HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 March 2007

LUCENTIS 10 mg/ml, solution for injection
Box of 1 x 0.3 ml vials (CIP: 378 101-5)

NOVARTIS PHARMA S.A.S.

ranibizumab

List I
Prescription-only medicine restricted to ophthalmologists

Marketing authorisation (MA) date: European decision of 22 January 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ranibizumab

1.2. Indications

LUCENTIS is indicated for the treatment of the neovascular (wet) form of age-related macular degeneration (AMD).

1.3. Dosage and method of administration

Single-use vial exclusively for intra-vitreous administration.

The recommended dose of Lucentis is 0.5 mg (0.05 ml).

Lucentis treatment starts with an induction phase of 1 injection per months for 3 consecutive months, followed by a maintenance phase during which the visual acuity of the patient should be monitored once a month. If the patient shows a loss in visual acuity of more than 5 letters on the "Early Treatment Diabetic Retinopathy Study" (ETDRS) scale, or the equivalent of one line on the Snellen scale, Lucentis should be administered. The interval between two doses should not be less than 1 month.

Lucentis should be administered by a qualified ophthalmologist who is experienced in giving intra-vitreous injections.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

S:	Sensory organs
S01:	Ophthalmologicals
S01L:	Medicines for AMD
S01LA:	Ocular anti-neovascularisation agents.
S01LA04:	ranibizumab

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Medicines of the anti-VEGF class indicated in the treatment of exudative AMD:

MACUGEN 0.3 mg (pegaptanib)

2.2.2. Competitor evaluation

None

2.3. Medicines with a similar therapeutic aim

VISUDYNE (verteporfin) is a photosensitising agent used in photodynamic therapy (PDT), which is indicated in the treatment of AMD with predominantly classic choroidal neovascularization (CNV) or with occult CNV showing signs of recent progression or in the course of the disease. VISUDYNE is also indicated in the treatment of subfoveal CNV due to pathological myopia.

3 ANALYSIS OF AVAILABLE DATA

The efficacy and tolerability of ranibizumab have been evaluated in 3 phase III studies, the chief characteristics of which are described in the following table[1].

Study	Design	Patients (study population)	Treatment regiment	Treatment (sample size)
FVF2598g **MARINA** Phase III	Randomised, double-blind **vs placebo (sham intra-vitreous injections)**	AMD with subfoveal CNV **minimally classic or totally occult** (n = 716)	Ranibizumab: monthly intra-vitreous injections for 24 months (maximum: 24 injections)	Ranibizumab 0.3 mg (n=238) Ranibizumab 0.5 mg (n=240) Sham injections (n=238)
FVF2587g **ANCHOR** Phase III	Randomised, double-blind, double-placebo **versus active treatment:** PTD with verteporfin	AMD with subfoveal CNV **predominantly classic:** (n = 423)	Ranibizumab: monthly intra-vitreous injections for 24 months (maximum 24 injections) -PDT with verteporfin every 3 months if required Results available for 12 months	Ranibizumab 0.3 mg (n=140) Ranibizumab 0.5 mg (n=140) PTD with verteporfin (n=143)
FVF3192g **PIER** Phase IIIb	Randomised, double-blind, **vs. placebo (sham intra-vitreous injections)**	AMD with subfoveal CNV (n = 184)	Ranibizumab: monthly intra-vitreous injections for 3 months then quarterly for 21 months Results available for 12 months	Ranibizumab 0.3 mg (n=60) Ranibizumab 0.5 mg (n=61) Sham injections (n=63)

3.1. Efficacy

MARINA Study

Phase III, randomised, double-blind study comparing ranibizumab 0.3 and 0.5 mg by monthly intra-vitreous injection for 24 months and sham intra-vitreous injections in patients with AMD and minimally classic or occult subfoveal CNV.

Inclusion criteria:

- age ≥ 50 years,
- in the eye studied, primary progressive or recurrent CNV secondary to AMD,
- lesions with occult CNV or some classic CNV if < 50% of the total lesion area,
- total area of CNV (both classic and occult) within the lesion being ≥ 50% of the total lesion area,
- total lesion area ≤ 12 papillary diameters,
- best corrected visual acuity between 20/40 and 20/320 (Snellen equivalent) on the ETDRS scale.

[1] For more details about the studies, see EPAR at www.emea.europa.eu

Treatment:
- Ranibizumab 0.3 mg (n=238)
- Ranibizumab 0.5 mg (n=240)
- Sham injections (n=238)

Intra-vitreous injections of ranibizumab or sham injections monthly for 24 months (maximum: 24 injections for 24 months).

