

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Visudyne 15 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15 mg of verteporfin.

After reconstitution, 1 ml contains 2 mg of verteporfin. 7.5 ml of reconstituted solution contains 15 mg of verteporfin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

Dark green to black powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Visudyne is indicated for the treatment of

- adults with exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) or
- adults with subfoveal choroidal neovascularisation secondary to pathological myopia.

4.2 Posology and method of administration

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

Posology

Adults, including the elderly (≥65 years old)

Visudyne photodynamic therapy (PDT) is a two-step process:

The first step is a 10-minute intravenous infusion of Visudyne at a dose of 6 mg/m² body surface area, diluted in 30 ml infusion solution (see section 6.6).

The second step is the light activation of Visudyne at 15 minutes after the start of the infusion (see “Method of administration”).

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

Treatment of the second eye with Visudyne

There are no clinical data to support concomitant treatment of the second eye. However, if treatment of the second eye is deemed necessary, light should be applied to the second eye immediately after light application in the first eye but no later than 20 minutes from the start of the infusion.

Hepatic impairment

Visudyne therapy should be considered carefully in patients with moderate hepatic dysfunction or biliary obstruction. No experience is available in these patients. Since verteporfin is excreted primarily via the biliary (hepatic) route, increased verteporfin exposure is possible. Verteporfin exposure is not significantly increased in patients with mild hepatic impairment (see “Biotransformation” and “Elimination” under section 5.2) and does not require any dose adjustment.

Visudyne is contraindicated in patients with severe hepatic impairment (see section 4.3).

Renal impairment

Visudyne has not been studied in patients with renal impairment. However the pharmacological characteristics do not indicate any need to adjust the dose (see “Biotransformation” and “Elimination” under section 5.2).

Paediatric population

The safety and efficacy of Visudyne in the paediatric population have not been established. Visudyne is not indicated in this population.

Method of administration

This medicinal product is intended for intravenous infusion only.

For the light activation of Visudyne, a diode laser generating non-thermal red light (wavelength $689 \text{ nm} \pm 3 \text{ nm}$) is used via a slit lamp mounted fibre optic device and a suitable contact lens. At the recommended light intensity of 600 mW/cm^2 , it takes 83 seconds to deliver the required light dose of 50 J/cm^2 .

The greatest linear dimension of the choroidal neovascular lesion is estimated using fluorescein angiography and fundus photography. Fundus cameras with a magnification within the range of 2.4 - 2.6X are recommended. The treatment spot should cover all neovascularity, blood and/or blocked fluorescence. To ensure treatment of poorly demarcated lesion borders, an additional margin of $500 \mu\text{m}$ should be added around the visible lesion. The nasal edge of the treatment spot must be at least $200 \mu\text{m}$ from the temporal edge of the optic disc. The maximum spot size used for the first treatment in the clinical studies was $6,400 \mu\text{m}$. For treatment of lesions that are larger than the maximum treatment spot size, apply the light to the greatest possible area of active lesion.

It is important to follow the above recommendations to achieve the optimal treatment effect.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Visudyne is also contraindicated in patients with porphyria and in patients with severe hepatic impairment (see “Hepatic impairment” under section 4.2).

4.4 Special warnings and precautions for use

Photosensitivity and exposure to light

Patients who receive Visudyne will become photosensitive for 48 hours after the infusion. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light such as tanning salons, bright halogen lighting, or high power lighting in surgery operating rooms or dental surgeries. Prolonged exposure to light from light-emitting medical devices such as pulse oximeters should also be avoided for 48 hours following Visudyne administration.

If patients have to go outdoors in daylight during the first 48 hours after treatment, they must protect their skin and eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions.

Ambient indoor light is safe. Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help eliminate the medicinal product quickly through the skin by a process called photobleaching.

Use in patients with moderate hepatic impairment or biliary obstruction

Visudyne therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since no experience has been gained in these patients. Since verteporfin is excreted primarily via the biliary (hepatic) route, increased verteporfin exposure is possible.

Risk of severe decrease of vision

Patients who experience a severe decrease of vision (equivalent to 4 lines or more) within one week after treatment should not be re-treated, at least until their vision has completely recovered to pre-treatment level and the potential benefits and risks of subsequent treatment have been carefully considered by the treating physician.

Extravasation of the solution for infusion

Extravasation of Visudyne, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling, blistering or discoloration at the injection site. The relief of pain may require analgesic treatment. If extravasation occurs, infusion should be stopped immediately. Protect the affected area thoroughly from bright direct light until swelling and discoloration have disappeared, and put cold compresses on the injection site. To avoid extravasation, a free-flowing intravenous line should be established before starting Visudyne infusion and the line should be monitored. The largest possible arm vein, preferably the antecubital, should be used for the infusion and small veins in the back of the hand should be avoided.

