HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

29 November, 2006

Review of the dossier of the proprietary drug included on the list of reimbursable products for a period of 5 years by the order of 13 February, 2001 (Official Journal of 22 February, 2001)

**VISUDYNE 15 mg, powder for solution for intravenous infusion**
**Box of 1 vial of 15 mg (CIP: 355 307-6)**

**Applicant : NOVARTIS PHARMA S.A.S.**

Verteporfin

List I
Prescription restricted to ophthalmologists. Medicine requiring special monitoring during treatment.
Exception drug status

Date of European Marketing Authorisation (MA): 27 July 2000

Date of MA adjustments:

| | |
|---|---|
| 20 March 2001: | Extension of indication: “treatment of patients with classic subfoveal choroidal neovascularisation subfoveal (SCNV) secondary to pathological myopia” |
| 22 August 2002: | Extension of indication: “treatment of age-related macular degeneration in patients with occult classic subfoveal choroidal neovascularisation (SCNV) with evidence of recent or ongoing disease progression” |
| 24 May 2002: | Undesirable effects and warnings and precautions for use |
| 29 March 2005: | Undesirable effects and warnings and precautions for use |

Reason for request: renewal of inclusion on the list of medicines reimbursed by National Insurance

Health Technology Assessment Division

## CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Verteporfin

### 1.2. Indications

Visudyne is indicated for the treatment of
- patients with exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (SCNV) or
- patients with subfoveal choroidal neovascularisation secondary to pathological myopia.

### 1.3. Dosage

Visudyne should be used only by ophthalmologists experienced in the management of patients with age-related macular degeneration or pathological myopia.

Visudyne photodynamic therapy is a two-steps process:

1. The first step is a 10-minutes intravenous infusion of Visudyne at a dose of 6 mg/m$^2$ body surface area, diluted in 30 ml of infusion solution.
2. The second step is the light activation of Visudyne at 15 minutes after the start of the infusion.

Patients should be re-evaluated every 3 months. In the event of recurrent SCNV leakage, Visudyne therapy may be given up to 4 times per year.

## 2 REMINDER OF THE TRANSPARENCY COMMITTEE'S OPINION AND CONDITIONS OF INCLUSION

Opinion of 11 October 2000:

**Treatment of AMD in patients with predominantly** classic subfoveal choroidal neovascularisation (SCNV)**:**
The actual benefit (AB) of Visudyne is substantial in this indication.

The improvement in actual benefit (IAB) is major (level I).

Opinion of 20 November 2002:

**Treatment of patients with** classic subfoveal choroidal neovascularisation (SCNV) **due to pathological myopia:**

The AB of Visudyne is substantial in this extension of indication.

The IAB is major (level I).

Opinion of 23rd July 2003:

**Treatment of patients with AMD with occult** classic subfoveal choroidal neovascularisation (SCNV) **with evidence of recent or ongoing disease progression:**

The AB of Visudyne is substantial.

A level I IAB is confirmed in the extension of indication to the treatment of patients presenting age-related macular degeneration with occult classic subfoveal choroidal neovascularisation (SCNV) with evidence of recent or ongoing disease progression.

Due to the lack of sufficient data, the Transparency Committee cannot reach an opinion on forms of subfoveal SCNV associated with pigment epithelium detachments or retinochoroidal anastomosis.

Investigations carried out to confirm the diagnosis must include fluorescein angiography followed by an ICG angiography. The ophthalmologist should keep records of all data obtained to justify institution of treatment.

Opinion of December 17, 2003 (addendum to opinion of July 23, 2003):

**New assessment of the indication for treatment of patients with AMD with occult** classic subfoveal choroidal neovascularisation (SCNV) **with evidence of recent or ongoing disease progression**

The AB is substantial in occult classic subfoveal choroidal neovascularisation (SCNV) AMD with evidence of recent or on-going disease progression (except in the case of pigment epithelium detachment and/or retinochoroidal anastamosis).

The AB is insufficient in the case of patients with pigment epithelium detachment.

The AB is minor in the case of patients with incipient retinochoroidal anastomosis, without pigment epithelium detachment.

The AB is insufficient in the case of patients with non-incipient retinochoroidal anastomosis (with scarring fibrosis).

In forms associated with incipient anastomosis (no scarring fibrosis) without pigment epithelium detachment, Visudyne provides a moderate IAB (level III) in terms of efficacy compared to the usual management.

## 3 SIMILAR MEDICINAL PRODUCTS

### 3.1. ATC Classification (2006)

L : Antineoplastics and immunomodulators
01 : Antineoplastic medicinal products
X : Other antineoplastic agents
D : Agents used in photodynamic therapy
02 : Verteporfin

### 3.2 Medicines in the same therapeutic category

None.

**Medicines with a similar therapeutic aim** : Pegaptanib (MACUGEN), with anti-angiogenic activity, recently obtained an MA (January 31, 2006) in the indication “treatment of the neovascular form (wet, exudative) of AMD”.

In exudative forms but non-subfoveal forms of AMD, the reference treatment is laser photocoagulation.

# 4 ANALYSIS OF AVAILABLE DATA

The results described below are based on studies concerning the indications of AMD with predominantly classic subfoveal choroidal neovascularisation (SCNV) and subfoveal SCNV due to pathological myopia. These studies followed by long-term extension phases were provided by the laboratory in the current dossier.

## 4.1 Efficacy

### 4.1.1 Efficacy of Visudyne on patients suffering from AMD with classic subfoveal SCNV: TAP A and B studies

Method: Two identical, 2-years, double-blind, randomised placebo-controlled studies.