Primary endpoint: percentage of patients having lost less than 15 letters (approximately 3 lines) in the measure of best corrected visual acuity (BCVA) at 12 months compared to the baseline value. Visual acuity is measured on the ETDRS scale at an initial distance of 2 metres.

Other endpoint: percentage of patients having gained at least 15 letters at 12 months compared to the baseline value

Results:
Before treatment, approximately 2/3 patients had occult CNV without classic CNV and 1/3 patients had lesions with minimal classic CNV.

The mean duration of treatment was 590 ± 191.2 days with sham injections, 651 ± 130.2 days with ranibizumab 0.3 mg and 639.9 ± 148.2 days with ranibizumab 0.5 mg.
The mean number of injections was 20.0 ± 6.6 with sham injections, 22.1 ± 4.4 days with ranibizumab 0.3 mg and 21.7 ± 5.0 days with ranibizumab 0.5 mg.
Over the two-year treatment period, 38 patients in the sham injection group (namely 15.8%) were treated at least once with PDT using verteporfin.

Percentage of patients having lost less than 15 letters of BCVA at an initial distance of 2 metres at 12 months (primary endpoint) and at 24 months:

	Sham injections (n=238) (n=238)		**Ranibizumab:**			
			0.3 mg (n= 238)		**0.5 mg (n=240)**	
	12 months	24 months	12 months	24 months	12 months	24 months
N patients having lost <15 letters, (%)	148 (62.2%)	126 (52.9%)	225 (94.5%)	219 (92.0%)	227 (94.6%)	216 (90.0%)
Difference vs. sham inj. (%)			32.3%	39.1%	32.4%	37.1%
p (vs. sham inj.)			<0.0001	<0.0001	<0.0001	<0.0001

At 12 months, the percentage of patients having lost less than 15 letters of BCVA was significantly greater with ranibizumab (94.5% with the 0.3 mg dose and 94.6% with the 0.5 mg dose) than with the sham injections (62.2%). This significant difference was maintained up to the 24-month point.

The percentage of patients having gained at least 15 letters of BCVA at 12 months was 24.8% with ranibizumab 0.3 mg, 33.8% with ranibizumab 0.5 mg and 4.6% with the sham injections (significant differences versus the sham injections, p<0.0001).

ANCHOR Study

Phase III, randomised, double-blind, double-placebo study with the aim of showing the non-inferiority of ranibizumab 0.3 or 0.5 mg administered as monthly intra-vitreous injections compared with photodynamic therapy with verteporfin (every 3 months if required over a period of 21 months) in patients with AMD with predominantly classic CNV.

Inclusion criteria:

- age ≥ 50 years,
- eligible for photodynamic therapy (PDT) in the eye studied according to recommendations for the product,
- patient awaiting PDT with verteporfin,
- subfoveal CNV secondary to AMD
- classic CNV (well delimited areas of hyperfluorescence in the early phase of angiography) ≥ 50% of the total lesion area,
- one lesion ≤ 5400µm in its greatest linear dimension,
- best corrected visual acuity between 20/40 and 20/320 (Snellen equivalent) on the ETDRS scale.

Treatment:

- Ranibizumab 0.3 mg (n=140)
- Ranibizumab 0.5 mg (n=140)

Monthly injections of ranibizumab (maximum: 24 injections for 24 months)

- PTD with verteporfin (n=143) every 3 months, if required, over 21 months

Primary endpoint: percentage of patients having lost less than 15 letters of BCVA (approximately 3 lines) in the measure of best corrected visual acuity at 12 months compared. Visual acuity is measured on the ETDRS scale at an initial distance of 2 metres.

Other endpoint: percentage of patients having gained at least 15 letters at 12 months compared to the baseline value

Results:

Only results for 12 months are available. On average, during this period, the patients in the 2 ranibizumab received approximately 12 injections, while those in the PDT with verteporfin group received approximately 2.8 injections.

The initial objective of this study was to show the non-inferiority of ranibizumab compared to photodynamic therapy with verteporfin. The results showed the superiority of ranibizumab 0.3 mg and 0,5 mg compared to verteporfin in terms of the percentage a 12 months of patients having lost less than 15 letters of BCVA: 94.4% with ranibizumab 0.3 mg, 96.4% with ranibizumab 0.5 mg and 64.3% with verteporfin (see table below).