Hypersensitivity reactions

Chest pain, vasovagal reactions and hypersensitivity reactions related to Visudyne infusion have been reported. Both vasovagal and hypersensitivity reactions are associated with general symptoms such as syncope, sweating, dizziness, rash, dyspnoea, flushing, and changes in blood pressure and heart rate. On rare occasions these reactions may be severe and potentially include convulsions. Patients should be under close medical supervision during the Visudyne infusion.

Anaesthesia

There are no clinical data on the use of Visudyne in anaesthetised patients. In sedated or anaesthetised pigs, a Visudyne dose significantly higher than the recommended dose in patients given as a bolus injection caused severe haemodynamic effects including death, probably as a result of complement activation. Pre-dosing with diphenhydramine diminished these effects, suggesting that histamine may play a role in this process. This effect was not observed in conscious non-sedated pigs, or in any other species, including man. Verteporfin at more than 5 times the expected maximum plasma concentration in treated patients, caused a low level of complement activation in human blood *in vitro*. No clinically relevant complement activation was reported in clinical trials but anaphylactic reactions have been reported during post-marketing surveillance. Patients should be under close medical supervision during the Visudyne infusion and caution should be exercised when Visudyne treatment under general anaesthesia is considered.

Other

Visudyne contains small amounts of butylated hydroxytoluene (E321), which may be irritant to eyes, skin and mucous membranes. Therefore it must be washed off extensively with water in the event of direct contact.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in humans.

Other photosensitising agents

It is possible that concomitant use of other photosensitising medicinal products (e.g. tetracyclines, sulphonamides, phenothiazines, sulfonyleurea, hypoglycaemic medicinal products, thiazide diuretics, and griseofulvin) could increase the potential for photosensitivity reactions. Caution should therefore be exercised when using Visudyne concomitantly with other photosensitising medicinal products (see “Photosensitivity and exposure to light” under section 4.4).

Agents which increase verteporfin uptake in the vascular endothelium

Agents such as calcium channel blockers, polymixin B, and radiation therapy are known to alter the vascular endothelium. Based on theoretical data and despite the lack of clinical evidence these agents might result in enhanced verteporfin tissue-uptake when used concurrently.

Free radical scavengers

Although there is no clinical evidence, theoretical data suggest that antioxidants (e.g. beta-carotene) or medicinal products which scavenge free radicals (e.g. dimethylsulfoxide (DMSO), formate, mannitol or alcohol) might quench the activated oxygen species generated by verteporfin, resulting in decreased verteporfin activity.

Medicinal products which antagonise blood vessel occlusion

Since blood vessel occlusion is the major mechanism of verteporfin action, there is a theoretical possibility that agents such as vasodilators and those which diminish clotting and platelet aggregation (e.g. thromboxane A2 inhibitors) can antagonise the action of verteporfin.

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available for verteporfin. Studies in animals have shown teratogenic effects in one species (rat) (see section 5.3). The potential risk for humans is unknown. Visudyne should not be used during pregnancy unless clearly necessary (only if the benefit justifies the potential risk to the foetus).

Breast-feeding

Verteporfin and its diacid metabolic are excreted in human milk in low amounts. It should therefore not be administered to nursing mothers, or breastfeeding should be interrupted for 48 hours after administration.

Fertility

There are no human fertility data for verteporfin. In non-clinical studies, no impairment of fertility and no genotoxicity have been observed (see section 5.3). The clinical relevance is unknown. Patients of reproductive age should be made aware of the lack of fertility data, and Visudyne should only be given after consideration of individual risks and benefits.

4.7 Effects on ability to drive and use machines

Following Visudyne treatment, patients may develop transient visual disturbances such as abnormal vision, vision decrease, or visual field defects that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist.

4.8 Undesirable effects

Most adverse reactions were mild to moderate and transient in nature. Undesirable effects reported in patients with pathological myopia were similar to those reported in patients with AMD.

The most frequently reported adverse reactions to Visudyne (verteporfin for infusion) are injection site reactions (including pain, oedema, inflammation, extravasation, rashes, haemorrhage, discolouration) and visual impairment (including blurred, fuzzy vision, photopsia, reduced visual acuity and visual field defects, including scotoma and black spots).