Inclusion criteria: patients > 50 years, with AMD with classic subfoveal choroidal neovascularisation (SCNV) and a corrected visual acuity score of between 34 and 73 letters (i.e. approximately 20/40 and 20/200) for the treated eye. The area of classic plus occult SCNV lesions was defined as ≥ 50% of the total lesion and the greatest linear dimension of the entire lesion was defined as ≤ 9 MPS disc area units. The presence of occult SCNV lesions was permitted.

Groups of patients :
- Verteporfin (n = 159): a single 10-minutes intravenous infusion of 6mg/m$^2$ body surface area of verteporfin, application of light at a dose of 50 J/cm$^2$, 15 minutes after the start of the infusion. Retreatment was allowed every three months, up to a maximum of four treatments per year if necessary. A single eye was treated per patient.

- Placebo (n = 83)

Primary efficacy endpoint : responder rate defined as the proportion of patients who lost less than 15 letters (equivalent to 3 lines) of visual acuity (measured with the ETDRS scale) at month 12 from baseline.

Results on the sub-group of patients with predominantly classic SCNV:

- Results at 1 year (intention-to-treat [ITT] analysis):

| % responders (n): | Verteporfin (n=159) | Placebo (n=83) | Difference (Visudyne - placebo) | p |
|---|---|---|---|---|
| <15 letters or 3 lines | 67.3% (107) | 39.8% (33) | 27.5% | p<0.001 |

- Results at 2 years (ITT analysis):

| % responders (n): | Verteporfin (n=159) | Placebo (n=83) | Difference (Visudyne - placebo) | p |
|---|---|---|---|---|
| <15 letters or 3 lines | 59.0% (94) | 31.0% (26) | 28.0% | p<0.001 |

Conclusion: After both 1 and 2 years of treatment, verteporfin as compared to placebo slowed the loss of visual acuity.

4.1.2 Efficacy of Visudyne on patients with macular degeneration with classic subfoveal choroidal neovascularisation (SCNV) secondary to pathological myopia: VIP-PM study

Method: Double-blind, randomised, placebo-controlled study over 2 years.

Inclusion criteria: patients >18 years with an eye requiring a distance correction of at least - 6 diopters (D; spherical equivalent) and had retinal abnormalities consistent with pathologic myopia (such as lacquer cracks) or if the axial length of the eye was at least 26.5 mm.

Treatment groups:
- Verteporfin (n = 81): a single 10-minutes intravenous infusion of 6 mg/m$^2$ body surface area of verteporfin, application of light at a dose of 50 J/cm$^2$ ,15 minutes after the start of the infusion. Retreatment was allowed every three months, up to a maximum of four treatments per year if necessary. Only one eye per patient was treated.
- Placebo (N = 39)

Primary efficacy endpoint : responder rate defined as the proportion of patients who lost less than 8 letters (equivalent to 1.5 lines) of visual acuity (measured with the ETDRS scale) at month 12 from baseline. In a second analysis requested by the FDA, a responder was re-defined as a patient who lost less than 15 letters.

Results:

- Results at 1 year (ITT analysis):

| % responders (n): | Verteporfin (n=81) | Placebo (n=39) | Difference (verteporfin - placebo) | 95% CI | p |
|---|---|---|---|---|---|
| <8 letters decrease | 71.6% (58) | 43.6% (17) | 28% | [9.6 ; 46.4] | p=0.003 |
| <15 letters decrease | 86.4% (70) | 66.7% (26) | 19.8% | [3.2 ; 36.3] | p=0.011 |

- Results at 2 years (ITT analysis):

| % responders (n): | Verteporfin (n = 81) | Placebo (n = 39) | Difference (verteporfin - placebo) | 95% CI | p |
|---|---|---|---|---|---|
| <8 letters decrease | 64.2% (52) | 48.7% (19) | 15.5 % | [-3.4 ; 34.3] | NS |
| <15 letters decrease | 79.0 % (64) | 71.8% (28) | 7.2 % | [-9.5 ; 23.9] | NS |

Conclusion:

This study included a very small number of patients.
The 1-year responder rate in the verteporfin group was statistically greater than that of the placebo group but this statistical superiority was not found at the end of the 2nd year.

According to experts, only a small number of patients may benefit from the treatment.

## 5 UPDATE OF AVAILABLE DATA SINCE THE PREVIOUS OPINION

### 5.1 Efficacy

The company provided the 5 years-results of studies previously reviewed by the Transparency Committee and conducted in patients with AMD with predominantly classic subfoveal choroidal neovascularisation (SCNV) (TAP A and B studies) and in patients with subfoveal SCNV caused by pathological myopia (VIP-PM study).
The EMEA is currently evaluating a trial on the treatment in patients with AMD associated with subfoveal occult choroidal neovascularian with evidence of recent or ongoing disease progression (VIO study). This trial will be subsequently examined by the Transparency Committee.

#### 5.1.1 Extension of the TAP A and B studies

Objective: The study of the long-term efficacy of verteporfin was a secondary objective of the trial.

Method: Three-years non-controlled study (the initial study lasted 2 years).

Inclusion criteria:

1) Patients who took part in the visit at 2 years at the end of the main study and who received (on this occasion) verteporfin treatment in 1 or both eyes if the ophthalmologist considered that at least 1 eye could benefit from treatment at the 1st evaluation of the follow-on study, in the absence or presence of leakage of choroidal neovessels.
2) Patients in whom the initially treated eye was not retreated during the visit at 2 years because of the lack of leakage of choroidal neovessels, if the ophthalmologist considered that at least 1 eye could benefit from treatment.

