HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version.

TRANSPARENCY COMMITTEE

OPINION

18 January 2012

LUCENTIS 10 mg/ml, solution for injection
Box of one 0.23 ml bottle (CIP code: 378 101-5)

Applicant: NOVARTIS PHARMA S.A.S.

ranibizumab
ATC code: S01LA04

List I
Prescription restricted to ophthalmology specialists

Exception drug

Date of Marketing Authorisation: European decision of 22 January 2007
Modification of MA: 19 December 2007 (modification of packaging)
6 January 2011 (extension of indication to diabetic macular oedema)
27 May 2011 (extension to macular oedema due to a branch retinal vein occlusion or a central retinal vein occlusion)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication in the treatment in adults of visual impairment due to macular oedema secondary to a branch retinal vein occlusion (BRVO) or a central retinal vein occlusion (CRVO).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ranibizumab

1.2. Indication

"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 (DMO)
- the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)."

1.3. Dosage

"Single-use vial for intravitreal use only.

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

[…]

Treatment of visual impairment due to either DMO or macular oedema secondary to retinal vein occlusion (RVO)
The recommended dose for LUCENTIS is 0.5 mg given 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 no improvement in visual acuity is observed after a first series of three injections, continuation of the 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 DMO or 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 1 month.

LUCENTIS and laser photocoagulation in DMO and in macular oedema secondary to BRVO.
LUCENTIS may be administered concomitantly with laser photocoagulation and also in patients previously treated with laser photocoagulation. When both treatments are given on the same day, LUCENTIS should be administered at least 30 minutes after laser photocoagulation.

Method of administration
As with all medicines for parenteral use, LUCENTIS should be visually inspected for particulate matter and discoloration prior to administration.

Before treatment, the patient should be instructed to self-administer antimicrobial drops (4 times daily for 3 days before and following each injection).

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.4). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

For information on preparation of LUCENTIS, see section 6.6.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.

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).

Paediatric population
LUCENTIS must not be used in children and adolescents as no safety and efficacy data are available in these sub-groups of patients.

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

Ethnicity
Experience with this treatment is limited in groups other than Caucasians."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

S Sensory organs
S01 Ophthalmologicals
S01L Ocular vascular disorder agents
S01LA Ocular anti-neovascularisation agents
S01LA04 Ranibizumab

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparator medicines

LUCENTIS 10 mg/ml is the only anti-VEGF indicated in the treatment of impaired visual acuity due to a macular oedema secondary to BRVO or CRVO.

2.2.2. Not strictly comparator medicines

OZURDEX 700 µg (dexamethasone in an intravitreal implant) is indicated in the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (substantial AB).

2.3. Medicines with a similar therapeutic aim

Grid laser photocoagulation can be used in the treatment of BRVO.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The applicant provided two 12-month phase III studies which compared ranibizumab with shame intravitreal injections (IVT), one in patients with a macular oedema secondary to branch retinal vein occlusion (BRVO), the other with central retinal vein occlusion (CRVO) (CRUISE).
The results of the 1 year open-label extension of these studies (scheduled for 2 years, HORIZON study) were provided. The main aim of this extension phase was to evaluate the safety in the medium term.

- **Initial BRAVO and CRUISE studies**

These studies were carried out using a similar protocol.

	BRAVO study	CRUISE study
Main aim	To evaluate the efficacy of monthly IVT of ranibizumab compared with placebo (shame IVT) in terms of improvement in best corrected visual acuity (BCVA) after 6 months of treatment.	
Method	Comparative study versus placebo, randomised, double-blind.	
Population studied	Patients with MO secondary to BRVO (affecting one quadrant or less of the retina) or hemi-BRVO (affecting more than one quadrant and up to 3 quadrants of the retina) with fovea affected. ≥ 18 years 1 single eye included per patient BCVA: between 20/40 and 20/400 (Snellen equivalent) CRT ≥ 250 µm	Patients with MO secondary to CRVO (affecting 3 quadrants or more of the retina) with fovea affected. ≥ 18 years 1 single eye included per patient BCVA: between 20/40 20/320 (Snellen equivalent) CRT ≥ 250 µm
Study plan	- 0 to 6 months: monthly injections - 6 to 12 months: follow-up of patients with monthly monitoring and possible re-treatment. The patients initially treated with shame IVT were transferred to the ranibizumab 0.5 mg group. Double-blind conditions were maintained. Re-treatment criteria: BCVA ≤ 20/40 or ECR ≥ 250 µm - 12 to 36 months: extension phase (HORIZON study). Follow-up of patients with a minimum three-monthly monitoring and possible re-treatment with ranibizumab 0.5 mg.	
Treatment groups	- ranibizumab 0.3 mg (dosage outside of Marketing Authorisation) - ranibizumab 0.5 mg - placebo (shame IVT)	

