HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 June 2011

LUCENTIS 10 mg/ml, solution for injection
B/1 bottle of 0.23 ml (CIP code: 378 101-5)

Applicant: NOVARTIS PHARMA SAS

ranibizumab
ATC classification: S01LA04

List I
Medicinal product which must be prescribed only by specialists in ophthalmology

Date of Marketing Authorisation: European decision of 22 January 2007
Date of Marketing Authorisation: 19 December 2007 (change in packaging)
6 January 2011 (extension of indication to diabetic macular oedema)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication “treatment in adults of reduced visual acuity due to diabetic macular oedema”.

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 (DME).”**

1.3. Dosage

“Single-use vial for intravitreal use only.

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

Treatment of neovascular AMD

In neovascular 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 with LUCENTIS starts with an induction phase with one injection a month for three consecutive months, followed by a maintenance phase during which patients’ visual acuity will be checked once a month. If the patient shows loss of visual acuity of more than 5 letters (ETDRS scale or equivalent to one line on the Snellen scale), LUCENTIS must be administered.

Treatment of visual impairment due to DME

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 at 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. Monthly injections should then be administered until stable visual acuity is reached again at three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month.

LUCENTIS can be administered concomitantly with laser photocoagulation and in patients who have received previous laser photocoagulation. When given on the same day, LUCENTIS should be administered at least 30 minutes after laser photocoagulation.

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 of the SPC).

Paediatric population: LUCENTIS must not be used in children and adolescents because there are no safety and efficacy data in these subgroups of patients.

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

Ethnicity: Experience with 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	Antineovascularisation agents
S01LA04	ranibizumab

2.2. Medicines in the same therapeutic category

There are no medicines with marketing authorisation in the same therapeutic category that are strictly comparable or not strictly comparable to LUCENTIS in the treatment of visual impairment due to diabetic macular oedema.

2.3. Medicines with a similar therapeutic aim

Other non-drug treatments:

- laser photocoagulation
- vitrectomy.

3 ANALYSIS OF AVAILABLE DATA

The company supplied four studies in support of its application:

- a phase III study (RESTORE) comparing ranibizumab to ranibizumab combined with laser and to laser alone;
- a phase II study (RESOLVE) comparing ranibizumab to placebo (shame intravitreal injections);
- two independent studies:
  - the DRCR Net study comparing ranibizumab combined with laser to laser alone
  - the READ-2 study comparing ranibizumab to combined ranibizumab + laser and to laser alone: no details will be given of this study since this is an open-label study with a treatment regimen that does not comply with the Marketing Authorisation.

3.1. Efficacy

➢ RESTORE study: ranibizumab versus ranibizumab + laser and versus laser

Objective	To demonstrate the superiority of ranibizumab 0.5 mg in monotherapy or combined with laser versus laser alone in patients with visual impairment due to diabetic macular oedema (DME).
Method	Randomised, double-blind phase III study of 12 months duration.
Inclusion criteria	≥ 18 years Type I or II diabetes with HbA1C ≤ 10% Visual impairment due to focal or diffuse DME in the eye eligible for laser treatment Best corrected visual acuity (BCVA) between 39 and 78 ETDRS letters at 4 metres (i.e. 20/32 to 20/160 Snellen equivalent)
Exclusion criteria included	Previous treatment with an anti-angiogenic agent (studied eye) within the piror three months, ocular comorbidities that needed or needs corticotherapy or laser photocoagulation (studied eye) within the prior six months or during the study.
Treatment groups	Ranibizumab 0.5 mg in intravitreal injection (IVT) + shame laser Ranibizumab 0.5 mg in IVT + laser Laser + shame IVT
Treatment regimen	<u>Intravitreal or shame injections of ranibizumab</u>: - Induction: monthly IVT for three months. - Maintenance (up to 12 months): one monthly IVT until visual acuity was stable = no improvement in BCVA or BCVA ≥ 84 letters over the course of the last two consecutive visits. Resumption of treatment in case of BCVA drop due to the DME progression in the investigator's opinion after OCT and/or other anatomical parameters Suspension of IVT in case of no BCVA improvement over the course of last two consecutive visits <u>Photocoagulation by active or shame laser</u>: On D1 based on ETDRS criteria in one or two sessions four weeks apart. Retreatment after three months based on ETDRS criteria on investigator

	opinion. Active or shame laser administered at least 30 min before IVT
Primary efficacy endpoint	Mean average change in BCVA* from month 1 to month 12 compared to baseline.
Secondary endpoints included	Mean BCVA change from baseline at 12 months Percentage of patients with BCVA ≥ 10 letters and ≥ 15 letters

*** :** BCVA: best corrected visual acuity
°: OCT: optical coherence tomography

Results:

Randomisation of 345 patients, 116 to the ranibizumab group, 118 to the ranibizumab + laser group and 111 to the laser group.