Treatment: A single10-minutes intravenous infusion of 6 mg/m$^2$ body surface area of verteporfin, application of light at a dose of 50 J/cm$^2$, 15 minutes after the start of the infusion.

Primary efficacy endpoint: responder rate defined as the proportion of patients who lost less than 15 letters (equivalent to 3 lines) of visual acuity (measured with the ETDRS scale).

Results:
The results presented below are those obtained in 121 patients who received verteporfin since the initial phase of the study, met the inclusion criteria and had a visit after the first 2 years of treatment.

**Responder rate: % patients losing less than 15 letters (or 3 lines)**

| | **Verteporfin** | | | |
|---|---|---|---|---|
| Visit | **2 years** | **3 years** | **4 years** | **5 years** |
| No. of patients included in the analysis | 121 | 105 | 93 | 77 |
| Response rate (n):<br>< 15 letters or 3 lines loss | 62.8% (76) | 58.1% (61) | 57.0% (53) | 64.9% (50) |

No definitive conclusion about the long term maintenance of the efficacy of verteporfin on patients with AMD characterised by predominantly classic subfoveal choroidal neovascularisation (SCNV) can be drawn from the results of this non-comparative extension phase of TAP studies.

5.1.2. Extension of VIP-MP study

Objective: long-term efficacy of verteporfin was a secondary objective of the study.

Method: Three-years, non-controlled study.

Inclusion criteria:

1) Patient had taken part in the visit at 2 years (at the end of the main study) and had received, on this occasion, treatment by verteporfin in 1 or both eyes when necessary, if the ophthalmologist considered that at least 1 eye could benefit from treatment at the 1st evaluation of the extension study, in the lack or presence of leakage of choroidal neovessels;

2) Patient in whom the initially treated eye was not retreated during the visit at 2 years because of the lack of leakage of choroidal neovessels, if the ophthalmologist considered that at least 1 eye could benefit from the treatment.

Treatment: a single 10- minutes intravenous infusion of 6mg/m2 body surface area of verteporfin, application of light at a dose of 50 J/cm2, 15 minutes after the start of the infusion.

Primary efficacy endpoint: responder rate defined as the proportion of patients who lost less than 8 letters (equivalent to 1.5 lines) of visual acuity (measured with the ETDRS scale)
In a second analysis requested by the FDA, a responder was defined as a patient who lost less than 15 letters (equivalent to 3 lines) of visual acuity.

Results:
The results presented below are those obtained in patients who received verteporfin from the initial phase of the study, met with the inclusion criteria and had a visit after the first two years, i.e. 67 patients.

**Responder rate: % patients losing less than 8 or 15 letters**

| Treatment | Verteporfin | | | |
|---|---|---|---|---|
| Duration of treatment | 2 years | 3 years | 4 years | 5 years |
| No. of patients included in the analysis | 67 | 59 | 55 | 52 |
| Responder rates (n): | | | | |
| <8 letters loss | 64.2% (43) | 67.8% (28) | 65.5% (36) | 67.3% (35) |
| <15 letters loss | 77.6% (52) | 78.0% (19) | 78.2% (43) | 76.9% (40) |

No definitive conclusion about the long-term maintenance of the efficacy of verteporfin on patients with classic subfoveal choroidal neovascularisation (SCNV) due to pathologic myopia can be drawn from the results of this non-comparative extension phase of VIP-PM studies.

### 5.2 Adverse effects

The adverse effects section of the SPC was compiled from spontaneous reports and safety results of long-term studies.

Hence the following rare adverse effects (<0.1%) were added:

- Ocular: retinal or choroidal vessel non perfusion.
- At the injection site: blistering.
- Systemic: vasovagal reactions and hypersensitivity reactions, which on rare occasions can be severe. General symptoms including headache, vasomotor flushes or changes in blood pressure and heart rate were also reported.
- Infusion-related back and chest pain, which may radiate to other areas, particularly to the pelvis, shoulder girdle or rib cage.

### 5.3 Conclusion

No definitive long-term conclusion can be drawn about the efficacy of verteporfin in AMD indications with predominantly classic subfoveal choroidal neovascularisation (SCNV) and subfoveal SCNV due to pathological myopia because of the methodology of the studies presented (non-comparative, follow-on phases of the TAP and VIP-PM studies).

In the current dossier, the laboratory provided no new data in AMD indication with occult classic subfoveal choroidal with evidence of recent or ongoing disease progression. However, a study is currently under evaluation by EMEA.

Results of long-term studies and safety data have led to updating the “adverse effects” section of the SPC. Possibility of occurrence of rare events such as non-perfusion of the retinal or choroid vessels, systemic effects such as vagal reaction or hypersensitivity, cardiovascular effects (changes in blood pressure and heart rate) and low back and chest pain were added.

## 6 DRUG USAGE DATA

In 2005, all indications pooled together, 35,000 units were sold in pharmacies (GERS database).

In 2001 then in 2003, the CEPS (Committee for pricing and reimbursement of healthcare products) and the Transparency Committee asked Novartis Ophthalmics to set up a validation study of the statistical reliability of the diagnostic procedures, as well as a study on the use of Visudyne in RMD in a real population. The results of these studies are presented below.

### 6.1 Aetiological analysis of angiograms in AMD: Final results

The objective of this study was to analyse the agreement in the reading of angiograms (fluorescein and/or indocyanine green) of patients suffering from exudative AMD, between prescribing doctors and a group of experts. Each film was studied by five experts and the collective opinion was then compared with the diagnosis and treatment decision of prescribing doctors.

For 95 solicited doctors, 33 responded favourably and 26 (distributed in 22 different centres) have been really active, making it possible to analyse 178 complete patient dossiers[1] .

