab/stabilisation group, +12.5 letters in the ranibizumab/activity group and +1.4 letters in the verteporfin group.
At 12 months, the gain from baseline BCVA was maintained with +13.8 letters in the ranibizumab/stabilisation group and +14.4 letters in the ranibizumab/activity group, with no significant difference between these groups.
The mean change in BCVA at 12 months compared to baseline was +9.3 letters in patients treated with verteporfin then potentially ranibizumab from month 3. The VISUDYNE group was not compared to the ranibizumab groups.

- Percentage of patients with a gain in BCVA of ≥ 15 letters or achieving ≥ 84 letters (ETDRS) at 3 months
The percentage of patients with a gain in BCVA of ≥ 15 letters or achieving ≥ 84 letters (ETDRS) at 3 months was higher in the ranibizumab/stabilisation (38.1%) and ranibizumab/activity groups

[3]Intention-to-treat population defined as patients who received at least one treatment and had at least one post-inclusion measurement of visual acuity.
[4]Per-protocol population defined as patients who took part in the study up to month 6 without any major deviations from the protocol.

(43.1%) than in the verteporfin group (14.5%), with a difference of 23.5% in favour of the ranibizumab/stabilisation group (p = 0.0020) and 28.6% in favour of the ranibizumab/activity group (p = 0.0002).

- Change in visual function at 3 months: VFQ-25 score
At inclusion, the VFQ-25 score was 69.3 D in the ranibizumab/stabilisation group, 71.0 D in the ranibizumab/activity group and 71.9 D in the verteporfin group.
At 3 months, the change in VFQ-25 score was +5.0 with ranibizumab/stabilisation, +3.9 with ranibizumab/activity and +0.3 with verteporfin. A statistically significant difference in favour of ranibizumab over verteporfin was only observed with ranibizumab/stabilisation. However, this difference cannot be considered as clinically relevant (the score ranges from 0 to 100). No statistically significant difference was observed between the two ranibizumab groups.

08.2 Adverse effects

8.2.1 RADIANCE Study

No patients in this study withdrew early due to an adverse event. Six patients stopped ranibizumab treatment temporarily because of an abnormal lab test.

- Safety at 3 months

The safety analysis population at 3 months comprised 106 patients in the ranibizumab/stabilisation group, 118 patients in the ranibizumab/activity group and 53 patients in the verteporfin group.

The percentage of patients who had an **ocular adverse event** in the eye studied was 27.4% in the ranibizumab/stabilisation group, 13.6% in the ranibizumab/activity group and 9.4% in the verteporfin group. These adverse events were primarily conjunctival haemorrhage observed in the ranibizumab/stabilisation (9.4%) and ranibizumab/activity (5.1%) groups, and punctate keratitis (5.7% and 2.5% respectively). The other, less frequent (< 3%) ocular adverse events were dry eye, ocular pain and increased IOP (1.9% in the ranibizumab/stabilisation group and 1.7% in the ranibizumab/activity group).
In the verteporfin group, the ocular events observed were punctate keratitis (n = 2, 3.8%) and increased IOP (1.9%).

The adverse events of interest were uncommon in the ranibizumab groups: 1 case of endophthalmitis (uveitis), 1 case of retinal tear, 4 cases of increased IOP, 5 cases of ocular hypersensitivity reaction, 1 case of glaucoma (ocular hypertension) and 4 cases of hypertension.

Non-ocular adverse events were observed in 25.5% of patients in the ranibizumab/stabilisation group, 25.4% of patients in the ranibizumab/activity group and 11.3% of those in the verteporfin group. Their frequency was less than 5%. In the groups treated by ranibizumab, these adverse events were nasopharyngitis, headache, pharyngitis, upper respiratory tract infections, lumbar pain, hypertension, asthenia, haemorrhoids and dental problems. In the verteporfin group, one case of nasopharyngitis (1.9%) and one case of hypertension (1.9%) were observed.

- Safety at 12 months

After 3 months, patients in the verteporfin group could receive either ranibizumab or verteporfin or ranibizumab plus verteporfin as decided by the investigator. Of the 53 patients in the verteporfin group, 38 patients received ranibizumab after 3 months and 15 did not receive ranibizumab.