Percentage of patients having lost less than 15 letters of BCVA at an initial distance of 2 metres:

	verteporfin PDT (n=143)	ranibizumab 0.3 mg (n= 140)	ranibizumab 0.5 mg (n= 140)
N analyses	143	140	139*
N patients having lost <15 letters, (%)	92 (64.3%)	132 (94.3%)	134 (96.4%)
p (vs verteporfin PDT)		<0.0001	<0.0001

* One patient without VA before treatment was excluded from the analysis.

The percentage of patients having gained at least 15 letters of BCVA at 12 months was 35.7% with ranibizumab 0.3 mg, 40.3% with ranibizumab 0.5 mg and 5.6% with verteporfin (significant differences versus verteporfin, p<0.0001).

N.B.: The difference observed between ranibizumab and verteporfin in the % of patients who lost less than 15 letters is of the same order as that observed between ranibizumab and sham injections (approximately 30%). It would have been desirable to have had a 3rd placebo arm to validate the level of efficacy of verteporfin in this study.

PIER Study

Phase III, randomised, double-blind study, comparing ranibizumab 0.3 and 0.5 mg administered as monthly intra-vitreous injections for 3 months and then quarterly for 21 months and sham injections (total study duration: 24 months), in patients with subfoveal CNV secondary to AMD, with or without classic CNV.

Inclusion criteria for patients:
- age ≥ 50 years,
- in the studied eye, subfoveal CNV, primary progressive or recurrent, secondary to age-related macular degeneration (AMD) with or without classic CNV,
- total area of CNV (both classic and occult) within the lesion being ≥ 50% of the total lesion area,
- total lesion area ≤ 12 papillary diameters,
- best corrected visual acuity in the studied eye of between 20/40 and 20/320 (Snellen equivalent) on the ETDRS scale.

Treatment:
- Ranibizumab 0.3 mg (n=60)
- Ranibizumab 0.5 mg (n=61)
- Sham injections (n=63)

Intra-vitreous injections of ranibizumab or sham injections monthly for 3 months and then quarterly for 21 months.

Primary endpoint: mean variation in the best corrected visual acuity after 12 months of treated, assessed using the ETDRS scale at an initial distance of 4 metres.

Other endpoint: percentage of patients having gained at least 15 letters at 12 months compared to the baseline value

Results:
Before treatment, approximately 40% of patients in the study had purely occult CNV, 40% had minimally classic CNV and 20% had predominantly classic CNV.

Mean visual acuity and mean variation in visual acuity of the studied eye at 12 months at an initial distance of 4 metres:

	Sham injections (n=63)	**ranibizumab**	
		0.3 mg (n= 60)	**0.5 mg (n= 61)**
Number of letters of visual acuity			
Mean (SD)	38.8 (21.1)	54.2 (18.7)	53.6 (19.6)
p (vs sham injection)		< 0.0001	< 0.0001
Variation in number of letters compared to baseline values			
Mean (SD)	-16.3 (22.3)	-1.6 (15.1)	-0.2 (13.1)
p (vs sham injection)		0.0001	< 0.0001

At 12 months, the loss in the number of letters in measures of visual acuity was significantly less with ranibizumab 0.3 mg (-1.6 letters) and 0.5 mg (-0.2 letters) than with sham injections (-16.3 letters). The curve of the changes in the mean variation in visual acuity compared to the baseline visual acuity of patients treated with ranibizumab shows that, following an initial increase (after 3 months with monthly administration), visual acuity returned to its baseline value after 12 months. However, of these patients, 90% had retained their visual acuity in the 12^{th} month.

Percentage of patients having lost less than 15 letters compared to baseline values:

	Sham injections (n=63)	**ranibizumab**	
		0.3 mg (n= 60)	**0.5 mg (n= 61)**
N patients having lost <15 letters, (%)	31 (49.2%)	50 (83.3%)	55 (90.2%)
Difference vs sham injection (%)		34.1%	41.0%
p (vs sham injection)		< 0.0001	< 0.0001

At 12 months, the percentage of patients having lost less than 15 letters of BCVA was significantly greater with ranibizumab 0.3mg (83.3%) and 0.5 mg (90.2%) than with the sham injections (49.2%).

The percentage of patients having gained at least 15 letters of BCVA at 12 months was 11.7% with ranibizumab 0.3 mg, 13.1% with ranibizumab 0.5 mg, and there was no significant difference versus the sham injections (9.5%). These percentages in gains of at least 15 letters are smaller then those obtained in the previous studies.