The kappa (agreement between expert opinions) may be qualified as "poor"[2,3] for the three criteria studied: presence of neovessels (kappa = 0.292), form of AMD (kappa = 0.264) and relevance of photodynamic therapy (PDT) (kappa = 0.215).

A collective opinion was provided in 95% of cases. The group decision was unanimous in 18% of cases, based on a strong majority in 27% of cases, a small majority in 33% of cases and, in 22% of cases, no opinion obtained more than 2 votes (minority).

The kappa coefficient evaluating the agreement between the experts group decision and doctors' practises (kappa = 0.445) could be qualified at best as "moderate"[2] or "poor"[3]. Opinions agreed in 72.8% of cases and disagreed in 27.2% of cases.

One third of the treatments decided by the doctors were deemed to be "inappropriate" by the experts. On the contrary, 10 of the 60 patients untreated by doctors would have been treated by the experts (17%).

Cross analyses to identify factors that may explain this lack of agreement failed to find any specific technical factor (quality and type of films, type of equipment used).

### 6.2 Observational study of the Population treated by PDT with Visudyne for AMD (OPV study): Interim analysis at 2 years

The company sent the Transparency Committee the results of the interim analysis on a cohort of patients treated by photodynamic therapy PDT with Visudyne for ARMD with predominantly classic or occult classic subfoveal choroidal neovascularisation[4] (SCNV). This interim analysis was carried out at the end of the second year of the study for patients enrolled between May 3, 2004 and July 24, 2006.

At database lock, 462 patients were enrolled in the study. Data were only completed for 383 patients, enrolled by 34 active doctors (doctors who recruited at least 1 patient). The interim analysis therefore only concerned these 383 patients.

At baseline, the patients had had AMD for a mean period of 8 months (with a median at 2 months). Patients were primarily women (68%), with an average age of 78 (± 8 years). In 58.5% of patients (n=224), the AMD also affected the contralateral eye. Among the latter, 68.8% were treated by Visudyne, 19.6% by other medication, 10.3% by laser and 6.3% did not receive any treatment.

Visudyne was prescribed in 76.2% of cases (n=203) for AMD with predominantly classic (n=181) or active occult (n=111) classic subfoveal choroidal neovascularisation (SCNV) corresponding to the marketing authorisation indications reimbursed by National Health Insurance.

[1] The protocol planned to include 30 centres and 210 patient dossiers
[2] FERMANIAN J. « Mesure de l'accord entre deux juges. Cas qualitatif. » Rev Epidemiol Sante Publique 1984;32(6):408-13
[3] GRENIER B. « Evaluation de la décision médicale: Introduction à l'analyse médico-économique. » Masson, Paris, 1999.
[4] The protocol planned the randomized inclusion of 30 centres and 1250 patients. During start up of the study, because of difficulties to include patients, the required sample size was reduced. Finally, 140 patients were included in each indication, i.e. a total of 280 patients were included in the study.

The diagnosis of AMD (for the studied eye) was made in 92.6% of the cases following a reduction in visual acuity. At baseline, a measurement of the visual acuity was made, either with the ETDRS scale for 225 patients (58.7 % of the cases), or by Monoyer score for 144 patients (37.6%).

The mean visual acuity was 40.7 letters (± 18.7) with the ETDRS scale and 0.22 (± 0.16) with the Monoyer scale.

Fluorescein angiography was conducted in almost all cases (n=374, i.e. 97.7%). In non symptomatic forms, 72.3% of the patients who had never been treated by Visudyne had indocyanine green angiography. These results are in agreement with the recommendations of the Prescription Guide (PG). Fluorescein angiography showed that 161 patients (42%) had predominantly classic subfoveal choroidal neovascularisation (SCNV) and 104 (27.2%) had occult subfoveal SCNV with evidence of recent progression (criteria eligible for reimbursement).

The mean time between diagnosis of AMD and the first injection was 6 months. The median time was 21 days for incident patients (receiving a first treatment on the day of enrolment) and 26 days for prevalent patients (patients already treated by PDT with Visudyne).

At baseline, 141 patients (37 %) had already been treated by PDT with Visudyne (for the studied eye). Previously treated patients had received on average 2 prior injections. The interval between the two injections was of 147 days, in agreement with the recommendations of the PG.

The mean volume injected at baseline was 5 (±1) $mg/m^2$ body surface area (the dose indicated in the PG is 6 $mg/m^2$).

To date, 343 patients (89.6%) have been seen after 3 months, 296 (77.3%) after 6 months and 194 (50.7%) after 1 year.

Since their inclusion in the study, 249 patients (65%) have been retreated, usually once (38%). The main reason for treatment readministration was angiographic evidence of leakage of lesions (61.4% of all cases of further treatment, whatever their date of occurrence).

The mean interval between two treatments was approximately 4 months, as recommended in the PG.

To date, only 194 patients (50.7%) have attained 12 months of follow-up. The change in visual acuity over 12 months is documented for 186 patients and was evaluated directly on the ETDRS scale for 85 patients (45.7%) or on the results of the Monoyer scale converted into ETDRS for 101 patients (54.3%).

At 12 months, the mean visual acuity of treated patients was 38 (± 17.8) letters on the ETDRS scale.

If 4 major categories are considered[5], 16.5% patients (n=32) were in treatment failure (more than 15 letters lost), 39.2% (n=76) were stabilised (between 0 and 15 letters lost) and 36.6% (n=71) were improved. Slightly less than half of the latter patients presented a clear improvement (n=34).