Patients' characteristics were homogeneous between groups for all parameters:

- mean age: 63 years
- diabetes type (mean for total population): type I (11.2%) and type II (88.8%)
- HbA1c (mean for total population): 7.3 %
- DME type (mean): focal (53.5%), diffuse (41.5%), not specified (5%)
- central retinal thickness (mean): 412 to 426 µm
- visual acuity (mean): 62 to 65 letters (ETDRS)
- intraocular pressure (mean for total population): 15.4 mmHg

- Primary endpoint:

The mean average change in BCVA from month 1 to month 12 compared to baseline was significantly greater in patients treated with ranibizumab (+5.4 letters vs laser) or with the combination of ranibizumab + laser (+4.9 letters vs laser) than in those treated with laser (see Table 1).

Table 1: Mean average change in BCVA* from month 1 to month 12 compared to baseline (RESTORE study)

	Ranibizumab 0.5 mg (n = 116)	**Ranibizumab 0.5 mg + laser (n = 118)**	**Laser (n = 111)**
Mean baseline BCVA (ETDRS letters)	64.7 ± 10.1	63.4 ± 9.99	62.6 ± 11.01
Mean average change **in BCVA* from month 1 to month 12 compared to baseline (ETDRS letters)**	6.1 ± 6.43	5.9 ± 7.92	0.8 ± 8.56
Comparison vs laser Difference 95% CI *p*	 +5.4 [3.5-7.4] <0.0001	 +4.9 [2.8-7.0] <0.0001	 -

- Secondary endpoints:

The mean BCVA change at the 12th month compared to baseline was 6.8 letters with ranibizumab, 6.4 letters with the combination of ranibizumab + laser and 0.9 letter with laser alone, i.e. differences vs laser alone were:

- 6.2 letters (95% CI = [3.6; 8.7]; $p < 0.0001$) in favour of ranibizumab
- 5.4 letters (95% CI = [2.4; 8.4]; $p < 0.0004$) in favour of the combination of ranibizumab + laser

The percentage of patients in which gained ≥ 10 letters was 37.4% in the ranibizumab group, 43.2% in the ranibizumab + laser group and 15.5% in the laser group.

The percentage of patients in which gained ≥ 15 letters was 22.6% in the ranibizumab group, 22.9% in the ranibizumab + laser group and 8.2% in the laser group.

- **DRCR Net study: ranibizumab + laser versus laser**

Objective	To demonstrate the superiority of ranibizumab 0.5 mg combined with laser versus laser alone for visual acuity in patients with visual impairment due to diabetic macular oedema. This study also included a laser + triamcinolone IVT arm which will not be described below since the use of triamcinolone in this indication is off-labelled.
Method	Double- or single-blind randomised study of 2 years duration.
Inclusion criteria	≥ 18 years Type I or II diabetes BCVA between 24 and 78 ETDRS letters at 3 metres (i.e. 20/32 and 20/320 Snellen equivalent). Retinal thickening due to DME involving the centre of the macula assessed to be the main cause of visual impairment. Retinal thickness measured by OCT ≥ 250 µm. The two eyes of the same patient could be included in the study. If the right eye was randomised: - to a group other than laser alone, the left eye was assigned to the group for treatment with laser alone - to the group for laser alone, the left eye was randomised to one of the three other groups.
Exclusion criteria included	Treatment of DME (studied eye) within the prior four months. Ocular comorbidities: - panretinal photocoagulation within the prior four months or anticipated need within the next six months - Eye surgery in the prior four months - History of open-angle glaucoma or increased IOP induced by corticosteroids that required IOP-lowering treatmentIOP ≥ 25 mmHg.
Treatment groups	**Ranibizumab 0.5 mg in IVT + concomitant laser:** monthly IVTs with a maximum of 13 injections in the first year and laser sessions within three to ten days after the IVT. **Ranibizumab 0.5 mg in IVT + deferred laser:** monthly IVTs with a maximum of 13 injections in the first year and laser sessions more than six months after the IVT (patients not masked for their treatment) **Triamcinolone 4 mg + concomitant laser** **Laser:** one monthly shame IVT + concomitant laser
Treatment regimen	Intravitreal or shame injections of ranibizumab: ▪ For 12 weeks: monthly IVT. ▪ Weeks 16 to 20: monthly IVT until success endpoints were reached = BCVA ≥ 84 letters or CRT ≤ 250 µm, and continuation of the IVTs at investigator discretion. ▪ Weeks 24 to 48: - success: continuation of the IVTs at investigator discretion - improvement (BCVA improvement ≥ 5 letters or CRT improvement ≥ 10% since the last ranibizumab injection or the first shame injection: new IVT - noimprovement: IVT at the investigator discretion - failure (BCVA reduction ≥ 10 letters versus baseline, CRT ≥ 250 µm and more than 13 weeks since complete laser treatment : IVT at investigator discretion or alternative treatment.