	BRAVO study	CRUISE study
Rescue treatment	- 0 to 6 months: laser rescue treatment (reference treatment only in BRVO) possible at month 3 in accordance with predefined criteria, following monthly re-assessment for patients who have not achieved these criteria. - 6 to 12 months: ditto as from month 9. Criteria of the laser rescue treatment: - BCVA ≤ 20/40 or CRT ≥ 250 µm - ET gain of less than 5 letters or loss of less than 50 µm of CRT between M3 or M9 and the 3 previous visits.	No rescue treatment in the absence of reference treatment in the CRVO.
Primary efficacy endpoint	Mean average variation in the BCVA at 6 months compared with the initial value measured on the ETDRS scale.	
Amongst the secondary endpoints	Percentage of patients with a gain in BCVA ≥ 15 letters at 6, 12 and 24 months. Percentage of patients with a loss of BCVA < 15 letters at 6 months. Average variation in the BCVA (ETDRS) at 12 and 24 months compared with the initial value.	

Results:

- BRAVO study (BRVO)

A total of 397 patients was included and randomised into 3 groups:
- 134 in the ranibizumab 0.3 mg group
- 131 in the ranibizumab 0.5 mg group
- 132 in the shame injections group

In the long-term study, 304 patients who had completed the first phase of the study and whom the investigator considered could benefit from extension of the treatment were included:
- 103 in the initially ranibizumab 0.3 mg group
- 104 in initially ranibizumab 0.5 mg group
- 97 in the initially shame injections/ranibizumab 0.5 mg group.

The patients' characteristics were homogeneous in the three groups.
The average age of the patients was approximately 66. The patients' average visual acuity was 53 to 56 letters (ETDRS) depending of the groups with a minimum of 16 letters and a maximum of 79 letters. The average central retinal thickness (CRT) was 488.0 to 551.7 µm depending of the groups with a minimum of 117 µm and a maximum of 1485 µm. Depending of the groups, 51.5 to 57.3% of the patients had had a diagnosis of retinal venous occlusion < 3 months.
Approximately 18% of the patients had received prior treatment for their RVO in the studied eye, 6% of whom with anti-VEGF.

The average number of injections during the first 6 months was 5.7 in the ranibizumab 0.5 mg group and 5.5 in the shame injection group.
Between 6 and 12 months, the average number of injections was 2.7 in the ranibizumab 0.5 mg group and 3.6 in the shame injection then ranibizumab 0.5 mg group.

Primary efficacy endpoint:

Since the 0.3 mg dose of ranibizumab is not recommended in the Marketing Authorisation, only the results obtained at the 0.5 mg dose will be presented.

The average variation in the BCVA at 6 months compared with the initial value was greater with ranibizumab 0.5 mg than with the shame injections with a difference of + 10.6 letters (see table 2).

Table 2: Evaluation of the BCVA on the ETDRS scale (BRAVO study)

	Ranibizumab 0.5 mg N = 131	Shame injections N = 132	p
Mean BCVA at baseline	53.0 ± 12.5	54.7 ± 12.2	-
Variation in the average BCVA at 6 months compared with baseline	+ 18.3 ± 13.2	+ 7.3 ± 13.0	<0.0001

Secondary endpoints:

At 6 months:

The percentage of patients who gained ≥ 15 letters was 61.1% with ranibizumab 0.5 mg and 28.8% with the shame injections.

The percentage of patients who lost < 15 letters was 98.5% with ranibizumab 0.5 mg and 95.5% with the shame injections.

As from 6 months, the patients in the shame injection group received ranibizumab 0.5 mg.

At 12 months:

The percentage of patients who gained ≥ 15 letters was 60.3% with ranibizumab 0.5 mg and 43.9% with the shame injections.

The percentage of patients who lost < 15 letters was 97.7% with ranibizumab 0.5 mg and 93.9% with the shame injections.

The average variation in the BCVA compared with the initial value was +18.3 (±14.6) letters in the ranibizumab 0.5 mg group and +12.1 (±14.6) letters in the shame injections group then ranibizumab 0.5 mg.