Twenty-seven serious adverse events occurred in the 383 patients studied, including 11 deaths, mainly due to cardiovascular disease (6 cases) and stroke (2 cases).

Concerning treatment discontinuations, 37 patients prematurely left the study. The main reasons were as follows: death (10 cases), voluntary patient's withdrawal, practical constraint and "no longer justifies treatment" (6 cases each).
In addition, 16 patients definitively stopped Visudyne treatment and 3 patients were considered to be lost to follow-up at the date of database lock.

# 7 TRANSPARENCY COMMITTEE CONCLUSIONS

## 7.1 Reassessment of Actual Benefit (AB)

**1. Treatment of patients with age-related macular degeneration (AMD) with predominantly classic classic subfoveal choroidal neovascularisation (SCNV) :**

Age-related macular degeneration (AMD) is the first cause of blindness in France in patients over age 50. Among the 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.
The efficacy/adverse effects ratio is moderate.
This proprietary drug provides first-line therapy.
There is an alternative drug therapy: pegaptanib (Macugen).

The AB of Visudyne is substantial.

**2. Treatment of patients with classic choroidal neovascularisation subfoveal (SCNV) secondary to pathological myopia:**

The neovascular complications of pathological myopia are among those with the most sudden onset and may be responsible for considerable disability due to the loss of central vision. This disability is all the more severe as it often occurs in patients of working age.

This proprietary drug is intended for curative treatment of the consequences of the disease.
The efficacy/adverse effects ratio is slight.
This proprietary drug is used for first-line therapy.
There is no alternative treatment in this indication.

The medical benefit of Visudyne is substantial.

[5] Definitions used
- Failure = more than 15 letters lost
- Stabilization = between 0 and 15 letters lost according to the ETDRS scale
- Improvement = between 0 and 15 letters won
- Considerable improvement = more than 15 letters won

**3. Treatment of patients with age-related macular degeneration with non symptomatic retrofoveal SCNV showing signs of recent progression or with active disease:**

The Transparency Committee will decide on the medical benefit of Visudyne in this indication only after it has seen the results of the VIO study.

## 7.2 Therapeutic use

In the treatment of exudative forms of AMD, laser photocoagulation may only be used in extrafoveolar forms. In the presence of classic subfoveal choroidal neovascularisation (SCNV), laser photocoagulation is impossible and photodynamic therapy using verteporfin as photosensitising agent may be used.

Since the marketing of Visudyne, the efficacy of anti-VEGF administered by intravitreal injection has been recognised in the treatment of wet AMD: pegaptanib, bevacizumab and ranibizumab. Currently only pegaptanib (Macugen) has obtained a marketing authorisation in France (31 January 2006) in the indication “treatment of the neovascular form (wet, exudative) of AMD”. Bevacizumab (Avastin) is used off-label and ranibizumab (Lucentis) is undergoing evaluation by EMEA.

There are currently no recommendations about the therapeutic strategy of treatment of wet AMD. Current data, although suggesting a similar efficacy, do not make it possible to clearly distinguish the respective value of Visudyne and Macugen in the therapeutic strategy. However, Visudyne is still considered to be the reference treatment.

Experts currently propose a case-by-case approach taking into account not only the characterisation of the neovascular lesions (angiography, optical coherence tomography), their topography and possible contraindications, but also the patients’ capacity to accept one or other of these treatments.

In case of lack of indication for Visudyne in the forms with barely visible classic subfoveal choroidal neovascularisation (SCNV) (i.e. minimally classic subfoveal SCNV), Macuguen may be prescribed as first-line treatment.

In parallel with treatment by Visudyne as single agent, experts mentioned that treatments increasingly combine the use of Visudyne with intravitreal injections of triamcinolone (Kenacort) (outside MA) or with an anti-VEGF in intravitreal injections (randomised studies are in progress).

In the treatment of classic subfoveal choroidal neovascularisation (SCNV) due to pathological myopia, laser photocoagulation is not recommended and only photo-dynamic therapy by verteporfin is currently validated.

### 7.3 Reassessment of the improvement in actual benefit

During the initial evaluation of Visudyne in the indications:

- AMD with predominantly classic subfoveal choroidal neovascularisation (SCNV),
- Subfoveal SCNV due to pathological myopia,

the Transparency Committee considered that Visudyne provided a major improvement in actual benefit (level I) because, despite the moderate effect observed during clinical studies, an important therapeutic benefit was expected with this first available treatment for the management of patients in these indications.

The Transparency Committee now considers that neither the new clinical data nor the experience acquired with this treatment since its marketing, can confirm this initial level of (expected) improvement in actual benefit (IAB), and re-evaluates this level as moderate (IAB III) in each of these indications despite the lack of any alternative treatment in the case of classic subfoveal choroidal neovascularisation (SCNV) due to pathological myopia.

In AMD indication with occult classic subfoveal choroidal neovascularisation (SCNV) with evidence of recent or ongoing disease progression the Transparency Committee will decide on the IAB with Visudyne in this indication only when it has seen the results of the VIO study

### 7.4 Recommendations of the Transparency Committee

Favourable opinion for keeping Visudyne on the list of medicines reimbursed by National Insurance

#### 7.4.1. Scope of reimbursement and corresponding dosages

Visudyne is reimbursed in the following indications (Official Journal of February 18, 2004):

1. Treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularisation (SCNV) with more than 50% of visible neovessels.

2. Treatment of age-related macular degeneration in patients with occult retrofoveal SCNV with evidence of recent or ongoing disease progression - excepting patients with retinal pigment epithelium detachments and/or nonincipient retinochoroidal anastomosis with scaring fibrosis.