	▪ After week 52: breaking of the code
	- end of shame IVTs
	- follow-up every four months in the laser + shame IVT group
	- in the two groups treated with ranibizumab:
	  - follow-up of eyes with failure every four months
	  - for eyes that have no failure: weeks 24 to 48 treatment criteria + the following two considerations:
	  1. treatment at investigator discretion including treatments other than the one assigned by randomisation for the eyes with failure or eyes with the minimum efficacy criteria e.g. BCVA ≥ baseline, CRT ≥ 250 µm, DME assessed to be the main cause of visual decrease and more than 29 weeks since last laser treatment)
	  2. eyes in success or no improvement at the prious two visits: doubling of the follow-up interval.
	<u>Laser photocoagulation</u>:
	Initial treatment within three to ten days after (concomitant) IVT or more than 24 weeks after (deferred) IVT
	After week 16:
	- concomitant laser: within three to ten days after the IVT unless:
	  - laser in the prious 13 weeks
	  - previous complete laser
	  - CRT < 250 µm and absence of oedema near the macula (within 500 µm of the centre of the macula and absence of liquid area of one papillary disk within a zone of one papillary disc of the centre of the macula)
	- Deferred laser: if no improvement in week 24 and following weeks since the last two IVTs, the laser was repeated until the macular oedema disappeared or until complete laser treatment was given at investigator discretion.

Primary efficacy endpoint	Mean variation in BCVA after one year by comparison with the baseline value.
Secondary endpoints included	Improvement and worsening of the BCVA by ≥ 15 letters. Variation in BCVA at two years.

<u>Results</u>:

A total of 854 eyes were included in the study, distributed among the groups as follows:
- ranibizumab 0.5 mg + concomitant laser: 187 eyes
- ranibizumab 0.5 mg + deferred laser: 188 eyes
- triamcinolone 4 mg + concomitant laser: 186 eyes
- laser + shame IVT: 293 eyes.

The patients' characteristics were homogeneous between groups for all the parameters:
- age: 63 years (mean)
- diabetes type (mean for total population): type I (7.8%), type II (90.0%) and uncertain (2.2%)
- HbA1c (mean for total population): 7.4%
- DME type (mean): focal (30.8%), diffuse (45.0%), neither focal nor diffuse (24.2%)
- central retinal thickness (mean): 371 to 407 µm
- visual acuity (median): 65 to 66 letters (ETDRS)
- intraocular pressue (mean for total population): 16 mmHg

- Primary efficacy endpoint:

The mean variation in BCVA at one year compared to baseline was statistically higher in the groups combining ranibizumab with laser (deferred or concomitant) than in the group laser + shame IVT (see Table 2).

Table 2: Mean variation in BCVA at one year compared to baseline (DRCR Net study).

	Laser + shame IVT n = 293	**Ranibizumab 0.5 mg + concomitant laser n = 187**	**Ranibizumab 0.5 mg + deferred laser n = 188**
Mean variation in BCVA at 1 year (ETDRS letters): Mean ± SD	+3 ± 13	+9 ± 11	+9 ± 12
Comparison vs laser + shame IVT Difference 95% CI *p*	-	+5.8 [+3.2 to +8.5] p < 0.001	+6.0 [+3.4 to +8.6] p < 0.001

- Secondary endpoints:

After 1 year of treatment, the percentage of eyes with a visual gain ≥ 15 letters in the ranibizumab + concomitant laser group (30%) and in the ranibizumab + deferred laser group (28 %) was greater than in the laser + IVT shame group (15%; p < 0.001 for each comparisons).

The percentage of eyes with visual loss ≥ 15 letters in the ranibizumab + concomitant laser group (2 %) and in the ranibizumab + deferred laser group (2%) was significantly lower than in the laser + shame IVT group (8% ; p = 0.009 and p = 0.01 respectively).

After two years of treatment, the statistically significant differences observed for the mean BCVA variation between the ranibizumab + laser groups (concomitant or deferred) and the laser + shame IVT group were maintained (see Table 3).

The percentage of eyes with a gain in visual acuity of ≥ 15 letters was 26% in the ranibizumab + concomitant laser group, 29% in the ranibizumab + deferred laser group (28%) and 17% in the laser + simulated IVT group.