3.2. Adverse effects/safety

The most frequently reported adverse events (>10%) in the 3 phase III studies (MARINA, ANCHOR and PIER) were ocular: conjunctival haemorrhage, ocular pain, vitreous floaters, retinal haemorrhage, increase in intraocular pressure, vitreous detachment, intraocular inflammation, ocular irritation, cataract, sensation of a foreign body in the eye, vision problems, blepharitis, subretinal fibrosis, ocular hyperaemia, vision problems/decrease in visual acuity, dry eyes, hyalitis.

Serious adverse events associated with the injection procedure, occurring with less than 0.1% of injections, including endophthalmia, rhegmatogenous retinal detachment, retinal tearing and iatrogenic traumatic cataracts.

Other serious ocular events were observed in less than 1% of patients treated with ranibizumab. They included intraocular inflammation and increased intraocular pressure.

With respect to systemic adverse events, arterial hypertension was also frequently observed (>10%).

In the MARINA et ANCHOR studies, after 1 year of treatment, serious adverse events (potentially associated with systemic anti-VEGF effects) were more frequent with ranibizumab 0.5 mg (3.8 – 5.7%) and 0,3 mg (2.9 – 3.4%) than with the sham injections (0.8 – 2.1%). These effects were mainly haemorrhage and thromboembolic accidents (0.8 – 2.1% with the sham injections, 1.3 – 2.2% with ranibizumab 0.3 mg and 2.1 – 4.3% with ranibizumab 0.5 mg). This absence of uniformity between the groups with respect to the occurrence of these adverse effects was not observed after 2 years of treatment in the MARINA study (3.8% with ranibizumab 0.3 mg, 4.6% with ranibizumab 0.5 mg and 4.6% with the sham injections).
However, following issue of a marketing authorisation for Europe, EMEA and Afssaps have been informed of preliminary results from a comparative study of tolerability (SAILOR study) between doses of 0.3 mg and 0.5 mg ranibizumab. This is an open study with planned inclusion of 5000 patients, for which preliminary results have shown an increased incidence of cerebrovascular accidents with 0.5 mg ranibizumab [1.2% (13/1217)] than with 0.3 mg ranibizumab [0.3% (3/1176)]. In the USA, these preliminary results have caused GENENTECH (holder of the MA for LUCENTIS in the USA) to distribute an informative letter to ophthalmologists. Following assessment by EMEA of the new preliminary results, it emerges that the difference previously observed between the doses in terms of cerebrovascular accidents has not been confirmed. While awaiting definitive results for the study, no specific mention has been added to the SPC.

A risk-management plan has been established to monitor in particular the occurrence over the long term of thromboembolic accidents and intraocular inflammation (possibly associated with the appearance of anti-ranibizumab antibodies).

3.3. Conclusion

The efficacy and tolerability of ranibizumab were investigated in 3 phase III, randomised, double-blind, comparative studies versus sham intra-vitreous injections or photodynamic therapy with verteporfin (non-inferiority study).

In these 3 studies, ranibizumab was administered at a dose of 0.3 mg or 0.5 mg (the dose cited in the MA is 0.5 mg). Two studies were performed using a dosage regimen of monthly intra-vitreous injections for 24 months (ANCHOR studies, for which results at 12 months are available, and the MARINA study). The 3rd study (PIER study) was conducted using injections monthly for 3 months and then quarterly for 21 months (total study duration: 24 months; results for 12 months available), in patients with AMD, with or without classic CNV.
In the MARINA study (n=716), ranibizumab was compared with sham injections in patients with AMD and occult subfoveal CNV or occult and minimally classic subfoveal CNV.
In the ANCHOR study (n=423) ranibizumab was compared with PDT using verteporfin (every 3 months if required for 21 months) in patients with AMD and predominantly classic CNV.
In the PIER study (n=184), ranibizumab was compared with sham injections. All CNV types were represented among the patients recruited (purely occult, predominantly classic and minimally classic).
The dosage regimen in the MA lies between the two dosage regiments used in the studies: 3 injections initially at intervals of 1 month followed by a maintenance phase with retreatment possible in the event of loss of vision equivalent to 5 letters on the ETDRS scale.

