Visudyne®

Ocular vascular disorder agents, Antineovascularisation agents.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Powder for solution for infusion.
Dark green to black cake.

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.

Active moiety

Verteporfin

Excipients

Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate, butylated hydroxytoluene.

INDICATIONS

Visudyne is indicated for the treatment of patients with subfoveal Choroidal Neovascularisation (CNV) that is:

- predominantly classic and due to age-related macular degeneration
- occult and due to age-related macular degeneration
- due to pathologic myopia

DOSAGE AND ADMINISTRATION

Visudyne therapy should only be administered by ophthalmologists experienced in the management of patients with age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.

Dosage

General target population (Adults)

Visudyne therapy is a two-step process:

The first step is a 10-minute intravenous infusion of Visudyne at a dose of 6 mg/m^2 body surface area, diluted in 30 mL infusion solution (see section INSTRUCTIONS FOR USE AND HANDLING).

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 and retreated in the event of recurrent CNV leakage. In the event of recurrent CNV leakage, Visudyne therapy may be given up to 4 times per year.

Special populations

Hepatic impairment

Visudyne therapy should be considered carefully in patients with moderate to severe hepatic impairment 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 section CLINICAL PHARMACOLOGY) and does not require any dose adjustment.

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 section CLINICAL PHARMACOLOGY).

Paediatrics patients

Use in the paediatric population has not been investigated. Visudyne is not indicated in this population.

Geriatric patients (65 years of age or above)

The posology is the same in the elderly (aged 65 years and above) as in younger adults.

Method of administration

This medicinal product is intended for intravenous infusion only.

For this, 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 to 2.6-fold 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 micrometers should be added around the visible lesion. The nasal edge of the treatment spot must be at least 200 micrometers from the temporal edge of the optic disc. The maximum spot size used for the first treatment in the clinical studies was 6,600 micrometers 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.

CONTRAINDICATIONS

Visudyne is contraindicated in patients with porphyria or a known hypersensitivity to verteporfin or to any of the excipients of Visudyne and in patients with severe hepatic impairment.

WARNINGS AND PRECAUTIONS

Photosensitivity following treatment

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 surgical operating rooms or dentist offices. Prolonged exposure to light from light-emitting medical devices such as pulse oximeters should also be avoided for 48 hours following Visudyne administration. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

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 drug more quickly through the skin by a process called photobleaching.

Use in patients with hepatic impairment or biliary obstruction

Visudyne therapy should be considered carefully in patients with moderate to severe hepatic impairment or biliary obstruction since no experience has been gained in these patients.

Decrease in visual acuity

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

Extravasation

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. Localized (skin) necrosis at the injection site following extravasation has also been reported.

To avoid extravasation, standard precautions include, but are not limited to, the following measures: a free-flowing IV 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. If extravasation occurs, infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. Cold compresses should be applied to the injection site.

Medical supervision during the infusion

Chest pain, vaso-vagal reactions and hypersensitivity reactions-related to Visudyne infusion, have been reported. Both vaso-vagal 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 medical supervision during the Visudyne infusion.

Cases of anaphylactic reactions have been observed in patients receiving Visudyne. If an anaphylactic or other serious allergic reaction occurs during or following infusion, administration of Visudyne should be discontinued immediately and appropriate therapy by initiated.

Use in anaesthetised patients

There are no clinical data on the use of Visudyne in anaesthetised patients. In sedated or anaesthetised pigs, a Visudyne dose of more than 10 times the recommended dose in patients given as a bolus injection caused severe hemodynamic 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 the risk of anaphylactic reactions due to complement activation cannot be excluded.

Treatment of second eye

The controlled trials only allowed treatment of one eye per patient. However, if the 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.

Use of incompatible lasers

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of Visudyne could result in incomplete treatment due to partial photoactivation of Visudyne, over-treatment due to over-activation of Visudyne, or damage to surrounding normal tissue.

Unstable heart disease

No clinical experience is available in patients with unstable heart disease (class III or IV and in patients with uncontrolled arterial hypertension).

Driving and using 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.