At 24 months, the average variation in the BCVA compared with the initial value was +17.1 (±16.9) letters in the ranibizumab 0.5 mg group and +15.1 (±13.9) letters in the shame injections then ranibizumab 0.5 mg group.

- CRUISE study (CRVO)

A total of 392 patients were included and randomised into 3 groups:
- 132 in the ranibizumab 0.3 mg group
- 130 in the ranibizumab 0.5 mg group
- 130 in the shame injections group.

In the long-term study, 304 patients who had completed the first phase of the study and whom the investigator considered could benefit from extension of the treatment were included:
- 107 in the initially ranibizumab 0.3 mg group
- 99 in the initially ranibizumab 0.5 mg group
- 98 in the initially shame injections/ranibizumab 0.5 mg group.

The characteristics of the patients were homogeneous in the three groups.
The patients' average age was approximately 67. The RVO was central (4 quadrants) in 91.6% to 96.9% of the patients on average. The average visual acuity of the patients was 47.4 to 49.2 letters (ETDRS) depending of the groups with a minimum of 16 letters and a maximum of 73 letters. The average central retinal thickness(CRT) was 679.9 to 688.7 µm depending of the groups with a minimum of 126 µm and a maximum of 1651 µm.

Approximately 13% of the patients had received prior treatment for their RVO in the studied eye, 7% of whom with anti-VEGF.

The average number of injections during the first 6 months was 5.6 in the ranibizumab group and 5.5 in the shame injection group.
Between 6 and 12 months, the average number of injections was 3.3 in the ranibizumab 0.5 mg group and 3.7 in the shame injections then ranibizumab 0.5 mg group.

Primary efficacy endpoint:

Since the 0.3 mg dose of ranibizumab is not recommended in the Marketing Authorisation, only the results obtained at the 0.5 mg dose will be presented.
The average variation in the BCVA at 6 months compared with the initial value was greater with ranibizumab 0.5 mg than with the shame injections with a difference of +13.8 letters (see table 3).

Table 3: Evaluation of the BCVA on the ETDRS scale (CRUISE study)

	Ranibizumab 0.5 mg N = 130	Shame injections N = 130	p
Mean BCVA at baseline	48.1 ± 14.6	49.2 ± 14.7	-
Variation in the average BCVA at 6 months compared to baseline	+ 14.9 ± 13.2	+ 0.8 ± 16.2	<0.0001

Secondary endpoints:

At 6 months:

The percentage of patients who gained ≥ 15 letters was 47.7% with ranibizumab 0.5 mg and 16.9% with the shame injections.

The percentage of patients who lost < 15 letters was 98.5% with ranibizumab 0.5 mg and 84.6% with the shame injections.

As from 6 months, the patients in the shame injections group received ranibizumab at a dose of 0.5 mg.

At 12 months:

The percentage of patients who gained ≥ 15 letters was 50.8% with ranibizumab 0.5 mg and 33.3% with the shame injections.

The percentage of patients who lost < 15 letters was 97.7% with ranibizumab 0.5 mg and 90.0% with the shame injections.

The average variation in the BCVA compared with the initial value was +13.9 (±14.2) letters in the ranibizumab 0.5 mg group and +7.3 (±15.9) letters in the shame injections then ranibizumab 0.5 mg group.

At 24 months, the average variation in the BCVA compared with the initial value was +12.9 (±17.9) letters in the ranibizumab 0.5 mg group and +6.3 (±17.3) letters in the shame injections then ranibizumab 0.5 mg group.

3.2. Adverse effects

3.2.1. Data from the clinical studies

The safety profile of ranibizumab observed during the BRAVO, CRUISE and HORIZON studies was similar to that observed in the patients treated with ranibizumab for a neovascular AMD and for a diabetic macular oedema.

3.2.2. Summary of product characteristics

The ocular adverse effects most frequently (≥ 1/10) reported after the injection of LUCENTIS are: ocular pain, ocular hyperhaemia, increase in intraocular pressure, hyalitis, vitreous detachment, retinal haemorrhage, visual disorders, vitreous floaters, conjunctival haemorrhage, ocular irritation, sensation of a foreign body in the eye, increased lachrymal secretions, blepharitis, dryness of the eyes and ocular pruritus.