The following adverse reactions were considered potentially related to Visudyne therapy. The adverse reactions are listed by system organ class and frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders	
Common	Hypersensitivity ¹ .
Metabolism and nutrition disorders	
Common	Hypercholesteraemia.
Nervous system disorders	
Common	Syncope, headache, dizziness ¹ .
Uncommon	Hyperesthesia.
Not known	Vasovagal reactions ¹ .
Eye disorders	
Common	Severe reduced visual acuity ² , visual impairment such as reduced visual acuity, blurred, fuzzy vision, or photopsia, visual field defect such as scotoma, grey or dark haloes and black spots.
Uncommon	Retinal detachment, retinal haemorrhage, vitreous haemorrhage, retinal oedema.
Rare	Retinal ischaemia (retinal or choroidal vessel non-perfusion).
Not known	Retinal pigment epithelial tear, macular oedema.
Cardiac disorders	
Not known	Myocardial infarction ³ .
Vascular disorders	
Uncommon	Hypertension.
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea ¹ .
Gastrointestinal disorders	
Common	Nausea.
Skin and subcutaneous tissue disorders	
Common	Photosensitivity reaction ⁴ .
Uncommon	Rash, urticaria, pruritus ¹ .

General disorders and administration site conditions

Common	Injection site pain, injection site oedema, injection site inflammation, injection site extravasation, asthenia.
Uncommon	Injection site hypersensitivity, injection site haemorrhage, injection site discoloration, pyrexia, pain.
Rare	Malaise ¹ .
Not known	Injection site-vesicles.

Injury, poisoning and procedural complications

Common	Infusion-related chest pain ⁵ , infusion-related reaction primarily presented as back pain ^{5,6} .
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¹ Vasovagal reactions and hypersensitivity reactions related to Visudyne infusion have been reported. General symptoms can include headache, malaise, syncope, hyperhidrosis, dizziness, rash, urticaria, pruritus, dyspnoea, flushing, and changes in blood pressure and heart rate. On rare occasions these reactions may be severe and potentially include convulsions.

² Severely reduced visual acuity, equivalent to 4 lines or more, within seven days after treatment was reported in 2.1 % of the verteporfin-treated patients in the placebo-controlled ocular Phase III clinical studies and in less than 1 % of patients in uncontrolled clinical studies. The reaction occurred mainly in patients with occult only (4.9 %) or minimally classic CNV lesions in patients with AMD and was not reported for placebo-treated patients. Partial recovery of vision was observed in some patients.

³ Myocardial infarction has been reported, particularly in patients with previous cardiovascular history, sometimes within 48 hours after the infusion.

⁴ Photosensitivity reactions (in 2.2 % of patients and <1 % of Visudyne courses) occurred in the form of sunburn following exposure to sunlight, usually within 24 hours from Visudyne treatment. Such reactions should be avoided by compliance with the photosensitivity protection instructions given in section 4.4.

⁵ Infusion-related back and chest pain, which may radiate to other areas, including, but not limited to, the pelvis, shoulder girdle or rib cage.

⁶ The higher incidence of back pain during infusion in the Visudyne group was not associated with any evidence of haemolysis or allergic reaction and usually resolved by the end of the infusion.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in Appendix V.

4.9 Overdose

Overdose of the medicinal product and/or light in the treated eye may result in non-selective non-perfusion of normal retinal vessels, with the possibility of severe vision decrease.

Overdose of the medicinal product may result in the prolongation of the period during which the patient remains photosensitive. In such cases, the patient should prolong skin and eye protection from direct sunlight or bright indoor light for a period proportionate with the overdose given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antineovascularisation agents, ATC code: S01LA01

Verteporfin, also referred to as benzoporphyrin derivative monoacids (BPD-MA) consists of a 1:1 mixture of the equally active regioisomers BPD-MA_C and BPD-MA_D. It is used as a light-activated medicinal product (photosensitiser).

By itself, the clinically recommended dose of verteporfin is not cytotoxic. It produces cytotoxic agents only when activated by light in the presence of oxygen. When energy absorbed by the porphyrin is transferred to oxygen, highly reactive short-lived singlet oxygen is generated. Singlet oxygen causes damage to biological structures within the diffusion range, leading to local vascular occlusion, cell damage and, under certain conditions, cell death.

The selectivity of PDT using verteporfin is based, in addition to the localised light exposure, on selective and rapid uptake and retention of verteporfin by rapidly proliferating cells including the endothelium of choroidal neovascularisation.

Age-related macular degeneration with predominantly classic subfoveal lesions

Visudyne has been studied in two randomised, placebo-controlled, double-masked, multicentre studies (BPD OCR 002 A and B or Treatment of Age-related Macular Degeneration with Photodynamic Therapy [TAP]). A total of 609 patients were enrolled (402 Visudyne, 207 placebo).

