Visudyne®

Photosensitiser, powder for solution for infusion

Composition

Each vial contains :

Active ingredient : Verteporfin 15 mg,

Excipients : Lactose 690 mg, dimyristoyl phosphatidylcholine 71 mg, egg phosphatidylglicerol 49 mg, Antioxidants : ascorbyl palmitate 0,15 mg (E304), butylated hydroxytoluene 0,015 mg (E321).

Properties and actions

Pharmacotherapeutic group : Other neoplastic agents; ATC, code : L01 XX26. Verteporfin, also referred to as benzomorphyrin derivative monoacid (BPD-MA) consist of a 1:1 mixture of the equally active regioisomers BPD-MAC and BPD-MAD. It is used as light-activated drug (photosensitiser).

By it self, 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.

<u>Age-related Macular Degeneration</u>

Visudyne has been studied in two randomized, placebo controlled, double blind, multicentre studies (BPD OCR 002 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 Photodynamic Therapy (PDT) with verteporfin in limiting the decrease in visual acuity in patients with subfoeval choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD).

The primary efficacy variable was responder rate, defined as the proportion of patients who lost less then 15 letters (equivalent to 3 lines) of visual (measured with the ETDRS charts at month).

The following inclusion criteria were considered for treatment: patients older than 50 years of age, presence of CNV secondary to AMD, presence of classic lesion components in the CNV (defined as well-demarcated area of the fluorescence on angiophaty), CNV located subfoevally (involved the geometric centre of the feoval vascular 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.

Result indicates thet, at least 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 group 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).

Another randomized, placebo controlled, double blind, multicentre, 24 month study (BPD OCR 003 AMD) was conducted in patients with AMD characterized by occult only subfoeval CNV, or classic CNV with a visual acuity score > 73 letters (20/40). At month 12 the study did not show any statistically significant results on the primary efficacy parameter (responder rate).

Phatological Myopia

One multicentre, double blind, placebo controlled, randomized study (BPD OCR 003 PM) was conducted in patients with subfoeval choroidal neovascularisation caused by pathologic myopia. A total of 120 patients (81 Visudyne, 39 placebo) were enrolled in the study. The posology and re-treatment were the same as in the AMD studies. A planned analysis of safety and efficacy was conducted at 12 months, with 96% of patients completing that portion of the study. The difference between treatment group statistically favoured Visudyne at the 12-month analysis for visual acuity endpoints. 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 who lost less than 1.5 lines was 72% Visudyne versus 44% placebo, showing a difference of 28% between treatment groups (p=0.003).

Pharmacokinetics

Distribution

Cmax 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 mg/ml, respectively. These value are somewhat higher (26% for the proposed dose of 6 mg/m^2) than those observed in young healthy volunteers and 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 favourable. A maximum 2-fold inter-individual variation in plasma concentrations at Cmax (immediately after end of the infusion) and at the time of light administration was found for each Visudyne dose administered.

For both regioisomers, Cmax and AUC values was proportional to the dose. Cmax values obtained at the end of infusion were higher for BPD-MA_D than for BPD-MA_C. The volume of distribution was 0,5 l/kg.

Protein – binding

In the whole human blood 90% of the verteporfin is associated with plasma and 10% associated with blood cells, of which very little is bound to membranes. In human plasma, 90% of the verteporfin is associated with plasma lipoprotein fractions and approximately 6% are 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 photosensitiser, but its systemic exposure is low (5-10% 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 enzyme.

Elimination
The plasma elimination half life mean values range from approximately 5-6 hours for the verteporfin.
The mean area under curve (AUC) for subjects with mild hepatic dysfunction were up to 1,4 times greater than those for subjects with normal hepatic function. This difference is not clinically relevant and does not require any dose adjustment to patients with mild hepatic impairment. Combined excretion of verteporfin and BPD-DA in human urine was less than 1% suggesting a biliary excretion.

Indications
Visudyne is indicated for the treatment of age related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularisation.