The intravitreal injections, including the injection with LUCENTIS, were associated with endophthalmia, intraocular inflammation, rhegmatogenous retinal detachment, retinal tears and iatrogenic traumatic cataracts. The intravitreal injections should be carried out under strict aseptic conditions (the AFSSAPS drew up guidelines on good intravitreal injection practice which were updated on 11 February 2011).
Furthermore, transient increases in intraocular pressure were very often observed in the 60 minutes following the injection of LUCENTIS. Prolonged increases in intraocular pressure have also been observed. Consequently, intraocular pressure and perfusion of the head of the optic nerve should be monitored and managed appropriately.

Frequent (≥ 1/100, < 1/10) urinary tract infections were observed but only in the patients treated for diabetic macular oedema.

The very common, non-ocular adverse effects are rhinopharyngitis, headache and arthralgia, and the common adverse effects are anaemia, hypersensitivity reactions, anxiety, cough and nausea.

3.2.3. Risk management plan (RMP)

The adverse effects monitored in the RMP are:

- identified risks: endophthalmia, intraocular inflammation, tear in the retinal pigment epithelium, retinal tear, retinal detachment, intravitreal haemorrhage, increase in intraocular pressure, traumatic cataract and hypersensitivity reactions;
- potential risks: myocardial infarction, non-myocardial, arterial thromboembolic events, venous thromboembolic events, hypertension, non-ocular haemorrhage, proteinuria and retinal blood flow change;
- other risks: use outside of the Marketing Authorisation, bilateral treatment and overdose.

1 http://www.afssaps.fr/Infos-de-securite/Mises-au-point/Bonnes-Pratiques-d-injection-intra-vitreenne-IVT-Mise-au-point

3.3. Conclusion

Ranibizumab was evaluated in two randomised, double-blind studies versus shame intravitreal injections (IVT) in patients with reduced visual acuity due to a macular oedema following branch retinal venous occlusion (BRVO) in one study (n = 397) or central retinal venous occlusion (CRVO) in another study (n = 392).
The protocol of these 2 studies was similar. The intravitreal injections of ranibizumab (0.5 mg) or shame injections were carried out once a month for 6 months. The patients, including those of the shame injections group, were then re-treated in accordance with best corrected visual acuity (BCVA) or central retinal thickness (CRT) with ranibizumab (0.5 mg) up to 12 months and for an extension phase of 2 years, of which only the results at 1 year are available.
The patients included in the BRAVO study could benefit from laser rescue treatment as from month 3, depending on their BCVA and their CRT. The average total number of injections up to 12 months was between 8 and 9 in each of the treatment groups and from 2 to 3 during the second year of treatment.

In patients affected with BRVO, the average variation in BCVA at 6 months compared with the initial value (primary efficacy endpoint) was greater with ranibizumab than with the shame injections (+18.3 letters on the ETDRS scale[2] vs +7.3 letters, i.e. a difference of +10.6 letters; $p < 0.0001$). The data suggest that the gain compared with the initial value was maintained up to 24 months (+17.1 letters) in the patients treated with ranibizumab throughout the study.
In the patients affected with CRVO, the average variation in the BCVA at 6 months compared with the initial value (primary efficacy endpoint) was greater with ranibizumab than with the shame injections (+14.9 letters vs +0.8 letters, i.e. a difference of +13.8 letters; $p<0.0001$). The data suggest that the gain compared with the initial value was maintained up to 24 months (+12.9 letters) in the patients treated with ranibizumab throughout the study.

The safety profile of ranibizumab in the patients affected with retinal venous occlusions is similar to that observed in the patients affected with neovascular AMD or diabetic macular oedema treated with ranibizumab. The intravitreal injections were associated with endophthalmia (< 1%), intraocular inflammation, rhegmatogenous retinal detachment, retinal tears and traumatic cataracts). Transient or prolonged increases in intraocular pressure were observed (≥ 10%). The very common, non-ocular adverse effects (≥ 10%) are rhinopharyngitis, headache and arthralgia, and the common ones are (≥ 1% and < 10%), anaemia, hypersensitivity reactions, anxiety, cough and nausea. The risk of myocardial and non-myocardial thromboembolic events are monitored in the ranibizumab risk management plan.