The objective was to demonstrate the long-term efficacy and safety of photodynamic therapy with verteporfin in limiting the decrease in visual acuity in patients with subfoveal choroidal neovascularisation due to age-related macular degeneration.

The primary efficacy variable was 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 charts) at month 12 relative to baseline.

The following inclusion criteria were considered for the treatment: patients older than 50 years of age, presence of CNV secondary to AMD, presence of classic lesion components in the CNV (defined as a well-demarcated area of the fluorescence on angiography), CNV located subfoveally (involved the geometric centre of the foveal avascular zone), area of classic plus occult CNV $\geq 50\%$ of the total lesion surface, greatest linear dimension of the entire lesion ≤ 9 Macular Photocoagulation Study (MPS) disc area, and a best-corrected visual acuity between 34 and 73 letters (i.e. approximately 20/40 and 20/200) in the treated eye. Presence of occult CNV lesions (fluorescence not well demarcated on the angiogram) was allowed.

Results indicate that, at 12 months, Visudyne was statistically superior to placebo in terms of the proportion of patients responding to the treatment. The studies showed a difference of 15 % between treatment groups (61% for Visudyne-treated patients compared to 46% placebo-treated patients, $p < 0.001$, ITT analysis). This 15% difference between treatment groups was confirmed at 24 months (53% Visudyne versus 38% placebo, $p < 0.001$).

The subgroup of patients with predominantly classic CNV lesions (N=243; Visudyne 159, placebo 84) were more likely to exhibit a larger treatment benefit. After 12 months, these patients showed a difference of 28% between treatment groups (67% for Visudyne patients compared to 39% for placebo patients, $p < 0.001$); the benefit was maintained at 24 months (59% versus 31%, $p < 0.001$).

In relation to TAP extension:

In patients followed from month 24 onwards and treated with uncontrolled, open-label Visudyne treatment as needed, long-term extension data suggest that month-24 vision outcomes may be sustained for up to 60 months.

In the TAP study in all lesion types, the average number of treatments per year were 3.5 in the first year after diagnosis and 2.4 in the second for the randomised placebo-controlled phase and 1.3 in the third year, 0.4 in the fourth and 0.1 in the fifth year for the open-label extension phase.

No additional safety concern was identified.

Age-related macular degeneration with occult with no classic lesions

The benefit of the product in the AMD patient population who have occult subfoveal CNV with evidence of recent or ongoing disease progression has not been demonstrated consistently.

Two randomised, placebo-controlled, double-masked, multicentre, 24-month studies (BPD OCR 003 AMD, or Verteporfin in Photodynamic Therapy-AMD [VIP-AMD], and BPD OCR 013, or Visudyne in Occult Choroidal Neovascularisation [VIO]) were conducted in patients with AMD characterised by occult with no classic subfoveal CNV.

The VIO study included patients with occult with no classic subfoveal CNV with a visual acuity score of 73-34 letters (20/40-20/200), and patients with lesions >4 MPS disc areas were to have baseline visual acuity <65 letters (<20/50). 364 patients (244 verteporfin, 120 placebo) were enrolled in this study. The primary efficacy parameter was the same as in TAP (see above), with an additional endpoint of month 24 defined. Another efficacy parameter was also defined: the proportion of patients who lost less than 30 letters (equivalent to 6 lines) of visual acuity at months 12 and 24 relative to baseline. The study did not show statistically significant results on the primary efficacy parameter at month 12 (15-letter responder rate 62.7% versus 55.0%, p=0.150; 30-letter responder rate 84.0% versus 83.3%, p=0.868) or at month 24 (15-letter responder rate 53.3% versus 47.5%, p=0.300; 30-letter responder rate 77.5% versus 75.0%, p=0.602). A higher percentage of patients who received Visudyne, compared with those who received placebo, experienced adverse events (88.1% versus 81.7%), associated adverse events (23.0% versus 7.5%), events leading to discontinuation (11.9% versus 3.3%) and events leading to death (n=10 [4.1%] versus n=1 [0.8%]). No death was considered to be related to treatment.

The VIP-AMD included patients with occult with no classic subfoveal CNV with a visual acuity score of >50 letters (20/100). This study also included patients with classic containing CNV with a visual acuity score >70 letters (20/40). 339 patients (225 verteporfin, 114 placebo) were enrolled in this study. The efficacy parameter was the same as in TAP and VIO (see above). At month 12, the study did not show statistically significant results on the primary efficacy parameter (responder rate 49.3% versus 45.6%, p=0.517). At month 24, a statistically significant difference of 12.9% in favour of Visudyne compared to placebo was observed (46.2% versus 33.3%, p=0.023). A group of patients who had occult with no classic lesions (n=258) showed a statistically significant difference of 13.7% in favour of Visudyne compared to placebo (45.2% versus 31.5%, p=0.032). A higher percentage of patients who received Visudyne, compared with those who received placebo, experienced adverse events (89.3% versus 82.5%), associated adverse events (42.7% versus 18.4%) and events leading to discontinuation (6.2% versus 0.9%). A lower percentage of Visudyne patients had events leading to death (n=4 [1.8%] versus n=3 [2.6%]); no death was considered to be related to treatment.