Dosage and method of administration
Visudyne should be used only by ophthalmologists experienced in the management of patients with age related macular degeneration.
Visudyne treatment 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, diluted in 30 ml infusion solution (see “instructions for use and handling”).
The second step is the light activation of Visudyne 15 minutes after the start of the infusion. For this, non-thermal red light (wave length 689 nm), generated by the diode laser, is directed towards the choroidal neovascular lesion by means of a glass-fibre optic device mounted on the slit lamp and with the use of a suitable contact lens. At the recommended light intensity of 600 mW/cm2, it takes 83 seconds to apply the required light dose of 50 J/cm^2.
The greatest linear dimension of the choroidal neovascular lesion is determined by means of fluorescein angiography and fundus photography. Fundus cameras with a magnification within the range of 2,4-2,6 X are recommended.
The light 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 for the first treatment in the clinical studies was 6400 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.
In order to achieve the optimal treatment effect, it important to adhere to the above recommendations.
In both eyes have to be treated, the 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.
Patients should be re-evaluated every 3 months. In the event of recurrent CNV leakage, the treatment with Visudyne therapy may be given up to 4 times per year.

Instructions for use and handling
Visudyne is dissolved in 7,0 ml water for injection in order to obtain 7,5 ml of a 2,0 mg/ml concentrated solution. For a dosage of 6 mg/m2 body surface (see “Dosage and methode of

administration") dilute the required amount of Visudyne solution in 5% dextrose for injection to a final volume of 30 ml (see "Incompatibilities").
Do not use in direct bright light. Do not use saline solutions.
If material is spilled, it should be contained and wiped up with a damp cloth. Eye and skin contact should be avoided.

Restrictions on use
Contraindications
• Patients with porphyria and in patients with severe hepatic impairment
• Known hypersensitivity to verteporfin or to any of the excipients

Precautions for use
Patients who receive Visudyne will become photosensitive for 48 hours after the infusion. During that period, patients should avoid exposure of an unprotected skin and 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 dentists offices. If patients have to go outdoors in daylight during the first 48 hours after treatment, they must protect their skin and eyes by wearing protected clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitive 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 quickly through the skin by a process called photobleaching.
Visudyne therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since no experience has been gained in these patients. Patients who experience severe vision loss (4 lines or more) within one week after the treatment should not be re-treated, at least until their vision completely recovered to pretreatment level and the potential benefits and risks of subsequent treatment are carefully considered by treating physician.

Extravasation of Visudyne can cause severe pain, inflammation, swelling or discoloration at the injection site. The relieve of pain may required analgesics treatment. If extravasation accurs, 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 IV line should be established before starting Visudyne infusion and the line should be monitored, the biggest possible arm vein, preferably the antecubital, should be used for the infusion and small veins in the back of the hand should be avoided.

There are no clinical data on the use of Visudyne in anaesthetized patients. In anaesthetized minipigs, a Visudyne dose of more than 10 times higher than the recommended dosage in patients given as a bolus injection cause severe haemodynamic effects including death, probably as a result of complement activation, which are possibly due to a complement activation, were observed. Although this effect was neither observed in conscious pig, nor in any other species including man, caution should be exercised when Visudyne treatment under general anaesthesia is considered.

There are no clinical data to support a concomitant treatment for the second eye. 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.

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

Pregnancy and lactation
Pregnancy category C.
In teratogenicity studies in rats, increasing incidences of anophthalmia and/or microphthalmia, wavy ribs and foetal alterations were observed at doses greater than approximately 70 times the exposure (based on AUC) of the recommended human dose. Visudyne has not been studied in pregnant women.

Therefore, Visudyne should be used in pregnant women only if the benefit justifies the potential risk to the foetus.

It is not known whether Visudyne is excreted in human milk, it should therefore not be administered to nursing mothers, or breast feeding should be interrupted for 48 hours after administration.