Table 3: Mean variation in BCVA at two years compared to baseline (DRCR Net study).

	Laser + shame IVT n = 163	**Ranibizumab 0.5 mg + concomitant laser n = 106**	**Ranibizumab 0.5 mg + deferred laser n = 112**
Mean variation in BCVA at 2 years (ETDRS letters)	+2	+7	+10
Comparison vs laser + simulated IVT Difference *p*	-	+5.0 p = 0.01	+7.2 p < 0.001

➢ **RESOLVE study: ranibizumab 0.3 mg and 0.5 mg versus placebo (shame injection)**

This study is presented for information purposes only since it is an exploratory study to determine the effective dose of ranibizumab by comparison with shame injections; this comparison was not used in the phase III study. Moreover, it should be noted that the dosage regimen planned a dose doubling after one month in case of no improvement and for the rest of the study, what is not in accordance with the regimen validated in the MA.

Objective	To evaluate the efficacy and safety of ranibizumab by comparison with shame injections in patients with visual impairment secondary to diabetic macular oedema. Pilot study: to evaluate efficacy on central retinal thickness after six months in a small number of patients Confirmatory study: if superiority of ranibizumab demonstrated in the pilot study compared to the shame injections, to confirm its superiority in the mean average change in BCVA* from month 1 to month 12 compared to baseline in a larger patients population
Method	Randomised, double-blind phase II study of 12 months duration.
Inclusion criteria	≥ 18 years Type I or II diabetes HbA1C level stable for six months and ≤ 12% Macular oedema (focal or diffuse) involving the central area in at least one eye Central retinal thickness ≥ 300 µm BCVA between 39 and 73 ETDRS letters at 4
Exclusion criteria included	Systemic corticosteroid therapy in the prior four months Laser photocoagulation in the prior six months Intravitreal or subtenon therapeutic agent (including corticosteroids)
Treatment groups	Ranibizumab 0.3 mg Ranibizumab 0.5 mg Placebo (shame intravitreal injection)
Treatment regimen	Injection at month 0 then monthly until the success or futility criteria are met. Success: CRT ≤ 225 µm AND BCVA ≥ 79 letters after three months Withdrawal if increase in CRT ≥ 50 µm OR reduction in BCVA ≥ 5 letters and BCVA < 74 letters. Minimum improvement: permanent withdrawal if no minimum improvement after three consecutive injections : reduction in CRT ≥ 50 µm (i.e. a reduction ≥ 20%) OR an BCVA increase ≥ 5 letters. Use of rescue laser is possible after three consecutive injections if reduction in BCVA > 10 letters between two consecutive visits at least one month apart AND if the investigator did not consider the macula to be flat (CRT ≤ 225 µm). From the first month, the dose could be doubled if: - at month 1: CRT > 300 µm - at any visit after month 1: CRT > 225 µm and reduction in œdema < 50 µm from the previous measurement. Once the dose was doubled for one injection, all the following doses were also doubled. Thus, patients could be treated with doses of 0.3 mg, 0.5 mg, 0.6 mg and 1.0 mg.
Primary efficacy endpoint	Confirmatory study°: Mean variation in BCVA from month 1 to month 12 compared to baseline (BCVA measured monthly).

*** :** BCVA: best corrected visual acuity
° : only the results of the confirmatory study will be presented below.

Results:

Randomisation of 42 patients in the pilot study then of 109 additional patients for the confirmatory study giving a total of 151 patients distributed as follows:

- ranibizumab 0.3 mg group: 51 patients
- ranibizumab 0.5 mg group: 51 patients
- shame injection group: 49 patients

Only the results of the ranibizumab 0.5 mg group will be presented below since this is the dose recorded in the MA.

The patients' characteristics were homogeneous between groups for all the parameters:

- age: 63 years (mean)
- diabetes type (mean for total population): type I (3%) and type II (97%)
- HbA1c (mean for total population): 7.4%
- DME type (mean): focal (47%), diffuse (50%), questionable, can't grade or missing (3%)
- central retinal thickness (mean): 448 to 459 µm
- visual acuity (mean): 59 to 61 letters (ETDRS)

About 20% of patients had previously been treated by laser.

The mean variation in BCVA from month 1 to month 12 was +6.4 (± 9.2) ETDRS letters with ranibizumab 0.5 mg and -0.1 (± 9.8) letter with shame injections (p = 0.0004).

The percentage of patients treated at least once with a double dose was 64.7% in the ranibizumab 0.5 mg group and 91.8% in the shame injection group. There was not shown to be any link between doubling the dose and the progression of the visual acuity or the central retinal thickness.