Pathological myopia

One multicentre, double-masked, placebo-controlled, randomised study (BPD OCR 003 PM [VIP-PM]) was conducted in patients with subfoveal choroidal neovascularisation caused by pathological myopia. A total of 120 patients (81 Visudyne, 39 placebo) were enrolled in the study. The posology and retreatments were the same as in the AMD studies.

At month 12, there was a benefit of Visudyne for the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity) – 86% for Visudyne versus 67% for placebo, $p=0.011$. The percentage of patients who lost less than 1.5 lines was 72% for Visudyne and 44% for placebo ($p=0.003$).

At month 24, 79% Visudyne patients versus 72% placebo patients had lost less than 3 lines of visual acuity ($p=0.38$). The percentage of patients who lost less than 1.5 lines was 64% for Visudyne and 49% for placebo ($p=0.106$).

This indicates that clinical benefit may diminish over time.

In relation to VIP-PM extension:

In patients followed from month 24 onwards and treated with uncontrolled, open-label Visudyne treatment as needed, long-term extension data suggest that month-24 vision outcomes may be sustained for up to 60 months.

In the VIP-PM study in pathological myopia, the average number of treatments per year were 3.5 in the first year after diagnosis and 1.8 in the second for the randomised placebo-controlled phase and 0.4 in the third year, 0.2 in the fourth and 0.1 in the fifth year for the open-label extension phase.

No additional safety concern was identified.

5.2 Pharmacokinetic properties

The two regioisomers of verteporfin exhibit similar pharmacokinetic properties of distribution and elimination and thus both isomers are considered verteporfin as a whole from the pharmacokinetic perspective.

Distribution

C_{max} after a 10-minute infusion of 6 and 12 mg/m² body surface area in the target population is approximately 1.5 and 3.5 µg/ml, respectively. The volume of distribution of around 0.60 l/kg at steady state and clearance of around 101 ml/h/kg has been reported following a 10-minute infusion in dose range of 3-14 mg/m². A maximum 2-fold inter-individual variation in plasma concentrations at C_{max} (immediately after end of the infusion) and at the time of light administration was found for each Visudyne dose administered.

In whole human blood, 90% of verteporfin is associated with plasma and 10 % associated with blood cells, of which very little was membrane associated. In human plasma, 90% of verteporfin is associated with plasma lipoprotein fractions and approximately 6% are associated with albumin.

Biotransformation

The ester group of verteporfin is hydrolysed via plasma and hepatic esterases, leading to the formation of benzoporphyrin derivative diacid (BPD-DA). BPD-DA is also a photosensitiser but its systemic exposure is low (5-10% of the verteporfin exposure, suggesting that most of the active substance is eliminated unchanged). *In vitro* studies did not show any significant involvement of oxidative metabolism by cytochrome P450 enzymes.

Elimination

Plasma elimination half-life mean values ranged from approximately 5–6 hours for verteporfin.

Combined excretion of verteporfin and BPD-DA in human urine was less than 1%, suggesting biliary excretion.

Linearity/non-linearity

The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m².

Special populations

Elderly (65 years age or above)

Although mean plasma C_{\max} and AUC values in elderly patients who received verteporfin are higher than those in young volunteers or patients, these differences are not considered to be clinically significant.

Hepatic impairment

In a study of patients with mild hepatic impairment (defined as having two abnormal hepatic function tests at enrolment), AUC and C_{\max} were not significantly different from the control group. Half-life, however, was significantly increased by approximately 20%.

Renal impairment

No studies on the pharmacokinetics of verteporfin in patients with renal impairment are reported. The renal excretion of verteporfin and its metabolite is minimal (<1% of the verteporfin dose) and thus, clinically significant changes in verteporfin exposure in patients with renal impairment are unlikely.

Ethnic groups/races

The pharmacokinetics of verteporfin have been reported to be similar in healthy Caucasian and Japanese men after a dose of 6 mg/m² by a 10-minute infusion.

Effects of gender

At the intended dose, pharmacokinetic parameters are not significantly affected by gender.