3. Treatment of patients with subfoveal SCNV secondary to pathological myopia.

Indocyanine green angiography must be systematically used for the initial diagnosis of occult subfoveal SCNV.

#### 7.4.2. Containing

Appropriate to the conditions of prescription.

#### 7.4.3. Reimbursement rate

65 %

#### 7.4.4. Medical product for exceptional use

This proprietary drug has exception drug status (drug available from pharmacies under strict conditions) and is described in the Prescription Guide (last version: Official Journal of 18 February 2004).

# 8 APPENDICES

## 8.1 Results of the semiological analysis of angiograms in AMD

### 8.1.1. Background information

In 2001 and then in 2003, the CEPS (Committee for Pricing and Reimbursement of Healthcare Products) and the Transparency Committee asked Novartis Ophthalmics to set up a study to validate the statistical reliability of diagnostic procedures. The protocol of this study was validated in October 2004 and the study began in July 2004 and was completed in April 2005. In July 2005, the company sent the Transparency Committee the final results of this study.

### 8.1.2. General methods

The study protocol planned to recruit 30 investigating centres and 210 patient dossiers.

Patients' inclusion criteria were: age over 50 years and AMD characterised by numerous drusen (and/or pigment migrations) and/or the presence of macular choroidal neovessels in one of the two eyes.

The two non-inclusion criteria were as follows: patients treated by photodynamic therapy (PDT) with Visudyne outside MA and patients whose treatment by PDT with Visudyne was not reimbursed by the national health insurance.

Each of the 5 members of the expert review board examined and gave an individual and independent opinion on the anonymised angiography dossiers of enrolled patients, in a standardised presentation. Neither the diagnosis made by the prescriber nor the treatment decision were documented at this stage of the expertise.

Statistical analysis was conducted in 3 stages:

- Measurement of the agreement between expert opinions about the presence of neovessels, the diagnosis of AMD and the indication for treatment by Cohen-Fleiss's unweighted kappa test;
- Procedure to establish a collective opinion from the 5 expert opinions[6] ;
- Determination of the agreement between the collective board of experts and the practice of the initial prescriber by a kappa test eliminating cases for which the collective decision was "don't know".

[6] Four situations were envisaged:
- Unanimous decision: 5 experts out of 5 made the same decision after the 1st reading
- Majority decision: 4 experts out of 5 made the same decision after the 1st reading OR 3 experts out of 5 made the same decision after the 1st reading and the board chairman agreed with the majority after a second reading
- Minority decision: 3 experts out of 5 made the same decision after the 1st reading and the board chairman agreed with the minority after a second reading
- Disagreement: no decision backed by 3 opinions or more

8.1.3. Results presented

➢ Remarks on the methodology used

- Only 33 of the 95 physicians contacted (in 71 centres), replied positively and **26 (in 22 different centres)[7] were very active** (returned at least one patient's dossier), so that **178 completed patients' dossiers** could be collected **(the protocol planned to include 30 centres and 210 patient dossiers)**. The small sample sizes made it impossible to compare the distribution of the active doctors according to their geographical site with that of the 421 doctors using PDT for more than 3 months in January 31, 2005[8].

A statistically significant difference (p = 0.003) was found in the conditions of practice of these physicians : the physicians recruited for the study mainly practiced in public hospital setting, whereas the 421 physicians using PDT for more than 3 months on January 31, 2005 mainly practiced in private hospitals.

- Eleven of the enrolled patients did not have neovascularisation. It should have been specified if these were atrophic forms.

After a reminder, the company specified that, in certain cases, the experts were unable to make a positive decision but did not necessarily tick the "don't know" box. Moreover, no request was made for further information when there was missing data on the questionnaires.

- Certain results sent were wrong (miscalculation). The laboratory corrected this table (cf. appendix 2) and elsewhere specified the references used in order to qualify and interpret the kappa values (cf. appendixes 3).

- The analysis failed to demonstrate any obvious factor explaining the cases of disagreement. After a reminder, the laboratory stated that there had in fact been expert meetings on this subject, but that their conclusions were mainly "qualitative": Certain ambiguities remained both concerning the reading of the angiograms and their interpretation.

➢ Agreement between the five expert opinions

For the three criteria studied: presence of neovessels (kappa = 0.292), form of AMD (kappa = 0.264) and relevance of dynamic phototherapy (DPT) (kappa = 0.215), the kappa could be qualified as "poor" (Ref. Fermanian, 1984[9] and Grenier, 1999[10]). The experts were unable to give an opinion in a large number of cases whatever criterion was considered: from 6% to 17% of the dossiers depending on the experts, for the presence of neovessels, 3% to 12% of dossiers for the form of AMD and from 4% to 34% of dossiers for the relevance of PDT.

- Collective decision of the five experts

A collective opinion was formed in 95% of cases. The group decision was unanimous in 18% of cases, based on a strong majority in 27% of cases, a small majority in 33% of cases and, in 21% of cases, no opinion obtained more than 2 votes (minority)

The collective opinion concluded that there was no indication for treatment by PDT with Visudyne in 49% of cases and that there was an indication for treatment in 46% of cases. No opinion could be formed for 9 patients (5% of cases).

[7] A single investigator per centre except for two hospital centres in which 2 investigators participated
[8] Cf appendix 1: geographical distribution of the 26 active investigators.
[9] FERMANIAN J. « Mesure de l'accord entre deux juges. Cas qualitatif. » Rev Epidemiol Sante Publique 1984;32(6):408-13
[10] GRENIER B. « Evaluation de la décision médicale: Introduction à l'analyse médico-économique. » Masson, Paris, 1999.