3.2. Safety

3.2.1. Clinical study data

RESTORE study

About 90% of the patients in the ranibizumab groups, whether or not combined with laser, and 80% of the patients in the laser group interrupted their treatment before the end of the study, mainly because of an improvement in visual acuity. Early termination of the study due to safety reasons concerned 3% and 5.9% of patients in the ranibizumab groups, whether or not combined with laser, and 15.5% of those in the laser group. Discontinuation due to lack of efficacy concerned 2% of patients in the ranibizumab groups, whether or not combined with laser, and 6% of those in the laser group.

Adverse events suspected to be related to treatment were reported in 24.3% of patients treated with ranibizumab, 22.5% of those treated with ranibizumab + laser and 18.2% of those treated with laser alone. The most frequently reported ocular adverse events (> 1%) in the groups treated with ranibizumab were: eye pain, conjonctival haemorrhage, conjonctival hyperaemia, foreign body sensation, ocular discharge, impaired vision, eye irritation, palpebral oedema, increased lacrimation, blurred vision. No cases of endophthalmitis were observed in any of the groups.

Non-ocular adverse events suspected to be related to treatment were reported in 7.8% of patients treated with ranibizumab, 2.5% of those treated with ranibizumab + laser and 1.8% of those treated with laser alone. Of these adverse effects, in the ranibizumab group there were two cases of pulmonary embolism, one case of arterial thrombosis in a limb and one case of hypertension. In the laser group, one case of a hypertensive episode was observed and in the ranibizumab + laser group, one case of coronary artery occlusion.

The serious adverse events necessitating discontinuation of the treatment were non-ocular and not linked to treatment.

DRCR Net study
In the ranibizumab group, three cases of endophthalmitis were reported for 3973 injections, i.e. an incidence of endophthalmitis after intravitreal injection of 0.08%.
An increase in IOP > 10 mmHg compared to baseline, an IOP > 30 mmHg or the use of antiglaucoma medications during the two study years were observed in 9% of the patients treated with ranibizumab + concomitant or deferred laser and 11% in the group with laser alone.
A vitreous haemorrhage was observed in 3 and 4% of the patients treated with ranibizumab + concomitant or deferred laser and in 9% of patients treated with laser alone.
The percentage of patients who underwent cataract surgery during the two years was 12% in the ranibizumab + concomitant laser group, 13% in the ranibizumab + deferred laser group and 12% in the laser group.
The frequency of non-ocular adverse events did not differ between the different groups; in particular, there was no increase in cardio- or cerebrovascular adverse events in the ranibizumab + concomitant or deferred laser groups compared with the group treated with laser alone.

3.2.2. Summary of product characteristics (update of 19 December 2007)

The safety profile for ranibizumab in patients treated for diabetic macular oedema is similar to that observed in those treated for wet AMD except for the frequent occurrence (≥ 1/100, < 1/10) of urinary tract infections observed only in patients treated for diabetic macular oedema.

The ocular adverse effects related to ranibizumab and to the intravitreal injection procedure that are common (≥ 1/100, < 1/10) to very common (≥ 1/10) (see the SPC) are numerous.
It should be noted that intravitreal injections, including those with LUCENTIS, were associated with endophthalmitis, intraocular inflammation, rheumatogenous retinal detachment, retinal tears and iatrogenic traumatic cataracts. Intravitreal injections must be given under strict aseptic conditions (the Afssaps has prepared good practice guidelines on intravitreal injections which were updated on 11 February 2011[1]).
Moreover, increases in intraocular pressure were very commonly observed within 60 minutes after the injection of LUCENTIS. Consequently, intraocular pressure and perfusion of the optic nerve head must be monitored and managed as appropriate.

The very common adverse effects are nasopharyngitis, headaches and arthralgia, the common ones anaemia, hypersensitivity reactions, anxiety, cough and nausea.

It should be noted that there is only limited safety data on the treatment of patients with macular oedema due to type 1 diabetes. LUCENTIS has not been studied in patients who have previously received intravitreal injections, or in patients with active systemic infections, proliferative diabetic retinopathy or concomitant eye disorders such as detachment of the retina or macular hole. There are also no data on treatment with LUCENTIS in diabetic patients with HbA1c level over 12% and uncontrolled hypertension.

There are no safety data on treatment in patients with diabetic macular oedema with history of stroke or transient ischaemic attack. Caution is needed when treating these patients because of the potential risk of arterial thromboembolic events after the intravitreal administration of VEGF inhibitors (vascular endothelial growth factor).