ADVERSE DRUG REACTIONS

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Adverse drug reactions from clinical trials

SOC/PT	Frequency category (CIMOS III)
Eye disorders	
Retinal detachment	Uncommon
Retinal haemorrhage	Uncommon
Vitreous haemorrhage	Uncommon
Visual impairment[1]	Common
Visual acuity reduced[2]	Common
Visual field defect[3]	Common
Retinal oedema	Uncommon
Retinal ischaemia (retinal, or choroidal vessel nonperfusion)	Rare
Gastrointestinal disorders	
Nausea	Uncommon
General disorders and administration site conditions	
Chest pain	Common
Asthenia	Common
Injection site oedema	Common
Injection site inflammation	Common
Injection site extravasation	Common
Pyrexia	Uncommon
Injection site pain[4]	Common
Injection site haemorrhage	Uncommon
Injection site discolouration	Uncommon
Injection site hypersensitivity	Uncommon
Malaise[5#]	Rare
Immune system disorders	
Hypersensitivity[5#]	Common
Musculoskeletal and Connective tissue disorders	
Back pain[4]	Common
Nervous system disorders	
Syncope[5#]	Common
Headache[5#]	Common
Dizziness[5#]	Common
Hypoaesthesia	Uncommon
Respiratory, thoracic and mediastinal disorders	
Dyspnoea[5#]	Common
Skin and subcutaneous tissue disorders	
Photosensitivity reaction[6]	Common
Rash[5#]	Uncommon
Urticaria[5#]	Uncommon
Pruritus[5#]	Uncommon
Vascular disorders	
Hypertension	Uncommon

[1]Abnormal vision such as blurry, hazy, fuzzy vision, or flashes of light

[2]Severe vision decrease, equivalent of 4 lines or more, within 7 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 event occurred mainly in patients with occult only CNV lesions due to AMD. Partial recovery of vision was observed in some patients.

[3]Visual field defect such as grey or dark haloes, scotoma and black spots.

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

[5]Vaso-vagal reactions (presyncope) and hypersensitivity reactions, related to Visudyne infusion have been reported. General symptoms can include headache, malaise, syncope, sweating, dizziness, rash, urticaria, pruritus, dyspnoea, flushing and changes in blood pressure or heart rate. On rare occasions these reactions may be severe, and potentially include convulsions

[6]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 of Visudyne infusion. Such reactions should be avoided by compliance with photosensitivity protection instructions under section WARNINGS AND PRECAUTIONS.

[#]The frequency categorization of the spontaneously reported ADRs is based on the pooled analysis of placebo-controlled clinical trials for age-related macular degeneration and pathological myopia.The following adverse drug reactions (Table 2) have been derived from post-marketing experience with Visudyne. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Table 2 Adverse drug reactions from spontaneous reports

SOC/PT
Eye disorders
Retinal pigment epithelial tear
Macular oedema
General disorders and administration site conditions
Injection site vesicles
Injection site necrosis
Immune system disorders
Anaphylactic reaction
Investigations
Heart rate irregular
Nervous system disorders
Presyncope(vaso-vagal reactions)
Reproductive system and breast disorders
Pelvic pain
Skin and subcutaneous tissue disorders
Hyperhidrosis
Vascular disorders
Blood pressure fluctuation
Flushing

INTERACTIONS

No specific drug-drug interaction studies have been conducted in humans.

Anticipated interactions to be considered

Other photosensitizing agents

It is possible that concomitant use of other photosensitising agents (e.g. tetracyclines, sulphonamides, phenothiazines, sulfonylurea, hypoglycemic agents, thiazide diuretics, and griseofulvin) could increase the potential for photosensitivity reactions.

Drugs increasing verteporfin uptake in the vascular endothelium

Agents such as calcium channel blocking agents, polymixin B, and radiation therapy are known to alter the vascular endothelium and may result in enhanced verteporfin tissue-uptake when used concurrently.

Free radical scavengers

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

Drugs antagonizing 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 antagonize the action of verteporfin.

PREGNANCY, BREAST-FEEDING AND FERTILITY

Pregnancy

There is insufficient experience with Visudyne in pregnant women. Verteporfin has shown teratogenic effects in one species (rat) at doses causing maternal toxicity (see NON-CLINICAL SAFETY DATA). The potential risk for humans is unknown.

Visudyne should be used in pregnant women only if the expected benefit to the mother outweighs the potential risk to the fetus.

Breast-feeding

Verteporfin and its diacid metabolite have been found in human milk. Following a 6 mg/m^2 dose infusion in a single individual, verteporfin breast milk levels were up to 66 % of the corresponding plasma concentrations, and declined below the limit of quantification (2 nano gram/mL) within 24 hours. The diacid metabolite exhibited lower peak concentrations but persisted up to at least 48 hours. The amount of diacid metabolite excreted with the milk on Day 2 post dose (i.e. from 24 to 48 hours post dose), was

estimated to be at most 7.5 micrograms, or approximately 0.075% of the maternal dose; thereafter, the amount of diacid metabolite excreted daily with the milk is estimated to decrease by at least 50% per day. Because of the potential for adverse reactions in nursing infants from Visudyne, treatment should either be postponed or women should interrupt breast-feeding – pump and discard the milk – for at least 48 hours following dosing. A decision to postpone treatment or prolong interruption of nursing should take into consideration the importance of the drug to the mother and the consequences of breast feeding interruption to both the baby and the mother.