5.3 Preclinical safety data

Single and repeated dose toxicity

The acute and light-dependent toxicity of verteporfin was characterised by dose dependent localised deep-tissue damage as a consequence of the pharmacological effect of PDT with verteporfin. Toxicity observed following multiple doses of verteporfin without light was associated mainly with effects on the haematopoietic system. The extent and severity of these effects were consistent among all studies and were dependent on drug dose and dosing duration.

Ophthalmic toxicity

Levels of ocular toxicity in healthy rabbits and monkeys, particularly on the retina/choroid, correlated with medicinal product dose, light dose, and time of light treatment. A retinal toxicity study in healthy dogs with intravenous verteporfin and ambient light on the eye showed no treatment-related ocular toxicity.

Reproductive toxicity

In pregnant rats, intravenous verteporfin doses of 10 mg/kg/day (approximately 40-fold human exposure at 6 mg/m² based on AUC_{inf} in female rats) were associated with an increased incidence of anophthalmia/microphthalmia and doses of 25 mg/kg/day (approximately 125-fold the human exposure at 6 mg/m² based on AUC_{inf} in female rats) were associated with an increased incidence of wavy ribs and anophthalmia/microphthalmia. There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day (approximately 20-fold human exposure at 6 mg/m² based on body surface area).

No effect on male or female fertility has been observed in rats following intravenous verteporfin doses of up to 10 mg/kg/day (approximately 60 and 40-fold human exposure at 6 mg/m² based on AUC_{inf} in male and female rats, respectively).

Carcinogenicity

No studies have been conducted to evaluate the carcinogenic potential of verteporfin.

Mutagenicity

Verteporfin was not genotoxic in the absence or presence of light in the usual battery of genotoxic tests. However, photodynamic therapy (PDT) induces the formation of reactive oxygen species and has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE) and mutations. It is not known how the potential for DNA damage with PDT agents translates into human risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Egg phosphatidylglycerol
Dimyristoyl phosphatidylcholine
Ascorbyl palmitate
Butylated hydroxytoluene (E321)

6.2 Incompatibilities

Visudyne precipitates in sodium chloride solution. Do not use normal sodium chloride solutions or other parenteral solutions.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf-life in the sealed vial

4 years

Shelf-life after reconstitution and dilution

Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and would normally not last longer than 4 hours below 25°C protected from light.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

15 mg of powder for solution for infusion in a single-use glass vial (type I), sealed with bromobutyl stopper and aluminium flip-off cap.

Pack containing 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitute Visudyne in 7.0 ml water for injections to produce 7.5 ml of a 2.0 mg/ml solution. Reconstituted Visudyne is an opaque dark green solution. It is recommended that reconstituted Visudyne be inspected visually for particulate matter and discoloration prior to administration. For a dose of 6 mg/m² body surface (see section 4.2) dilute the required amount of Visudyne solution in dextrose 50 mg/ml (5%) solution for infusion to a final volume of 30 ml. Do not use sodium chloride solution (see section 6.2). Use of a standard infusion line filter with hydrophilic membranes (such as polyethersulfone) of a pore size of not less than 1.2 µm is recommended.

The vial and any unused portion of reconstituted solution should be discarded after single use.

If material is spilled, it should be contained and wiped up with a damp cloth. Eye and skin contact should be avoided. Use of rubber gloves and eye protection is recommended. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/140/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2000

Date of latest renewal: 27 July 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Visudyne 15 mg powder for solution for infusion
verteporfin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15 mg of verteporfin. After reconstitution, 1 ml contains 2 mg of verteporfin.
7.5 ml of reconstituted solution contains 15 mg of verteporfin.

3. LIST OF EXCIPIENTS

Lactose monohydrate, dimyristoyl phosphatidylcholine, egg phosphatidylglycerol, ascorbyl palmitate,
butylated hydroxytoluene (E321).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

1 vial of powder.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not dissolve in sodium chloride solution.
Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.
Shelf-life after reconstitution and dilution: see package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After single use the vial and any unused portion of reconstituted solution should be disposed of after single use in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/140/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Visudyne 15 mg powder for solution for infusion
verteporfin
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 15 mg of verteporfin

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Visudyne 15 mg powder for solution for infusion verteporfin

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Visudyne is and what it is used for
2. What you need to know before you are given Visudyne
3. How Visudyne is used
4. Possible side effects
5. How to store Visudyne
6. Contents of the pack and other information

1. What Visudyne is and what it is used for

What Visudyne is

Visudyne contains the active substance verteporfin, which is activated by light from a laser in a treatment called photodynamic therapy. When you are given an infusion of Visudyne, it is distributed within your body through the blood vessels, including the blood vessels at the back of the eye. When the laser light is shone into the eye, Visudyne is activated.