The percentage of patients having had an **ocular adverse event** after 12 months was:
- 43.4% in the ranibizumab/stabilisation group and 37.3% in the ranibizumab/activity group;
- 42.1% in patients treated initially with verteporfin, then with ranibizumab;
- 26.7% in patients who did not pursue their treatment with ranibizumab.

In the two ranibizumab/stabilisation and ranibizumab/activity groups, the most common ocular adverse event was conjunctival haemorrhage (11.3% and 10.2%). The other ocular adverse events

were observed in variable proportions between the two groups. The events noted were punctate keratitis in 7.5% of patients in the ranibizumab/stabilisation group (2.5% in the ranibizumab/activity group), vitreous floaters (4.7% and 0.8%), dry eye (3.8% and 1.7%), ocular pain (3.8% and 3.4%), increased IOP (2.8% and 5.9%) and allergic conjunctivitis (0.9% and 4.2%).

Among the serious ocular adverse events, one case of corneal erosion suspected to be related to the injection procedure was observed in the ranibizumab/stabilisation group during the first 3 months of the study.

In the ranibizumab groups, the adverse events of interest were: 2 cases of endophthalmitis (2 cases of uveitis), 5 cases of intraocular inflammation, 5 cases of cataract, 10 cases of transient increased IOP, 3 cases of retinal tear (1 case suspected to be related to the injection procedure and 2 cases considered as unrelated to either the procedure or the product), 12 cases of ocular hypersensitivity, 6 cases of hypertension, 5 cases of non-ocular haemorrhage (subdural, gastro-mediastinal, rectal or uterine) and 1 case of another (non-myocardial) thromboembolic arterial event.

In patients treated with verteporfin only, the ocular adverse events were dry eye (1/15), ocular pain (1/15) and posterior capsule opacification (1/15).

The percentage of **non-ocular adverse events** was 45.3% in the ranibizumab/stabilisation group, 43.2% in the ranibizumab/activity group, 50% in the verteporfin then ranibizumab group and 33.3% in the verteporfin only group.

The most common non-ocular adverse events in the ranibizumab/stabilisation and ranibizumab/activity groups were nasopharyngitis (11.3% and 10.2%) and headache (7.5% and 9.3%), and to a lesser extent, hypertension (2.8% and 4.2%) and upper respiratory tract infections (2.8% and 3.4%). Hypertension was also observed in 7.9% of patients treated with verteporfin then ranibizumab, but not in any patients treated with verteporfin alone. In the latter group, the most common non-ocular adverse events were nasopharyngitis (2/15), pain in extremities (1/15), dental caries (1/15) and tinnitus (1/15).

8.2.2 RISK MANAGEMENT PLAN

The risk management plan provides for special monitoring of the following risks:

- "Identified" important risks:
  - hypersensitivity reactions
  - retinal pigmented epithelial tear
  - endophthalmitis
  - retinal detachment
  - retinal tear
  - cataracts
  - intraocular inflammation
  - elevated intraocular pressure
  - vitreous haemorrhage
  - glaucoma

- "Potential" important risks:
  - hypertension
  - non-ocular haemorrhage
  - proteinuria
  - myocardial infarction
  - non-myocardial arterial thromboembolic events
  - venous thromboembolic events
  - deterioration in retinal blood flow (including central retinal artery occlusion)

8.2.3 SPC DATA

Since the previous Transparency Committee opinion (in September 2012), the SPC was modified on 17 January 2013 in the sections "Special warnings and precautions for use" and "Undesirable effects", and was updated by the decision of 4 July 2013 regarding the extension of indication in pathologic myopia in order to state the risk of systemic effects linked to intravitreal use of VEGF inhibitors (harmonisation of SPCs for intravitreal VEGF inhibitors):

Special warnings and precautions for use[5]
[…]
"~~History of stroke or transient ischaemic attacks~~ **Systemic effects following intravitreal use**
Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors.
There are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients ~~due to the potential risk of thromboembolic arterial events following intravitreal administration of VEGF (vascular endothelial growth factor) inhibitors~~ (see section 4.8)."