Undesirable effects
In placebo-controlled clinical trials, in patients with subfoveal CNV, with classical lesions, the following side effects, which much be assumed to have a causal relationship with the Visudyne theraphy, were observed:

Ocular side effects
Visudyne placebo (1-10 %): Abnormal vision such as blurry, fuzzy, hazy, or flashes of light decrease vision, visual-field defects such as grey or dark haloes, scotoma and black spots.
Severe vision decrease, equivalent of 4 lines or more, within seven days 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 or minimally classic CNV lesions in-patients with AMD and was not reported for placebo-treated patients. A partial or complete recovery of vision to baseline values has been observed for most of these patients.

Uncommon effects (0.1-1%) : Retinal detachment (nonrhegmatogenous), subretinal haemorrhage, vitreous haemorrhage.

In 1% of the patients severe vision loss (4 lines or more) occurred within seven days. In another placebo-controlled study in patients with predominantly occult CNV lesions, in 4% of the patients severe vision loss was also observed within seven days after the treatment. The sight improved completely or partly in most of these patients.

Side effects at the injection site
Common effect (1-10%) : Pain, oedema, inflammation, extravasation.

Uncommon effect : Haemorrhage, discoloration, hypersensitivity.

Systemic side effects

Common effects (1-10%) : Infusion-related pain primarily presenting as back pain, but may also radiate to other areas such as the pelvis, shoulder girdle or rib cage, nausea, photosensitivity reaction, asthenia, pruritus, and hypercholesterolemia.

Photosensitivity reactions (in 2.2% of patients and < 1% of Visudyne courses) occurred in the sunburn following exposure to sunlight usually within 24 hours from Visudyne treatment. Such reactions should be avoided by compliance with photosensitivity protection instructions under Section “Precaution for use”.

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

Uncommon effects (0.1-1%) : Pain, hypertension, hypesthesia, fever.

Rare undesirable effects in clinical trials (0.1%) or spontaneously reported during post marketing surveillance included:

Ocular side effects: retinal or choroidal vessel nonperfusion;

Systemic side effects: chest pain, syncope, and severe allergic reactions with dyspoea and flushing.

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

Interactions

No specific drug-drug interaction studies have been conducted in humans. Based on the mechanism of action, some drugs could influence the effect of the Visudyne treatment.

Possible examples are given below:

- The concomitant use of other photosensitizing agents (e.g. tetra-cyclines, sulphonamides, phenothiazines, sulfonylurea, hypoglycaemic agents, thiazide diuretics, and griseofulvin) could increase the potential for photosensitivity reactions.
- Compounds that scavenge active oxygen species or radicals, such as dimethyl sulfoxide, β-carotene, ethanol, formiate and mannitol would be expected to decrease verteporfin activity.
- Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of verteporfin uptake by the vascular endothelium.
- Anticoagulants, vasoconstrictors or platelet-aggregation inhibitors such as thromboxane A2 inhibitors could decrease the efficacy of Visudyne.

Overdose

No case of overdose has been reported. 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 can prolong the patient’s photosensitivity by several days. With a dose of about 20 mg/m^2, i.e. 3 times the normal dose, the period of photosensitivity was increased to 6.7 days. Therefore in such cases, depending on the amount of the overdose the patients should prolong the period of protection of the skin and the eyes against sunlight or strong artificial light.

Further information

Effects on the 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 who develop such symptoms should not drive or use machines as long as these symptoms persist.

Incompatibilities

Visudyne precipitates in saline solutions. Do not use normal saline or other parental solutions. Do not mix Visudyne in the same solution with other drugs. Protect from direct bright light.

Shelf life

Visudyne vials may be used up to the date indicated with “EXP” on the container.

Do not store above 25°C. Protect from light. After reconstitution and dilution protect from light until used and use within a maximum of 4 hours. Keep out of the reach of children.

Presentation

Medicinal products subject to medical prescription.

Packing and Registration Number

Vial containing 15 mg of verteporfin

Harus Dengan Resep Dokter

Manufactured by Parkdale Pharmaceuticals, Inc., Rochester, MI, USA, for NOVARTIS Opthalmics AG, Hettlingen, Switzerland, Imported by PT. Novartis Biochemie, Bogor, Indonesia.