What Visudyne is used for

Visudyne is used to treat the wet form of age-related macular degeneration and pathological myopia.

These diseases lead to vision loss. Vision loss is caused by new blood vessels (choroidal neovascularisation) that damage the retina (the light-sensitive membrane that lines the back of the eye). There are two types of choroidal neovascularisation: classic and occult.

Visudyne is used for the treatment of predominantly classic choroidal neovascularisation in adults with age-related macular degeneration, and also for the treatment of all types of choroidal neovascularisation in adults with pathological myopia.

2. What you need to know before you are given Visudyne

You should not be given Visudyne

- if you are **allergic** to verteporfin or any of the other ingredients of this medicine (listed in section 6).
- if you have **porphyria** (a rare condition that may increase sensitivity to light).
- if you have any severe **liver problems**.

If any of these apply to you, **tell your doctor. You should not be given Visudyne.**

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given Visudyne

- **If you experience any infusion-related problems or symptoms during the treatment** such as chest pain, sudden loss of consciousness, sweating, dizziness, rash, breathlessness, flushing, irregular heart beat or seizure, please tell your doctor or nurse.
- **If you have any liver problems or a blockage of your bile duct**, please tell your doctor before starting Visudyne therapy.
- **If, during the infusion, Visudyne goes outside the vein**, and especially if the affected area is exposed to light, this can cause pain, swelling, blistering and a change in skin colour in the area of the leakage. If this happens, the infusion needs to be stopped and the skin treated with cold compresses and thoroughly protected from light until the skin colour returns to normal. You may need to take a painkiller.
- **You will be sensitive to bright light for 48 hours after the infusion.** During that time, avoid exposure to direct sunlight, bright indoor lights such as in tanning salons, bright halogen lighting, high power lighting as used by surgeons or dentists, or light from light-emitting medical devices such as pulse oximeters (used to measure oxygen in blood). If you have to go outdoors during daylight in the first 48 hours after treatment, you must protect your skin and eyes by wearing protective clothing and dark sunglasses. Sunscreens offer no protection. Normal indoor lighting is safe.
- **Do not stay in the dark** because exposure to normal indoor lighting will help your body to eliminate Visudyne more quickly.
- **If you experience any eye problems after the treatment**, such as a vision loss, talk to your doctor.

Other medicines and Visudyne

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor or pharmacist if you are taking any of the following medicines, as they may increase your sensitivity to light:

- tetracyclines or sulphonamides (used to treat bacterial infection),
- phenothiazines (used to treat psychiatric disorders, or nausea and vomiting),
- sulfonylurea (used to treat diabetes),
- medicines used to lower blood sugar,
- thiazide diuretics (used to reduce high blood pressure),
- griseofulvin (used to treat fungal infection),
- calcium channel blockers (used to treat high blood pressure, angina and abnormal heart rhythms),
- antioxidants such as beta-carotene or medicines that can remove or inactivate free radicals (such as dimethylsulfoxide (DMSO), formate, mannitol and alcohol),
- vasodilators (used to widen blood vessels resulting from smooth muscle relaxation),
- or, if you are undergoing radiation therapy,

Pregnancy and breast-feeding

- There is very little experience of using Visudyne in pregnant women. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or if you plan to become pregnant. You should only be given Visudyne if your doctor considers it absolutely essential.
- Verteporfin passes into human milk in low amounts. Please tell your doctor if you are breastfeeding. He/she will decide whether you should be given Visudyne. It is recommended that, if you are given Visudyne, you do not breastfeed for 48 hours after administration.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

After Visudyne treatment you may have some vision problems, such as abnormal or decreased vision, which may be temporary. If this happens to you, do not drive or use any tools or machines until your vision improves.

Visudyne contains small amounts of butylated hydroxytoluene (E321)

This ingredient is irritant to eyes, skin and mucous membranes. **If you come into direct contact with Visudyne, you must therefore wash it off thoroughly with water.**

3. How Visudyne is used

Treatment with Visudyne is a two-step process

- First your doctor or the pharmacist will prepare the Visudyne infusion solution. It will be administered by your doctor or nurse into a vein using a drip (intravenous infusion).
- The second step is the activation of Visudyne in the eye 15 minutes after the start of the infusion. Your doctor will put a special contact lens onto your eye and treat your eye using a special laser. It takes 83 seconds to deliver the laser dose required to activate Visudyne. During this time, you will have to follow your doctor's instructions and keep your eyes still.

If necessary, Visudyne therapy can be repeated every 3 months, up to 4 times per year.

Use in children

Visudyne is a treatment for adults only and not indicated for the use in children.