It is clear from these studies, which included patients with AMD and occult or minimally classic (MARINA study) or classic subfoveal CNV (ANCHOR study) or all 3 types of lesion (PIER study), that the ranibizumab effect (0.3 mg or 0.5 mg) can be considered substantial compared to that observed in patients given sham injections or treated with PDT using verteporfin. In fact, the percentage of patients losing less than 15 letters of visual acuity (ETDRS) ranged from 90 to 96% in the ranibizumab groups and the observed differences versus sham injections or verteporfin were of the order of 30 to 40%.
Ranibizumab did not only enable a significant slowing of the decrease in visual acuity, but also improved visual acuity in a significant percentage of patients (35 to 40% vs. 5.6% with verteporfin in the ANCHOR study and 4.6% with the sham injections in the MARINA study). The absence of a placebo arm in the non-inferiority study versus verteporfin is nevertheless regrettable, since the internal validity of the study could not be ensured. It should be noted that such a significant percentage of patients gaining at least 15 letters on the ETDRS scale was not observed in the PIER study, in which ranibizumab was injected every 3 months after the induction phase (11.7% and 13.1% with ranibizumab 0.3 mg and 0.5 mg, with no significant difference compared to sham injections).

The adverse events observed in the studies were primarily ocular and were associated with the procedure of intra-vitreous injection. A risk-management plan associated with the placement of ranibizumab on the European market provides for specific monitoring of thrombolembolic adverse effects as well as intraocular inflammatory (possible association with the appearance of anti-ranibizumab antibodies).
A greater incidence of systemic thromboembolic adverse effects, especially cerebrovascular accidents with the 0.5 mg ranibizumab dose compared to the 0.3 mg dose was suspected following the first preliminary analysis of the American SAILOR study on tolerability, but was not confirmed in a second preliminary analysis by EMEA. The definitive results of the SAILOR study are awaited.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Age-related macular degeneration (AMD) is the primary cause of blindness in France in patients aged over 50. Among severe forms of AMD, the exudative or neovascular forms are responsible for the greatest number of cases of severe visual acuity loss.

This proprietary drug is intended to provide curative treatment of the consequences of the disease.

Public health benefit:

The burden on public health imposed by subfoveal wet AMD is modest.

Improving the management of AMD is a public health requirement (priority for GTNDO[2]).

In view of the available data, and taking into account the existing therapies, a moderate impact of the proprietary product LUCENTIS is expected on the morbidity associated with AMD (essentially in terms of maintaining visual acuity).

However, there is no guarantee that the results of trials will be transposed into actual practice because:

- there are doubts about efficacy being maintained over the long term,
- it is not known what the optimum number of intravitreous injections is and there are questions about criteria for repeat treatment,
- there are doubts about the injection procedure being mastered and scrupulously observed in order to prevent local serious adverse events from occurring.

Notwithstanding, LUCENTIS should be able to provide a supplementary response to the identified public health requirement.

Consequently, LUCENTIS is expected to have an impact on public health. This benefit is moderate.

The efficacy and tolerability of LUCENTIS have been investigated in studies which included only patients affected by AMD with subfoveal CNV. In these patients the efficacy/adverse effects ratio for this product is considered to be substantial.

Ranibizumab is a first-line treatment.

There are other alternative therapies (MACUGEN, VISUDYNE).

The actual medical benefit provided by LUCENTIS is substantial in the case of subfoveal wet AMD.
In view of the absence of data on the efficacy and tolerability of LUCENTIS in non-subfoveal wet AMD, the committee cannot comment on the actual medical benefit provided by LUCENTIS for this type of condition.

[2] National Technical Group for Defining Public Health Objectives (DGS-2003)

4.2. Improvement in actual benefit

LUCENTIS 10 mg/ml, solution for injection, provides a significant improvement in actual benefit (level II) in the management of patients with AMD and subfoveal CNV.

4.3. Therapeutic use

In the treatment of exudative forms of AMD, laser photocoagulation may only be used in extrafoveal forms. When subfoveal CNV is present, laser photocoagulation is not possible and other forms of treatment may be used.

Photodynamic treatment using verteporfin (VISUDYNE) as the photosensitising agent was the first treatment available for subfoveal lesions. Since the marketing of VISUDYNE was authorised, the efficacy of anti-VEGF agents administered by intra-vitreous injection has been acknowledged for the treatment of wet AMD: pegaptanib, bevacizumab and ranibizumab. Pegaptanib (MACUGEN) and ranibizumab (LUCENTIS) are currently the only drugs which have obtained marketing authorisation in France for the indication “treatment of the neovascular (wet) form of AMD”. Another anti-VEGF agent, bevacizumab (AVASTIN), is used outside the scope of its MA.