Undesirable effects
[…]
"Product-class-related adverse reactions
In the wet AMD phase III studies, the overall frequency of non-ocular haemorrhages, an adverse event potentially related to systemic VEGF (vascular endothelial growth factor) inhibition, was slightly increased in ranibizumab-treated patients. However, there was no consistent pattern among the different haemorrhages. There is a theoretical risk of arterial thromboembolic events, **including stroke and myocardial infarction**, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the LUCENTIS clinical trials in patients with AMD, DME, RVO and PM and there were no major differences between the groups treated with ranibizumab compared to control."

08.3 Summary & discussion

The efficacy and safety of ranibizumab in the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia were evaluated in a randomised, double-blind, double-dummy study over 12 months which compared two ranibizumab treatment regimens to photodynamic therapy using verteporfin (VISUDYNE) as a photosensitiser.
The two ranibizumab (0.5 mg) treatment regimens used re-treatment criteria based either on stabilisation of visual acuity (ranibizumab/stabilisation) or on signs of disease activity (ranibizumab/activity):

- Ranibizumab/stabilisation: stabilisation was defined as the absence of any change in best corrected visual acuity (BCVA) from the two previous monthly visits.
  Patients received 2 successive injections at 1-month intervals, then:
  - treatment stopped when BCVA stabilisation criteria were met, in month 2 at the earliest;
  - if BCVA deteriorated, monthly injections were resumed until stabilisation across 3 consecutive monthly evaluations.
- Ranibizumab/activity: disease activity was defined as the presence of visual impairment attributable to the presence of intraretinal or subretinal fluid or to an active leakage secondary to pathologic myopia (OCT examination and/or fluorescein angiography).
  Patients received 1 injection then from month 1, the injections were only resumed if the activity criteria were met. Injections were then continued until the activity criteria were no longer met.

[5]Deleted text: text removed from the old version.
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The “photodynamic therapy” group used verteporfin (VISUDYNE) as a photosensitiser (one session) then from 3 months, depending on disease activity, a new session of photodynamic therapy or ranibizumab (0.5 mg) or both could be given.

Only 15 patients were treated with verteporfin alone up until 12 months.

The 277 randomised patients (2:2:1), comprising 106 in the ranibizumab/stabilisation group, 116 in the ranibizumab/activity group and 55 in the verteporfin group, had a mean age of 55 years and primarily had subfoveal choroidal neovascularisation (68.6%). The number of injections given during the 12-month period was 4.6, 3.5 and 3.2 in the ranibizumab/stabilisation, ranibizumab/activity and verteporfin then ranibizumab groups respectively.

After 3 months:
- The mean average BCVA change (ETDRS scale) from month 1 to month 3 compared to baseline (the primary endpoint) superior in the ranibizumab/stabilisation (+10.5 letters) and ranibizumab/activity (+10.6 letters) groups than in the verteporfin group (+2.2 letters, $p < 0.00001$). These differences are clinically relevant (≥ +5 letters).
- The percentage of patients with a gain in BCVA of ≥ 15 letters or achieving ≥ 84 letters (ETDRS) was higher in the ranibizumab/stabilisation (38.1%) and ranibizumab/activity (43.1%) groups than in the verteporfin group (14.5%), with a difference of 23.5% in favour of the ranibizumab/stabilisation group ($p = 0.0020$) and 28.6% in favour of the ranibizumab/activity group ($p = 0.0002$).

After 6 months, the mean average BCVA change (ETDRS scale) from month 1 to month 6 compared to baseline was non-inferior between the ranibizumab/stabilisation (+11.9 letters) and ranibizumab/activity (+11.7 letters) groups. Indeed, the difference was -0.1 letter (95% CI = [2.2; 2.0]), with the upper limit of the confidence interval being below the predefined non-inferiority margin of +5 letters.