If you are given more Visudyne than you should be

Overdose of Visudyne may prolong the time during which you are sensitive to light and you may need to follow the protection instructions given in section 2 for longer than 48 hours. Your doctor will advise you.

Overdose of Visudyne and light in the treated eye may result in severe vision decrease.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious:

Common (may affect up to 1 in 10 people)

- **Eye disorders:** severe decrease of vision (loss of 4 lines or more within 7 days of treatment), visual disturbances such as blurred, hazy or fuzzy vision, flashes of light, decreased vision, and a change in the field of vision in the treated eye such as grey or dark shadows, blind spots or black spots.
- **General disorders:** Hypersensitivity (allergic reactions), syncope (fainting), headache, light-headedness, breathlessness.

Uncommon (may affect up to 1 in 100 people)

- **Eye disorders:** bleeding of the retina or into the vitreous humour (the clear gel-like substance that fills the eyeball behind the lens), swelling or fluid retention in the retina and displacement of the retina in the treated eye.
- **Infusion site side effects:** as with other types of injections, some patients experienced bleeding at the infusion site, change in skin colour and hypersensitivity. If this happens to you, there will be increased sensitivity to light in that part of the skin until the green discolouration disappears.
- **General disorders:** rash, hives, itching

Rare (may affect up to 1 in 1,000 people)

- **Eye disorders:** lack of blood circulation to the retina or choroids (the vascular layer of the eye) in the treated eye.
- **General disorders:** feeling unwell.

Not known (frequency cannot be estimated from the available data)

- **Eye disorders:** tear in the coloured layer of the retina, swelling or fluid retention in the macula.
- **General disorders:** vasovagal reactions (fainting), sweating, flushing, or changes in blood pressure. On rare occasions the vasovagal and hypersensitivity reactions may be severe and potentially include seizures.
- **Heart attack** has been reported, particularly in patients with a history of heart disease, sometimes within 48 hours after treatment with Visudyne. In the event of suspected heart attack, seek medical attention immediately.

If you experience any of these, **tell your doctor straight away**.

Other side effects:

Common (may affect up to 1 in 10 people)

- **Infusion site side effects:** as with other types of injections, some patients experienced pain, swelling, inflammation, and weeping from the infusion site.
- **General disorders:** feeling sick (nausea), sunburn-like reactions, tiredness, infusion-related reaction, primarily presented as chest pain or back pain, and increased cholesterol levels.

Uncommon (may affect up to 1 in 100 people)

- **General disorders:** pain, increased blood pressure, increased sensation, and fever.

Not known (frequency cannot be estimated from the available data)

- **Infusion site side effects:** as with other types of injections, some patients experienced blistering.
- **General disorders:** changes in heart rate. Infusion-related reaction, which may radiate to other areas, including but not limited to, the pelvis, shoulders or rib cage.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Visudyne

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, the medicine should be used immediately. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and would normally not last longer than 4 hours below 25°C protected from light.

6. Contents of the pack and other information

What Visudyne contains

- The active substance is verteporfin. Each vial contains 15 mg of verteporfin. After reconstitution, 1 ml contains 2 mg of verteporfin. 7.5 ml of reconstituted solution contains 15 mg of verteporfin.
- The other ingredients are dimyristoyl phosphatidylcholine, egg phosphatidylglycerol, ascorbyl palmitate, butylated hydroxytoluene (E321) and lactose monohydrate.

What Visudyne looks like and contents of the pack

Visudyne is supplied as a dark green to black powder in a clear glass vial. The powder is reconstituted in water prior to use to form an opaque dark green solution.

Visudyne is available in packs containing 1 vial of powder.

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Manufacturer

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Reconstitute Visudyne in 7.0 ml water for injections to produce 7.5 ml of a 2.0 mg/ml solution. Reconstituted Visudyne is an opaque dark green solution. It is recommended that reconstituted Visudyne be inspected visually for particulate matter and discoloration prior to administration. For a dose of 6 mg/m² body surface (the dose recommended for the treatment) dilute the required amount of Visudyne solution in dextrose 50 mg/ml (5 %) solution for infusion to a final volume of 30 ml. Do not use sodium chloride solution. Use of a standard infusion line filter with hydrophilic membranes (such as polyethersulfone) of a pore size of not less than 1.2 µm is recommended.

For storage conditions, please see section 5 of this leaflet.

The vial and any unused portion of reconstituted solution should be discarded after single use.

If material is spilled, it should be contained and wiped up with a damp cloth. Eye and skin contact should be avoided. Use of rubber gloves and eye protection is recommended. Any unused medicine or waste material should be disposed of in accordance with local requirements.