No data are available making a direct comparison between LUCENTIS and OZURDEX (dexamethasone implant dosed at 700 µg), the only other medicinal product with a Marketing Authorisation for macular oedema following retinal venous occlusion. However, the results of the efficacy studies for these two medicines suggest that LUCENTIS has a greater magnitude of effect in terms of improvement in visual acuity than OZURDEX. Furthermore, more long-term results are available for LUCENTIS, up to 2 years, showing that the improvement in visual acuity obtained is maintained after the first year of treatment. The current dosage regimen of OZURDEX allows re-treatment only 6 months after injection of the first implant. However, this dosage regimen of two injections of OZURDEX at an interval of 6 months can offer a first-line benefit in some patients, particularly the elderly, compared with multiple injections of LUCENTIS (8-9 injections in the first year of treatment).
As a reminder, the data available for OZURDEX show in one study that included patients affected with macular oedema secondary to BRVO or a CRVO that the percentage of

[2] *Early Treatment Diabetic Retinopathy Study*

patients who gained at least 15 letters (primary efficacy endpoint) was greater than with the shame injection of the implant after 3 months of treatment (22.4% versus 12.4%; p = 0.008). This difference is no longer noted after 6 months (19.4% versus 18.3% in one study and 23.5% versus 17.0% in another study).
With LUCENTIS, the percentage of patients with a gain in BCVA of at least 15 letters at 6 months (secondary endpoints) was greater than with the shame injections in the BRVO (61.1% versus 28.8%) and in the CRVO (47.7% versus 16.9%).

The safety profile is different with OZURDEX (only ocular, the most common being an increase in ocular pressure (24%) and conjunctival haemorrhage (14.7%, linked with the injection procedure).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Retinal venous occlusion is an eye disorder affecting the retina and, at its centre, the macula responsible for detailled vision. It causes a circulatory delay, leakages and a macular oedema responsible for visual acuity impairement.
The functional prognosis depends on the clinical form of the retinal venous occlusion: two main forms are distinguished: an ischaemic form with a poor visual prognosis and a well perfused form (known as oedematous) which has a better prognosis.

This product is a symptomatic treatment.

Public health benefit:

The public health burden represented by retinal venous occlusions is small.
Reduction of visual impairment is a public health need (a GTNDO priority).
In the light of the data available, in the short-term, it is expected that the product LUCENTIS will have a moderate impact on the morbidity linked with these pathologies, essentially in terms of maintaining visual acuity.
In the absence of available data, the impact of LUCENTIS on quality of life and organisation of care is not quantifiable.
It is questionable whether the results of the trials can be transferred into practice, particularly because of the uncertainty concerning compliance with management procedures (in particular concerning routine performance of angiography before treatment), the optimum number of injections and the re-treatment criteria.
However, the product LUCENTIS might still be able to provide a partial response to the identified public health need.
Consequently, a public health benefit is expected for the product LUCENTIS in this indication. This benefit is small.

The efficacy/safety ratio is substantial.

This medicinal product is a first-line therapy.

There is an alternative drug therapy (OZURDEX).

The actual benefit of LUCENTIS 10 mg/ml injectable solution is substantial.

4.2. Improvement in actual benefit

LUCENTIS provides a minor improvement in actual benefit (IAB IV) compared with OZURDEX in the treatment of visual impairment due to a macular oedema secondary to retinal venous branch occlusion or a central retinal venous occlusion.

4.3. Therapeutic use

4.3.1. Therapeutic use

A distinction is made between two main forms of retinal venous occlusion: an ischaemic form with a poor visual prognosis and a well perfused form (known as oedematous) with a better prognosis.

The aim of the treatment of an oedematous retinal venous occlusion is to facilitate the return of normal retinal venous circulation, prevent progression to an ischaemic form, or prevent or treat macular complications, in particular cystoid macular oedema.

The aim of the treatment of a mixed or ischaemic venous occlusion is to prevent or treat neovascular complications.

The dexamethasone intravitreal implant (OZURDEX) has a Marketing Authorisation for the treatment of adult patients with macular oedema secondary to branch venous occlusion or central retinal venous occlusion since July 2010. It is a first-line treatment.

Various medicinal products are routinely used outside of a Marketing Authorisation without having been evaluated in clinical studies.
Triamcinolone retard (KENACORT retard) is used outside of a Marketing Authorisation in an intravitreal injection. Its formulation is unsuited to the intravitreal route and contains a preservative which exposes the patient to local reactions of the pseudo-endophthalmia type. The other complications are an almost constant cataract after two injections and ocular hypertonia.

Other therapies are used:

- Grid laser photocoagulation in the oedematous forms and panretinal photocoagulation in the ischaemic forms dating back at least 3 months.
- Surgical treatment of macular oedema: vitrectomy, radial optic neurotomy, chorioretinal venous anastomosis, adventitious arteriovenous goniotomy. These treatments have not been evaluated in a clinical study.