- Agreement between the collective decision and doctors' practice

The kappa coefficient evaluating the agreement between the collective decision and investigator's practice (kappa = 0.445) can at best be described as "moderate" (Ref. Fermanian, 1984)[2] or "poor" (Ref. Grenier, 1999)[3]. Opinions agreed in 72.8% of cases and disagreed in 27.2% of cases.

One third of the treatments decided by the physicians were deemed to be "inappropriate" by the experts. On the other hand, 10 of the 60 patients untreated by the doctors would have been treated by the experts (17%).

The more consensual the expert opinion, the better the agreement.

Cross analyses performed to try and explain this lack of agreement failed to demonstrate any particular technical factor (quality and type of films, type of equipment used).

- Conclusion

Whatever the criterion considered [presence of neovessels (kappa = 0.292), form of AMD (kappa = 0.264) and relevance of PDT (kappa = 0.215)], the agreement between the experts could be described as "poor".

Moreover, there were a considerable number of cases about which the experts were unable to form an opinion in particular about the relevance of PDT.

The agreement between the group decision and doctors' practices could at best be described as moderate: In one third of cases, the treatments decided by the physicians were deemed to be "inappropriate" by the experts.

This agreement could only be described as "good" (kappa = 0.687) when there was a unanimous expert opinion. However, this only occurred in 20% of cases.

Appendix 1: geographical distribution of the 26 active investigators

| Location | N | % |
|---|---|---|
| Paris-Paris region | 5 | 19.2 |
| North-West | 6 | 23.1 |
| North-East | 3 | 11.5 |
| South-West | 4 | 15.4 |
| South-East | 8 | 30.8 |

Appendix 2: corrected table concerning the collective decision

| Collective decision rule | N | Collective decision | | |
|---|---|---|---|---|
| | | "Yes" | "No" | Don't know |
| Unanimous | 32 | 13 | 19 | 0 |
| Strong Majority (4 out of 5) | 49 | 16 | 32 | 1 |
| Weak Majority (3 out of 5) | 59 | 35 | 22 | 2 |
| Minority | 38 | 19 | 13 | 6 |
| **Total** | **178** | **83** | **86** | **9** |

Appendix 3: bibliographical references used for the calculation and interpretation of kappa


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## 8.2 Observational study of the Population treated by PDT with Visudyne for AMD (OPV study) 1-year and 2-year interim analyses

### 8.2.1. Background information

In 2001 and then in 2003, the CEPS (Committee for Pricing and Reimbursement of Healthcare Products) and the Transparency Committee asked Novartis Ophthalmics to set up a study on the use of Visudyne by a real population. The protocol of this study was validated in March 2003 and the study began in May 2004. The database for the first data collected was locked on May 26, 2005. In July 2005, the company sent the Transparency Committee the interim results at one year. In June 2006 the company was asked to provide new results, in particular about changes in visual acuity and renewed treatments, in order to renew the inclusion of Visudyne on the list of the reimbursable pharmaceutical products. A 2-year interim analysis report was sent to the Transparency Committee on September 5, 2006.

### 8.2.2. Design

It was a multicentre, longitudinal study on a cohort of patients treated by PDT with Visudyne for AMD with predominantly classic or asymptomatic subfoveal SCNV. The study protocol planned the randomised recruitment of 30 centres and 1,250 patients.

During the set up of the study and because of the difficulties enrolling patients, the number of subjects required was revised downwards, without any real statistical justification. In the end only 140 patients were included in each indication, i.e. a total of 280 patients were included in the study.

The primary objective of this study was to describe the conditions of Visudyne prescription and the diagnostic procedures used, to characterise the population treated by Visudyne for AMD, to follow the clinical outcome of the patient cohort and to analyse the incidence and factors leading to Visudyne treatment.

- Remarks on the methodology used

- While this study was being set up, during enrolment, the laboratory reported that because of the difficulties in obtaining the participation of centres[11] a new a posteriori calculation of the sample size had to be made. Several exchanges took place with the laboratory in order to find out the rationale for this change in sample size.

- The sampling of doctors enrolled in the study is not necessarily representative.The sample recruited differs from the national sample in terms of practice and geographical location. There are more private doctors and less doctors practising in private clinics than at national level and the Paris region is under-represented at the expense of the South-East.
Besides, the Visudyne treated patients registry was not analysed in comparison with the patients enrolled in the OPV study.

- Concerning the change in visual acuity, this would have been best described according to whether the patients had been retreated or not.
During the 2-year interim analysis, the company presented results in terms of visual acuity measured on the ETDRS scale. However, the complete description of the change in visual acuity will only be made for the final analysis.

[11] After a reminder letter, the laboratory provided the number of included patients each month (cf. appendix 1)

- This 2-year interim analysis was carried out at the end of the second year of the study for patients enrolled between 3 May 2004 and 24 July 2006. At the date of database lock, 462 patients were enrolled in the study. Complete data were obtained for only 383 patients, enrolled by 34 active doctors. The interim analysis therefore only concerned these 383 patients.

- To date, 194 patients (50.7% of enrolled patients) have been followed up for 12 months. The evaluation of the change in visual acuity at 12 months for treated patients may therefore only be clearly analysed when the study is terminated.

- Comparison of the population of patients enrolled in the study with that of the exhaustive registry of treated patients (for the results of the 1-year interim analysis): This comparative analysis has not been presented in the report given to the Transparency Committee.