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

3.2.3. Risk management plan (RMP)

The adverse effects monitored in the RMP are:

- identified risks: endophthalmitis, intraocular inflammation, tear in the retinal pigmented epithelium, retinal tears, retinal detachment, intravitreal haemorrhage, increased intraocular pressure, traumatic cataract and hypersensitivity reactions;
- potentiel risks: myocardial infarction, non-myocardial arterial thromboembolic events, venous thromboembolic events, hypertension, non-ocular haemorrhage, proteinuria and impairment of retinal blood flow;
- other risks: off-label use, bilateral treatment and overdose.

3.3. Conclusion

In a double-blind, randomised phase II study in patients with impaired visual acuity due to focal or diffuse diabetic macular oedema involving the centre of the macula (RESOLVE study), the efficacy of ranibizumab 0.5 mg in monthly intravitreal injections (n = 51) was demonstrated compared to placebo (shame intravitreal injections, n = 49) on the mean average change of best corrected visual acuity (BCVA) during the 12 months of treatment: +6.4 (± 9.2) ETDRS letters with ranibizumab versus -0.1 (± 9.8) letters with shame injections (p = 0.0004).

Ranibizumab 0.5 mg in monotherapy was compared to the combination of ranibizumab 0.5 mg + laser and to laser alone in a double-blind, randomised phase III study in 345 patients with focal or diffuse diabetic macular oedema with BCVA between 39 to 78 letters (RESTORE study). Ranibizumab was administered in monthly intravitreal injections for three months then for an additional nine months until visual acuity stabilised (absence of improvement in BCVA at the last two visits or BCVA ≥ 84 ETDRS letters). After stabilisation, patients could be treated with ranibizumab again. Laser photocoagulation was carried out on D1 in one or two sessions four weeks apart. Patients could receive renewed laser treatment after three months if this was considered necessary by the investigator.
The mean average change of BCVA from 1 to 12 months was 6.1 letters in the ranibizumab group, 5.9 letters in the ranibizumab + laser group and 0.8 letter in the group with laser alone. The differences observed between the ranibizumab groups, combined with laser or not, and the laser alone group were statistically significant (p < 0.0001).

Ranibizumab 0.5 mg in combination with concomitant or deferred laser was compared to laser in monotherapy in an independent study (DRCR Net). This study was randomised and double-blind, except for the group treated with deferred laser, and included 854 eyes with diabetic macular oedema involving the centre of the macula. The intravitreal injections were given monthly for three months then monthly for 12 months until stabilisation or, from the sixth month, according to the improvement obtained, at investigator's discretion. Laser photocoagulation was carried out three to ten days after the first intravitreal injection (concomitant laser) or at least six months after (deferred laser). Concomitant laser could be repeated after four months, deferred laser after six months. At inclusion, BCVA patients had to be between 24 and 78 letters.
After one year, the mean variation in BCVA compared to baseline was statistically higher (p < 0.001) in the groups combining ranibizumab with laser than that in the laser group (+ shame intravitreal injection) with differences of +5.8 letters (concomitant laser) and +6.0 letters (deferred laser) which represents a gain of 1/10.
After 1 year, the percentage of patients with a visual gain ≥ 15 letters in the ranibizumab + concomitant laser group (30%) and in the ranibizumab + deferred laser group (28%) was higher than in the laser + shame IVT group (15%; p < 0.001 for each comparisons). These values were maintained after two years.

The safety profile for ranibizumab in patients treated for diabetic macular oedema is similar to that observed in those treated for wet AMD except for the frequent occurrence (≥ 1/100, < 1/10) of urinary tract infections observed only in patients treated for diabetic macular oedema.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Diabetic macular oedema is a complication of diabetic retinopathy. It is asymptomatic but progresses towards visual impairment and blindness, which is a disability and leads to a marked deterioration in quality of life.

This pharmaceutical speciality is used for the curative treatment of impaired visual acuity due to diabetic macular oedema.

Public health benefit:

Diabetic retinopathy is a major cause of impaired vision and the leading cause of blindness in patients under 60 years of age, in the general population, in all industrialized nations.[2,3] Diabetic macular oedema (DME) is the leading cause of impaired visual acuity in diabetic patients. It is estimated that about 5% of diabetic patients will develop macular oedema.[4] Few epidemiological data are available on the prevalence of DME in France.

The burden of macular oedema is due to the visual acuity impairment and the related disability and quality of life deterioration. It may also have major repercussions at a psychosocial or professional level, all the more major in younger patients. The public health burden of DME can be regarded as moderate.

Reduction in frequency and severity of diabetes complications, improvement of screening and treatment of systemic disorders leading to ophthalmological complications and quality of life improvement for persons suffering from chronic diseases are established public health needs priorities (objectives 55 and 66 of the French Law of 9 August 2004 on public health policy, Plan for improving quality of life for patients with chronic diseases 2007-2011).