At 12 months, no significant difference was observed between the ranibizumab/stabilisation and ranibizumab/activity groups in terms of mean change in BCVA from baseline (+13.8 letters versus +14.4 letters, i.e. a difference of 0.6 letters). The mean change in BCVA was +9.3 letters in patients in the verteporfin group (who could receive ranibizumab from month 3) Due to the possibility of ranibizumab treatment from month 3, the verteporfin group was not compared to the ranibizumab/stabilisation and ranibizumab/activity groups at 12 months; however, these results suggest that delaying the initiation of ranibizumab treatment do not permit to achieve the same level of efficacy found in patients immediately treated with ranibizumab.

After 12 months, the safety profile of ranibizumab in patients with visual impairment due to choroidal neovascularisation secondary to pathologic myopia was consistent with the safety profile for other indications. The percentages of ocular adverse events were 43.4% and 37.3% in the ranibizumab/stabilisation and ranibizumab/activity groups respectively. The main adverse events were conjunctival haemorrhage (11.3% and 10.2%), punctate keratitis (7.5% and 2.5%), vitreous floaters (4.7% and 0.8%), dry eye (3.8% and 1.7%), ocular pain (3.8% and 3.4%) and increased IOP (2.8% and 5.9%). Systemic adverse events including non-ocular haemorrhages and (non-myocardial) arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, necessitating caution if there is a history of cerebrovascular accident or transient ischaemic attacks.
No conclusions on safety in comparison to verteporfin can be drawn, since only 15 patients were treated with verteporfin alone overl month 12.

08.4 Planned studies

The EMA has recommended undertaking an observational study including 300 patients in order to study the long-term (3 years) efficacy and safety of ranibizumab in the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia, the course of the

disease after stopping treatment, efficacy in patients with a history of verteporfin treatment, and combinations with laser therapy or verteporfin.
Data are expected from patients with peripapillary atrophy (in late 2013).
In addition, patients with pathologic myopia will be included in the ongoing LUMINOUS observational study (monitoring long-term efficacy and safety in patients treated with ranibizumab) and will be followed up for 2 years (end of study: early 2017).

09 THERAPEUTIC USE

As LUCENTIS permit to gain visual acuity at 12 months, whereas VISUDYNE only maintains visual acuity (VIP study results), LUCENTIS is now the first-line therapy for visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia.
However, the data are very limited in patients with extrafoveal CNV, only 4% of the population included in the RADIANCE study.

Initial treatment with VISUDYNE followed by treatment with LUCENTIS is not recommended. Indeed, the data, although limited, from 3 published studies (Chan et al. Br J Ophthalmol 2009, Ruiz-Moreno et al. Br J Ophthalmol 2009[6]) and from the RADIANCE study (38 patients in the verteporfin group were treated with ranibizumab after 3 months) suggest that delayed treatment with LUCENTIS do not permit to achieve maximum improvement in vision.

The initial diagnosis of choroidal neovascularisation should be confirmed with a fluorescein angiography and an optical coherence tomography (OCT) before treatment with ranibizumab. This measures the size of any neovessels, and allows to differentiate it from an haemorrhage caused by rupture of the Bruch's membrane, which improves spontaneously but has a clinical picture very similar to a neovascularisation.

The follow-up requires a careful evaluation of visual acuity, fundus examination, and OCT which helps guide for re-treatment (reduction in visual acuity and/or signs of disease activity). Retinal angiography may be necessary, especially in case ofvisual impairment difficult to explain with OCT and/or if OCT is difficult to interpret due to the particular anatomical features of pathologic myopia (distension of the posterior pole related to excessive axial lengthening in myopic eyes, thinning of the retina, choroid and sclera) and the infiltration of fluid which is often undetected in these patients (only 34.5% to 40.5% of patients in the RADIANCE study had fluid infiltration on OCT at diagnosis). Angiography may show an extension of the neovessels which is not always get with a clear fluid infiltrate or retina thickening shown on OCT.

A specific monitoring of the risk of retinal tear and retinal detachment is recommended in patients with pathologic myopia. Indeed, the important risk of retinal tear and retinal detachment associated with pathologic myopia can be added to the risk of retinal tear associated with ranibizumab treatment. In the RADIANCE study, 3 of the 262 patients treated with ranibizumab (1.14%) had a retinal tear. Retinal tear and detachment are included in the adverse events monitored by the risk management plan.