There are currently no recommendations about the therapeutic strategy of treatment of wet AMD.

VISUDYNE has a more restricted indication than those of MACUGEN and LUCENTIS; in particular VISUDYNE is not indicated in AMD with minimally classic CNV.

MACUGEN has not been compared with VISUDYNE; however, the results suggest that these two treatments have an efficacy of the same order of magnitude.

On the contrary, LUCENTIS has been compared with VISUDYNE in patients with AMD and predominantly classic subfoveal CNV. LUCENTIS is superior to VISUDYNE (monthly injections) in terms of slowing loss of visual acuity and promoting a gain in visual acuity: the observed percentage of patients showing a gain in visual acuity of at least15 letters on the ETDRS scale was 40.3% versus 5.6% with VISUDYNE (patients treated with monthly injections).

Although the results of studies versus placebo (sham intra-vitreous injections) suggest better efficacy of LUCENTIS compared to MACUGEN, so far no direct comparative data exist.

At the same time as using VISUDYNE as a single treatment, the experts point out that combined treatments are being increasingly used, where VISUDYNE is combined with triamcinolone (KENACORT) in intra-vitreous injections (off-label indication) or with an anti-VEGF in intra-vitreous injections (randomised studies are in progress).

4.4. Target Population

Although the indication for LUCENTIS includes all types of wet AMD, LUCENTIS should be reserved for purely subfoveal forms because laser treatment remains the standard for extrafoveal forms. The target population for LUCENTIS, as estimated below, is defined by the patients affected by AMD with choroidal neovascularisation (wet AMD), located subfoveally.

In order to estimate the target population for LUCENTIS, the incidence approach was preferred to the prevalence approach as it is newly diagnosed cases which will be likely to benefit from treatment.

A recent study (Korobelnik J.-F. et al., 2006) estimated the annual incidence of the number of eyes affected by treatable AMD in France, using the Markov model specifically developed in order to take into account mortality, treatment duration, mean age of the diagnosis and the probability of AMD affecting the second eye. The data used in the model came from a comprehensive review of the literature. The results of the Rotterdam study (van Leeuwen R. et al., 2003) were chosen for estimating the annual rate of incidence of AMD in the first eye. They were then standardised based on age (direct standardisation method based on United Nations data).

The results were determined based on the following assumptions formulated after analysing the literature data and creating a basic scenario:

- a mean treatment duration of 2 years
- a mean age for the diagnosis of the illness of 75 years
- an incidence of AMD in the second eye of 30% in the 5 years after diagnosis in the first eye.

The results obtained based on the model, according to the basic scenario, indicate that the number of treatable eyes for subfoveal wet AMD would have been between 37,000 and 39,000 in 2005. The model provides for a 2% increase per year up to 2025.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services.

The Transparency Committee wishes to be provided with data on the follow-up of the patients with AMD being treated with LUCENTIS in France. The purpose of this is to document in a real-life treatment situation:

- conditions for initiation of treatment (characteristics of treated patients, previous treatments, associated treatments….),
- the conditions of use of this product, especially the dosage regiment (dosage and frequency of injections) and the manner in which visual acuity is monitored,
- the impact of this treatment on the changes in visual acuity over the medium and long term and on the quality of life and avoided disablement of these patients.
- the impact of tolerability on the maintenance of treatment,
- the factors predictive of response to treatment.

If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted.
The study duration, determined by an independent scientific committee, must be justified and sufficient to answer the Committee demand.

4.5.1. Reimbursement criteria and corresponding dosages

The committee recommends reimbursement for LUCENTIS in the treatment of AMD with choroidal neovascularisation only in subfoveal forms and at the dosage approved by the Marketing Authorisation.

4.5.2. Packaging

LUCENTIS is packaged in a single-use vial of 0.3 ml, the dose taken being 0.05 ml. The Committee considers that the packaging is not suitable for the conditions of prescription and recommends a new packaging that is better adapted, such as a pre-filled syringe.

4.5.3. Reimbursement rate

65%

4.5.4. Exception drug status

The committee recommends awarding LUCENTIS the status of special exception drug. A prescription guide will specify the scope of reimbursement and the relevant dosage, along with the conditions for initiating treatment, monitoring patients and discontinuing treatment with LUCENTIS.