Based on the available data, LUCENTIS is expected to have low impact, by comparison with laser photocoagulation, on morbidity associated with DME (mainly in terms of visual acuity improvement) and on the treated patients quality of life . This impact is however considered moderate in the subpopulation of patients who cannot benefit from laser treatment.
However, the transposability of clinical study results to real life practice is not assured because of:

- doubts about the maintenance of its long-term efficacy in a population suffering from a chronic disorder such as diabetes;
- the unknown optimal number of intravitreal injections, the need for frequent reinjections and questions about retreatment criteria ;
- the insufficiency of data on poorly controlled diabetic patients.

Moreover, an impact on health care organisation is expected because of very regular follow-up consultations for patients with mobility issues.

[2] Porta M, Bandello F. Diabetic retinopathy. A clinical update. Diabetologia 2002; 45(12): 1617-34.
[3] Frank RN. Diabetic retinopathy. N Engl J Med 2004; 350(1): 48-58.
[4] Delcourt C, Massin P, Rosilio M. Epidemiology of diabetic retinopathy : expected *vs* reported prevalence of cases in the French Population. Diabetes Metab 2009; 35 (6): 431-8.

LUCENTIS should, despite everything, be able to provide an additional response to the identified public health need.

Consequently, LUCENTIS is expected to have a public health benefit in this indication. This benefit is **low**.

The efficacy/adverse effects ratio is high. Additional data are needed to confirm the long-term efficacy of ranibizumab in monotherapy.

Laser photocoagulation is the reference treatment for impaired visual acuity due to diabetic macular oedema. In absence of long-term data and because of the treatment regimen is unwieldy to implement, requiring monthly injections until stable visual acuity is reached at three consecutive monthly assessments under treatment, LUCENTIS should be reserved for patients who cannot benefit from laser treatment, i.e. in cases of diffuse macular oedema or leaks close to the centre of the macula. Treatment with ranibizumab can be initiated when visual acuity is less than or equal to 5/10 and diabetes management has been optimised.

There is an alternative treatment: laser photocoagulation in focal forms.

The actual benefit provided by LUCENTIS 10 mg/ml, solution for injection, is **important** in patients with visual impairment less or equal to 5/10 due to diabetic macular oedema in cases of diffuse type or leaks close to the centre of the macula and where diabetes management has been optimised.
It is **insufficient** in the other cases.

4.2. Improvement in actual benefit (IAB)

Since there are no data on the long-term maintenance of the efficacy of LUCENTIS 10 mg/ml, solution for injection, in monotherapy on visual acuity, this product is regarded as providing a minor improvement in actual benefit (IAB IV) in the strategy for treatment of visual impairment due to diabetic macular oedema in with diffuse type or leaks close to the centre of the macula for patients with visual acuity less than or equal to 5/10 and in whom diabetic management has been optimised.

4.3. Therapeutic use

4.3.1. Therapeutic strategy

Diabetic macular oedema is a complication of diabetic retinopathy. Maintaining glycaemia[5] and blood pressure[6] balance reduces the risk of developing macular oedema.

Laser photocoagulation is the only treatment with proven efficacy in reducing visual impairment due to diabetic macular oedema. It does permit any gain in visual acuity.
There are two laser photocoagulation techniques for diabetic macular oedema:

- focal photocoagulation pointed at focal lesions responsible for the oedema (microaneurysm and/or specific blood vessels)
- “staggered” perifoveal non-confluent photocoagulation (“grid” photocoagulation) for the treatment of diffuse macular oedema.

Laser treatment is effective for focal types.
When lesions are close to the centre of the macula, the expected benefits of this treatment must be weighed up against the possible complications: paracentral scotoma, accidental

[5] DCCT – The diabetes control and complications trial research group. The effect of intensive treatment of dibetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.
[6] UK Prospective Diabetes Study Group Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-13

foveal impact, neovascularisation that develops from a photocoagulation scar. Because of these side effects, the number of retreatments must be limited.

According to the ETDRS recommendations[7], all patients with clinically significant macular oedema must receive laser treatment, whatever their visual acuity, to limit the macular oedema progression.
Clinically significant oedema is defined by one of the following 3 criteria:

- retinal thickening and/or exudates reaching the centre of the macula
- retinal thickening and/or exudates located less than 500 µm from the centre of the macula but not reaching it
- retinal thickening with a surface area of 1 papilla diameter (PD) or more, located at least in part less than 1 PD from the centre of the macula.

Surgical treatment by vitrectomy is indicated for rare cases of tractional macular oedema induced by contraction of the thickened and condensed premacular hyaloid membrane.