Data presented in the 1-year complementary analysis report, there was no statistically significant difference between patients of the two sexes. The average age is slightly higher in patients in the OPV study (78.3 years on average) than in the register patients (75.2 years on average). There was a different age distribution: the 70-80 and 80-90 year age brackets were better represented in the OPV study than in the registry ($p < 0.001$).
In terms of indication, if the type of AMD alone is taken into account there seem to be more mixed forms and less occult forms in the OPV study than in the register.
Concerning the examinations performed, the visual acuity was measured with the ETDRS scale at the same frequency. Fluorescein angiography was performed more systematically in the OPV study than in patients in the register (which included 88/826, i.e. nearly 11%, of patients who did not have this examination).

### 8.2.3. Main results of the 2-years interim analysis

➢ Patient profile

In most cases (68%), the patients were women, aged on average 78 years (± 8 years). For nearly 60% of included patients, the AMD also affected the contralateral eye (n=224). Among these patients, 68.8% were treated with Visudyne, 19.6% by medication, 10.3% by laser and 6.3% received no treatment.
The mean time interval between diagnosis of AMD in the study eye and inclusion was approximately 8 months (with a median at 2 months).
Concomitant eye disorders were present in nearly one quarter of cases. These were mainly cataract and glaucoma.
Non-ocular disorders were detected in 65.5% of cases (mainly cardiovascular disorders and high blood pressure).
**Visudyne was prescribed in 76.2% of cases (n=292) for AMD with predominantly classic (n=181) or active occult (n=111) subfoveal SCNV corresponding to the indications in the MA reimbursed by the National Health Insurance.**
Diagnosis of AMD (for the study eye) was made in 92.6% of the cases following a reduction in visual acuity.
At inclusion, the mean visual acuity was 40.7 letters (± 18.7) on the ETDRS scale and 0.22 (± 0.16) on the Monoyer scale.

➢ Visudyne treatment procedures

At baseline, 141 patients (37 %) had already been treated by PDT with Visudyne (for the studied eye) and had received on average 2 previous injections. The interval between the two injections was 147 days, in agreement with the recommendations of the Prescription Guide.
The mean time interval between diagnosis of AMD and the first injection was 6 months. The median time was 21 days for incident patients (receiving the first treatment on the day of inclusion) and 26 days for prevalent patients (already treated by PDT with Visudyne).

The mean dose injected at baseline was 5 (±1) mg/m$^2$ body surface area (the dose indicated in the prescription guide is 6 mg/m$^2$).

- Diagnostic investigations

At baseline, a total of 369 patients had a visual acuity measurement: the measure was made on the ETDRS scale in 225 patients (58.7% of cases) and by a Monoyer score in 144 patients (37.6%), converted later into the ETDRS scale.
Fluorescein angiography was conducted in almost all cases (n=374, i.e. 97,7% of cases). In the case of the non symptomatic forms, 72.3% of the patients who had never been treated by Visudyne had indocyanine green angiography. These results are in agreement with the recommendations of the prescription guide.

- Follow-up of patients receiving PDT by Visudyne

For follow-up, 343 patients (89.6%) had a visit at 3 months, 296 (77.3%) at 6 months and 194 (50.7%) at 1 year.
Since their inclusion in the study, 249 patients (65%) have been retreated, usually once (38%). The main reason for renewed treatment was angiographic evidence of leakage of lesions (61.4% of all cases of further treatment, whatever their date of occurrence).

During the visit at 3 months, 168 patients (49% of the 343 patients seen on this date) received renewed treatment. At 6 months, this concerned 74 patients (25% of 296 patients) and at 12 months, 18 patients (out of 194). The mean interval between two treatments was approximately 4 months, as recommended in the prescription guide.

To date, only 194 patients (50.7%) have reached 12 months of follow-up. The change in visual acuity at 12 months is documented for 186 patients and was evaluated directly using the ETDRS scale for 85 patients (45.7%) or the results of the Monoyer scale converted into ETDRS for 101 patients (54.3%).
The results presented here concern the change between enrolment and 1 year of follow-up, as the sample sizes were too low at 2 years (N=14) to be used.

On inclusion, the mean visual acuity was 40.7 letters read (± 18.7) on the ETDRS scale and 0.22 (± 0.16) on the Monoyer scale. At 12 months, the mean visual acuity of treated patients was 38 (± 17.8) letters read (ETDRS scale). If the 4 major categories are considered[12], 16.5% patients (n=32) who had a follow-up visit at 1 year were in treatment failure (more than 15 letters lost), 39.2% (n=76) had stabilised (between 0 and 15 letters lost) and 36.6% (n=71) were improved. Slightly less than half of the latter patients presented a clear improvement (n=34).
Twenty-seven serious adverse events had occurred in the 383 patients studied, including 11 deaths, mainly due to cardiovascular disease (6 cases) and stroke (2 cases).

Concerning treatment discontinuations, 37 patients prematurely left the study. The main reasons cited were as follows: death (10 cases), voluntary withdrawal of the patient, practical constraint and “no longer justifies treatment” (6 cases each).
In addition, 16 patients definitively stopped Visudyne treatment and 3 patients were considered to be lost to follow-up at the date of database lock.

[12] Definitions used
- Failure = more than 15 letters lost
- Stabilization = between 0 and 15 letters lost according to ETDRS scale
- Improvement = between 0 and 15 letters won
- Considerable improvement = more than 15 letters won

### 8.2.4 Conclusion

The sample of doctors is not completely representative.
The procedures for using Visudyne followed recommendations (dosage, dosing regimen). However, as only preliminary results were presented (only half the patients had reached one year of follow-up), it is still premature to analyse the outcome for visual acuity (which will be interpreted when the study is terminated). To date, the analysis of this endpoint, on the basis of the interim results, provides little evidence for the benefit of treatment.