[6] EPAR: EMA/716504/2012 (30 May 2013).

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗The neovascular complications of pathologic myopia are among the most sudden and can cause substantial disability through the loss of central vision. This disability has all the more consequences since it often occurs in patients of working age.

◗This proprietary medicinal product is intended as curative therapy for the consequences of the disease.

◗The efficacy/adverse effects ratio is high. Further data are needed on the long-term efficacy and safety of ranibizumab in patients previously treated with VISUDYNE or laser photocoagulation.

◗This proprietary medicinal product is a first-line therapy for visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

◗There is a less effective treatment alternative: photodynamic therapy with VISUDYNE.

◗Public health benefit:

Pathologic myopia, which would affect 2% to 4% of adults,[7] is complicated in 5% of cases by choroidal neovascularisation resulting in a progressive and irreversible loss of visual acuity, leading to blindness. The burden of this rare but serious disease (pathologic myopia complicated by choroidal neovascularisation leading to visual impairment) can therefore be considered as low.

Reducing the frequency of vision disorders, in children and adults, is one of the objectives of the Law of 9 August 2004 and constitutes a public health need.

In view of the short-term and medium-term data available, the impact of LUCENTIS on reducing morbidity (visual acuity) is low, especially since a negative impact cannot be ruled out in view of the safety data (particularly retinal tears). The potential anticipated impact on the quality of life of treated patients, through improvement of their visual acuity, has not been demonstrated. LUCENTIS is not expected to have any impact on the organisation of healthcare.

There is no guarantee that these data are transposable to everyday practice, primarily because of the selection criteria for patients in the study, in particular the lack of previous treatment with VEGF inhibitors and/or verteporfin, uncertainty on the optimal number of intravitreal injections and doubts on the efficacy maintenance in the long term.

LUCENTIS therefore provides a partial response to an identified public health need.

Overall, LUCENTIS is expected to benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of LUCENTIS 10 mg/mL, solution for injection is substantial in the "treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia".

[7]Affortit-Demoge A, Metge-Galatoire F, Metge P. Myopie Forte. EMC (Elsevier Masson SAS, Paris), Ophtalmologie, 21-244-A-20, 2011.

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 extension of indication to "treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia" and at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit

LUCENTIS 10 mg/mL, solution for injection provides a moderate improvement in actual benefit (level III) in terms of efficacy in comparison with VISUDYNE in the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

010.3 Target population

The target population for LUCENTIS is defined as patients with visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

Pathologic myopia would affect 2% to 4% of adults,[8] which in the French population (INSEE 2013 data) would be 590,000 to 1,180,000 patients aged 49 to 75 years (the age group corresponding most closely to the disease treated).
In 5% of cases, with an annual incidence of 1%,[9] pathologic myopia is complicated by CNV leading to progressive and irreversible loss of visual acuity, i.e. 30,000 to 60,000 patients with pathologic myopia and CNV, including 5,900 to 11,800 incident cases each year.
With a 15% rate of bilateral cases, the number of eyes affected by CNV secondary to pathologic myopia can be estimated as 6,800 to 13,600 eyes per year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescription conditions.

Specific requests relating to reimbursement
Exception drug status.

Request for data
The Committee requests that data regarding:
- long-term efficacy and safety (retinal tear in particular);
- efficacy in cases where there is a history of treatment with VISUDYNE (studies suggest that ranibizumab is more effective in patients who have not been previously treated with verteporfin) and laser photocoagulation (limits efficacy due to the extension of scar tissue)

are collected.

[8] Affortit-Demoge A, Metge-Galatoire F, Metge P. Myopie Forte. EMC (Elsevier Masson SAS, Paris), Ophtalmologie, 21-244-A-20, 2011.
[9] Ohno-Matsui K, Yoshida T, Futagami S, Yasuzumi K, Shimada N, Kojima A, Tokoro T, Mochizuki M. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. Br J Ophthalmol. 2003 May;87(5):570-3.