SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Visudyne 15 mg powder for solution for infusion

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

The first step is a 10-minute intravenous infusion of Visudyne/Verteporfin at a dose of 6 mg/m^2 body surface area, diluted in 30 ml infusion solution (see section 6.6).

The second step is the light activation of Visudyne/Verteporfin 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/Verteporfin therapy may be given up to 4 times per year.

Treatment of the second eye with Visudyne/Verteporfin
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.

Special populations

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

Renal impairment
Visudyne/Verteporfin 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/Verteporfin in the paediatric population have not been established. Visudyne/Verteporfin is not indicated in this population.

Method of administration

This medicinal product is intended for intravenous infusion only.

For the light activation of Visudyne/Verteporfin, a diode laser generating non-

thermal red light (wavelength 689 nm ± 3 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 neovasculature, blood and/or blocked fluorescence. To ensure treatment of poorly demarcated lesion borders, an additional margin of 500 µm should be added around the visible lesion. The nasal edge of the treatment spot must be at least 200 µm from the temporal edge of the optic disc. The maximum spot size used for the first treatment in the clinical studies was 6,400 µm. 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/Verteporfin 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/Verteporfin 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/Verteporfin 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/Verteporfin 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/Verteporfin, 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. Localised (skin) necrosis at the injection site following extravasation has also been reported. 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/Verteporfin 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/Verteporfin 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/Verteporfin infusion.

Cases of anaphylactic reactions have been observed in patients receiving Visudyne/Verteporfin. If an anaphylactic or other serious allergic reaction occurs during or following infusion, administration of Visudyne/Verteporfin

should be discontinued immediately and appropriate therapy initiated.

Anaesthesia

There are no clinical data on the use of Visudyne/Verteporfin in anaesthetised patients. In sedated or anaesthetised pigs, a Visudyne/Verteporfin 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/Verteporfin infusion and caution should be exercised when Visudyne/Verteporfin treatment under general anaesthesia is considered.

Other

Visudyne/Verteporfin 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, sulfonylurea, hypoglycaemic medicinal products, thiazide diuretics, and griseofulvin) could increase the potential for photosensitivity reactions. Caution should therefore be exercised when using Visudyne/Verteporfin 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/Verteporfin 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/Verteporfin should only be given after consideration of individual risks and benefits.

4.7 Effects on ability to drive and use machines

Following Visudyne/Verteporfin 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 (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/Verteporfin therapy. The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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].
Not known	Anaphylactic reaction.
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, injection site necrosis.
Injury, poisoning and procedural complications	
Common	Infusion-related chest pain[5], infusion-related reaction primarily presented as back pain[5, 6].

[1] Vasovagal reactions and hypersensitivity reactions related to Visudyne/Verteporfin infusion have been reported. General symptoms can include headache, malaise, syncope, hyperhydrosis, 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/Verteporfin courses) occurred in the form of sunburn following exposure to sunlight, usually within 24 hours from Visudyne/Verteporfin 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/Verteporfin 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Mechanism of action

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 neovasculature.

Clinical efficacy and safety

Age-related macular degeneration with predominantly classic subfoveal lesions

Visudyne/Verteporfin 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/Verteporfin, 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 ≥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/Verteporfin 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/Verteporfin-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/Verteporfin versus 38% placebo, $p<0.001$).

The subgroup of patients with predominantly classic CNV lesions (N=243; Visudyne/Verteporfin 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/Verteporfin 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/Verteporfin 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/Verteporfin 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/Verteporfin, 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/Verteporfin 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/Verteporfin compared to placebo (45.2% versus 31.5%, p=0.032). A higher percentage of patients who received Visudyne/Verteporfin, 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/Verteporfin 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/Verteporfin, 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/Verteporfin for the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity) – 86% for Visudyne/Verteporfin versus 67% for placebo, p=0.011. The percentage of patients who lost less than 1.5 lines was 72% for Visudyne/Verteporfin and 44% for placebo (p=0.003).

At month 24, 79% Visudyne/Verteporfin 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/Verteporfin 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/Verteporfin 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/m^2 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/m^2. 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/Verteporfin 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/m^2.

Special populations

Elderly (65 years of 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/m^2 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/m^2 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/m^2 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/m^2 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/m^2 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/Verteporfin 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

Reconstitute Visudyne/Verteporfin in 7.0 ml water for injections to produce 7.5 ml of a 2.0 mg/ml solution. Reconstituted Visudyne/Verteporfin is an opaque dark green solution. It is recommended that reconstituted Visudyne/Verteporfin be inspected visually for particulate matter and discoloration prior to administration. For a dose of 6 mg/m^2 body surface (see section 4.2) dilute the required amount of Visudyne/Verteporfin 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

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