4.3.2. Place of the proprietary medicinal product in therapeutic use

In absence of long-term data on the use of ranibizumab in monotherapy and because the treatment regimen is unwieldy to implement, requiring monthly injections until stable visual acuity is reacged at three consecutive monthly assessments under treatment, treatment by laser photocoagulation remains the reference treatment.
Ranibizumab should be reserved for patients who cannot benefit from laser treatment, i.e. in cases of diffuse type or of leaks close to the centre of the macula. Treatment with ranibizumab must be initiated when visual acuity becomes less than or equal to 5/10, as it is done with laser photocoagulation, and only if diabetes management has been optimised.

In absence of specific data, LUCENTIS is not recommended in diabetic macular oedema with focal and diffuse components.

The place of ranibizumab in diabetic macular oedema with focal and diffuse components has still to be ascertained.

4.4. Target population

The target population for LUCENTIS in its extension of indication is defined as patients with impaired visual acuity of less than or equal to 5/10 due to diabetic macular oedema in the case of the diffuse type or central leaks and in whom diabetes management has been optimised.

The prevalence of diabetes in France is 4.4% (Entred[8]) i.e., given the general population of France (INED 2010 data), is a population of 2 839 000 patients.
The prevalence of diabetic macular oedema has been estimated as 4.8% (Delcourt, 2009[9]), i.e. 136 000 patients.
About 2/3 of patients are thought to have associated impairment of visual acuity (expert opinion), i.e. 89 760 patients.
About half are thought to have glycemic equilibrium (Entred), i.e. 44 880 patients.

About half the DME cases are diffuse (Romero, 2007[10]), i.e. about 22 000 patients.

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[7] Early Treatment Diabetic Retinopathy Study Report Number 1: Photocoagulation for diabetic macular edema, Early Treatment Diabetic Retinopathy Study Research Group Arch. Ophtalmol 1985; 103(12): 1796-1806.

[8] Entred InVS study results 2007-2010: http://www.invs.sante.fr/entred/

[9] Delcourt et al. Epidemiology of diabtetic retinopathy : expected *vs* reported prevalence of cases in the French Population. Diabetes Metab (2009), doi:10.1016/j.diabet.2009.06.002

DME with central leaks (expert opinion): about 10 000 patients.

The target population for LUCENTIS in its extension of indication can therefore be estimated at about 32 000 patients. Account must also be taken of the fact that a number of patients could have both eyes treated.

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 extension of indication subject to the conditions defined below and in the dosage in the MA.

Scope of reimbursement

The reimbursement of LUCENTIS 10 mg/ml, solution for injection, in the extension of indication is limited to patients with impairment of visual acuity of less than or equal to 5/10 due to diabetic macular oedema which is not eligible for laser treatment, i.e. in cases with diffuse type or leaks close to the centre of the macula and in cases where diabetes management has been optimised.

Exceptional medicinal product: The prescribing information for LUCENTIS will be updated accordingly.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%

Study requests

Taking into account:

- the unknown optimal number of intravitreal injections and the need for frequent reinjections associated with follow-up in very regular patient consultations,
- the insufficiency of long-term efficacy data both on the maintenance of the visual acuity improvement (in a population with a chronic disease like diabetes) and on the quality of life and the avoided disability,
- the insufficiency of data on poorly controlled diabetic patients (HBA1c, blood pressure),
- uncertainty about the place of the treatment by comparison with laser,

the Transparency Committee asks the company to supply additional data that will allow it to assess the place of LUCENTIS by comparison with the available alternatives (laser, corticosteroids, others, etc.) in the treatment of diabetic macular oedema in France and the impact of LUCENTIS on the progression of visual acuity (in the medium and the long term), on the quality of life and the avoided disability of patients treated. Predictive factors for the treatment response must be analysed.

[10] Romero P et al. Diabetic macular edema and its relationship to renal microangiopathy: a sample of Type I diabetes mellitus patients in a 15-year follow-up study. J Diabetes Complications 2007; 21(3) Pages: 172-180.

In particular, data must be submitted on:

- conditions of the initiation of treatment (characteristics of treated patients, in particular type and duration of diabetes) and follow-up (monitoring of HBA1c, monitoring of blood pressure, previous treatments, combined treatments);
- the conditions for use of specialty, in particular the injection frequencies and the methods of visual acuity monitoring;
- compliance with treatment and the reasons for continuing and stopping it (tolerance, lack of efficacy, other, etc.);

In the case of scheduled or ongoing studies, particularly as part of the European Risk Management Plan, do not provide data that answer all the questions asked by the Transparency Committee, a specific study will have to be carried out.

The duration of the study, determined by the independent scientific committee, will have to be justified and sufficient to answer the Committee's questions.