Fertility

No information is available about fertility in humans with Verteporfin. No effect on male or female fertility has been observed in rats (see section NON-CLINICAL SAFETY DATA). The clinical relevance is unknown. Patients of reproductive age should be made aware of the lack of fertility data, and Visudyne should be given after consideration of individual risks and benefits.

OVERDOSAGE

Overdose of drug 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 drug 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.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties (PD)

Verteporfin, also referred to as benzoporphyrin derivative monoacids A ring (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 drug (photosensitiser). The regioisomers have been reported to have similar photodynamic properties.

Verteporfin 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 Photodynamic Therapy (PDT) using verteporfin is based, in addition to the localized light exposure, on rapid uptake and selective retention of verteporfin by rapidly proliferating cells including the endothelium of choroidal neovasculature.

Pharmacokinetic properties (PK)

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 micrograms/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 level studied.

In human plasma, 90 % of verteporfin is associated with plasma lipoprotein fractions and approximately 6 % is associated with albumin.

Metabolism

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 photosensitizer but its systemic exposure is low (5 to 10 % of the verteporfin exposure suggesting that most of the drug is eliminated unchanged). In vitro studies did not show any significant involvement of oxidative metabolism by cytochrome P450 enzymes.

Elimination

Following intravenous infusion, verteporfin exhibits a bi-exponential elimination. Plasma elimination half-life mean values ranged from approximately 5 to 6 hours for verteporfin. Combined excretion of verteporfin and BPD-DA in human urine was less than 1 % suggesting a biliary excretion.

Dose linearity

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

Special populations

Geriatric patients (65 years of age or above)

The C_{max} of verteporfin are somewhat higher (26 % for the proposed dose of 6 mg/m²) in the elderly than in young healthy volunteers and this may result in a higher exposure. The clinical relevance of this age-related difference is remote as the risk/benefit assessment determined in the target population is favorable.

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 has 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.

CLINICAL STUDIES

Age-related Macular Degeneration with predominantly classic subfoveal CNV

Visudyne has been studied in two randomized, placebo-controlled, double-masked, multicenter studies BPD OCR 002 A and B (Treatment of Age-related Macular Degeneration with Photodynamic Therapy [TAP] A and B). 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 (PDT) with verteporfin in limiting the decrease in visual acuity in patients with subfoveal choroidal neovascularisation (CNV) due to AMD.

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 fluorescence on angiography), CNV located subfoveal (involved the geometric center 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 areas, 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. During these studies retreatment was allowed every 3 months if fluorescein angiograms showed any recurrence or persistence of leakage.

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 (classic component comprised 50% or more of the area of the entire lesion) (N=242; Visudyne 159, placebo 83) 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, $p < 0.001$) and this benefit was maintained at 24 months (59 % versus 31 %, $p < 0.001$). Severe vision loss (≥ 6 lines of visual acuity from baseline) was experienced by only 12 % of Visudyne-treated patients compared to 33 % of placebo-treated patients at Month 12, and by 15 % of Visudyne-treated patients compared to 36 % of placebo-treated patients at Month 24.

In patients followed from Month 24 onwards and receiving Visudyne treatment as needed in an uncontrolled, open-label extension study (TAP A+B extension study), data suggest that Month-24 vision outcomes may be sustained for up to 60 months. No additional safety concern was identified in the extension study.

In the TAP study in all lesion types, the average number of treatments per year was 3.5 in the first year after diagnosis and 2.4 in the second for the randomized, 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.

Age-related Macular Degeneration with occult with no classic subfoveal CNV

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 randomized, placebo-controlled, double-blind, multicenter, 24-month studies BPD OCR 003 AMD (Verteporfin in Photodynamic Therapy-AMD [VIP-AMD]) and BPD OCR 013 (Visudyne in Occult Choroidal Neovascularization [VIO]) were conducted in patients with AMD characterized by occult with no classic subfoveal CNV.

In one study (BPD OCR 003 AMD) statistically significant treatment benefit was demonstrated at 2 years; however this statistically significant benefit was not confirmed in the second study (BPD OCR 013). The benefit of Visudyne in this patient population has not been consistently shown. The details of the study results are summarised below.