4.3.2. Place of the proprietary medicinal product

Like OZURDEX, LUCENTIS is a first-line treatment of visual impairment due to macular oedema secondary to branch retinal venous occlusion or central retinal venous occlusion**.** In the absence of data for a direct comparison between LUCENTIS and OZURDEX, of the choice between these medicinal products will be done taking into account their own efficacy, the patient's characteristics, the contraindications, the potential adverse effects and the monitoring constraints. Consequently, the patient's age, his ability to travel to receive monthly injections in the case of LUCENTIS, the presence of the crystalline lens and the existence of glaucoma because of the risk of increased intraocular hypertension and cataracts with OZURDEX will be important criteria to take into account for initiating one or other of these treatments.
Fluorescein angiography should be carried out before starting treatment in order to exclude the ischaemic forms which are not indications of LUCENTIS. Progression of the oedematous form to the ischaemic form is possible under treatment and it is recommended that this be monitored.

The absence of any improvement in visual acuity after 3 consecutive monthly injections justifies discontinuation of the treatment.

4.4. Target population

According to the data of the "Beaver Dam Eye Study"[3,4] the annual incidence of BRVO is estimated at 0.12% and annual incidence of CRVO is estimated at 0.03% in a population aged between 43 and 84 years. If these figures are placed in the context of the French

3 Klein R., Klein BEK., Moss SE., Meuer SM. The epidemiology of retinal vein occlusion – the Beaver Dam Eye Study. Tr Am Ophth Soc 2000; 898:133-43
4 Klein R, Moss SE., Meuer S. The 15-year cumulative incidence of retinal vein occlusion. Arch Ophthalmol 2005; 123: 807-14

population aged 43 and over, it is estimated that 35,000 patients are affected with BRVO each year and 10,000 patients are affected with CRVO. [5]
In the "*Beaver Dam Eye Study*", [2] 17 cases of macular oedema were identified out of the 61 cases of BRVO (28%) and 7 cases out of the 18 cases of CRVO (39%).
On the basis of these data, the annual number of patients who develop macular oedema secondary to retinal venous occlusion is thus estimated at approximately 14,000.
However, these data do not allow an estimation to be made of the number of patients for whom treatment with LUCENTIS will be justified (possibility of spontaneous regression of macular oedema or progression to an ischaemic form that cannot be treated, criterion of visual acuity to be taken into account).

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication of treatment of visual impairment due to macular oedema secondary to branch retinal venous occlusion (BRVO) or central retinal venous occlusion (CRVO), at the doasages in the Marketing Authorisation.

Exception drug: the treatment information sheet will be updated accordingly.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%

The Committee wants to re-evaluate LUCENTIS in this indication within 2 years on the basis of updated efficacy and safety data.

Request for a study:
The Transparency Committee wants to have additional data (supporting document, see annex) in the medium- and long-term to re-evaluate LUCENTIS on the following main points:
- the characteristics of the patients treated for retinal venous occlusion with or without LUCENTIS;
- the procedures for treating these patients (examinations carried out during the assessment and during the follow-up, different treatments undertaken, number of re-treatments possible and re-treatment schedule);
- the adverse effects in patients treated with LUCENTIS, with frequency of discontinued treatment and the reasons for this;
- the development of visual acuity and quality of life of the patients.

The duration of patient follow-up will have to be justified and sufficient to meet the Transparency Committee's request.
Data will have to be available at the time of the LUCENTIS re-evaluation.
If the studies scheduled or in progress, particularly within the context of the European Risk Management Plan, cannot answer all of the questions raised by the Transparency Committee, a special study will have to be carried out.

5 Population of 43 years and over in France as at 1 January 2010: 29 453 771 (source: http://www.insee.fr)

ANNEX: Document supporting the request for additional data

For the proprietary medicinal product LUCENTIS**,** indicated in the treatment of visual impairment due to macular oedema following branch retinal venous occlusion (BRVO) or central retinal venous occlusion (CRVO), additional data were requested by the Transparency Committee during the meeting on 16/11/2011.
This request for additional information is justified by the lack of data, in the medium- and long-term, in the file submitted to the Transparency Committee on the following three main points:
- compliance with treatment procedures (in particular, routine performance of angiography before treatment), the optimum number of intravitreal injections and the re-treatment criteria;
- the impact on benefit in actual conditions of use;
- the place of LUCENTIS in the current therapeutic strategy for the treatment of retinal venous occlusions, in the absence of data comparing it with OZURDEX.