BPD OCR 003 AMD included patients with occult with no classic subfoveal CNV with a visual acuity score ≥ 50 letters (20/100), or 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 BPD OCR 002 (see above).

At Month 12, although the secondary efficacy parameter (such as mean changes of visual acuity and contrast sensitivity, angiographic outcomes, development of classic components in patients with occult only CNV) were statistically significantly in favour of Visudyne, the study did not show any statistically significant results in the primary efficacy parameter (responder rate).

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).

Exploratory subgroup analysis suggested that the treatment benefit was greater for occult with no classic patients who presented with either small lesions (< 4MPS-DA) or lower levels of vision (VA score of <65 letter) at baseline (N=187). In those patients, the responder rate difference was 26.2 % in favour of Visudyne compared to placebo patients (51.2 % versus 25 % at Month 24, p <0.001).

BPD OCR 013 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 BPD OCR 002 and BPD OCR 003 AMD (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=0.158; 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).

Pathologic Myopia

One randomized, placebo-controlled, double-masked, multicenter study BPD OCR 003 PM (Verteporfin in Photodynamic Therapy-Pathologic Myopia [VIP-PM], was conducted in patients with subfoveal choroidal neovascularisation caused by pathologic myopia. A total of 120 patients (81 Visudyne, 39 placebo) were enrolled in the study. The dosage and retreatment eligibility were the same as in the AMD studies. A planned analysis of safety and efficacy was conducted at 12 and 24 months, with 96 % and 95 % of patients completing each portion of the study, respectively.

At month 12, the difference between treatment groups statistically favoured Visudyne. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of approximately 20 % between groups (86 % for Visudyne versus 67 % for placebo, p=0.011). The percentage of patients with stabilized vision defined as vision loss of less than 1.5 lines was 72 % (Visudyne) versus 44 % (placebo), showing a difference of 28 % between treatment groups (p=0.003). 26 Visudyne-treated patients (32 %) and 6 placebo-treated patients (15 %) gained more than 1 line of visual acuity.

At Month 24, the percentage of patients who lost less than 3 lines of visual acuity was 79 % for Visudyne patients and 72 % for placebo patients showing a difference of 7 % between groups (p=0.381). The difference between Visudyne and placebo patients who lost less than 1.5 lines was 16 % (64% for Visudyne versus 49 % for placebo, p=0.106). 32 Visudyne treated patients (40 %) gained more than 1 line of vision, 10 of them more than 3 lines. In comparison, 5 patients treated with placebo (13 %) improved by 1 line or more, and none improved by 3 lines or more. In patients followed from Month-24 onwards and receiving Visudyne treatment as needed in an uncontrolled, open-label, extension study (VIP-PM extension), data suggest that Month-24 vision outcomes may be sustained for up to 60 months. No additional safety concern was identified in the extension study.

In the VIP-PM study in pathologic 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 randomized 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.

Presumed ocular histoplasmosis

One open-label study BPD OCR 004 (Visudyne in Ocular Histoplasmosis [VOH]) was conducted in patients with CNV caused by ocular histoplasmosis syndrome. A total of 26 patients were treated with Visudyne in the study. The posology and re-treatments were the same as in the AMD studies. After Visudyne therapy, visual acuity scores improved 7 or more letters from baseline in 46 % of the patients after 24 months of follow-up, with 36 % of patients gaining 15 or more letters of visual acuity. These results show that verteporfin therapy demonstrates an improvement in vision compared to the natural progression of the disease, which resulted in loss of vision.

NON-CLINICAL SAFETY DATA

Single and repeated dose toxicity

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

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 administration of verteporfin for injection 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) as a class 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.

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.

INCOMPATIBILITIES

Visudyne precipitates in saline solutions. Do not use normal saline or other parenteral solutions. Do not mix Visudyne in the same solution with other drugs.

STORAGE

See folding box.

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 product should be used immediately.

Visudyne should not be used after the date marked “EXP” on the pack.

Visudyne should be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Reconstitute Visudyne in 7.0 mL water for Injection to produce 7.5 mL of a 2 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 area (see DOSAGE AND ADMINISTRATION), dilute the required amount of Visudyne solution in 5 % Glucose/Dextrose for Injection to a final volume of 30 mL. Do not use saline solution (see INCOMPATIBILITIES). Use of a standard infusion line filter is recommended; infusion line filters with a pore size of not less than 1.2 micrometres were used in clinical trials.

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. All materials should be disposed of properly.

Manufacturer:

See folding box.

Package Leaflet

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