

NEW ZEALAND PI – VISUDYNE® (VISUDYNE) 15 MG POWDER FOR INFUSION

1 NAME OF THE MEDICINE

Visudyne

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Verteporfin, also referred to as benzoporphyrin derivative monoacids ring A (BPD-MA), consisting of a 1:1 mixture of the equally active structural isomers BPD-MA_C and BPD-MA_D.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Visudyne (verteporfin) is a sterile powder for intravenous infusion.

Verteporfin is a dark green to black powder that is soluble in tetrahydrofuran, sparingly soluble in acetonitrile, methanol and methylene chloride and insoluble in water, other than at extremes of pH.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Visudyne is indicated for the treatment of patients with predominately classic or occult subfoveal choroidal neovascularisation due to age-related macular degeneration (AMD), or with subfoveal choroidal neovascularisation caused by other macular diseases.

4.2 DOSE AND METHOD OF 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 treatment 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 4.2).

The second step is the light activation of Visudyne 15 minutes after the start of the infusion (see section 4.2).

Patients should be re-evaluated every 3 months. In the event of recurrent CNV leakage, Visudyne treatment should be repeated. In clinical studies, patients have been treated up to 9 times within 2 years.

There are, as yet, no clinical data to support concomitant treatment of the second eye. Controlled trials only allowed treatment of one eye per patient. Therefore, concomitant treatment of both eyes is not recommended.

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.

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 5.2).

Paediatric 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 dosage and administration 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 the light activation, a diode laser generating non-thermal red light (wavelength 689 nm \pm 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/cm², it takes 83 seconds to deliver the required light dose of 50 J/cm².

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 2.6X 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 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.

Instructions for Use and Handling

Reconstitute Visudyne with 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 discolouration prior to administration. For a dose of 6 mg/m² body surface area (see section 4.2) dilute the required amount of Visudyne solution in 5% dextrose for injection to a final volume of 30 mL.

Use in one patient on one occasion only. Contains no antimicrobial preservative.

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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Photosensitivity Following Treatment

Patients who receive Visudyne will become photosensitive for 48 hours after the infusion and should wear a wrist band to remind them to avoid direct sunlight for 48 hours. 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 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 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. Ambient indoor light is safe. UV sunscreens are not effective in protecting against photosensitivity reactions. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

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 be retreated, at least until their vision completely recovers to pretreatment level and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Extravasation

Extravasation of Visudyne, especially if the area is exposed to light, can cause severe pain, inflammation, swelling, blistering or discolouration 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, the infusion should be stopped immediately. Protect the affected area thoroughly from bright direct light until swelling and discolouration have disappeared in order to prevent the occurrence of a local burn which could be severe, 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 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.

Medical supervision during the infusion

Chest pain, vaso-vagal 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 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 be initiated

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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 haemodynamic effects including death, probably as a result of complement activation. Pre-dosing with antihistamine (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 any other species including man.

Verteporfin, at about 6 times the expected maximum plasma concentration in treated patients, caused a low level ($\leq 40\%$) of complement activation in human blood *in vitro*. Complement activation tended to be greatest in serum samples from people with anti-cardiolipin (anti-phospholipid) antibodies. No clinically relevant complement activation was reported in five patients treated with verteporfin, but the risk of anaphylactic reactions due to complement activation cannot be excluded. Patients should be supervised during Visudyne infusion and caution should be exercised when Visudyne treatment under general anaesthesia is considered.

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, overtreatment due to overactivation of Visudyne, or damage to surrounding normal tissue.

Use in Patients with Heart Disease or Hypertension

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

Use in hepatic impairment

Verteporfin is cleared by the liver and excreted in the bile. Visudyne therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since no experience has been gained in these patients .

Use in the elderly

Approximately 90% of the patients treated with Visudyne in the clinical efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

Paediatric use

Safety and effectiveness in paediatric patients have not been established.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Anticipated Interactions to be Considered

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of Visudyne therapy. Possible examples are given below.

Drugs increasing verteporfin uptake in the vascular endothelium:

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

Other photosensitising agents:

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

Free radical scavengers:

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

Drugs antagonising 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

Effects on fertility

No effect on male or female fertility was observed in rats following intravenous administration of verteporfin up to 10 mg/kg/day (approximately 60 and 40 fold human exposure at 6 mg/m² based on AUC_(0-∞) in male and female rats, respectively).

Use in pregnancy – Pregnancy Category B3

Foetal levels of verteporfin and/or metabolites were about 1% of maternal concentrations after intravenous administration of radiolabelled verteporfin in pregnant rats.

Rat foetuses of dams administered verteporfin for injection intravenously at 25 mg/kg/day during organogenesis showed increased incidences of anophthalmia / microphthalmia, bent or wavy ribs. The no-observed-effect-level (NOEL) was 10 mg/kg/day for foetal damage (approximately 40 fold the human exposure at 6 mg/m² based on AUC in female rats) and 2 mg/kg/day for maternal toxicity (approximately 4 fold the human exposure at 6 mg/m² based on AUC in female rats).

No evidence of foetal toxicity or teratogenic activity was observed in rabbits given verteporfin intravenously at doses up to 10 mg/kg/day, while 25 mg/kg/day was fatal in pregnant rabbits. The NOEL for foetal damage was 10 mg/kg/day (approximately 24 fold the human exposure at 6 mg/m² based on body surface area) and 3 mg/kg/day for maternal toxicity (approximately 7 fold the human exposure at 6 mg/m² based on body surface area).

There are no adequate and well-controlled studies in pregnant women. Visudyne should be used during pregnancy only if the expected benefit to the mother outweighs the potential risk to the foetus.

Use in lactation.

It is not known whether Visudyne is excreted in human milk. However, many drugs are excreted in human milk. Visudyne should therefore not be administered to nursing mothers, or breast-feeding should be interrupted.

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 ($\geq 1/10$); 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 ($< 1/10,000$).

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	Common
Retinal oedema ³	Uncommon
Retinal ischaemia [#]	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	

SOC/PT	Frequency category (CIMOS III)
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

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

²Severe 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.

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

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

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.

⁶Photosensitivity 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 6 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 categorised as not known.

Table 2 Adverse drug reactions from spontaneous reports

SOC/PT
Eye disorders
Retinal pigment epithelial tear
Macular oedema
Reproductive system and breast disorders
Pelvic pain
General disorders and administration site conditions
Injection site vesicles
Injection site necrosis

SOC/PT

Immune system disorders

Anaphylactic reaction

Investigations

Heart rate irregular

Nervous system disorders

Presyncope (vaso-vagal reactions)

Skin and subcutaneous tissue disorders

Hyperhidrosis

Vascular disorders

Blood pressure fluctuation

Flushing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 OVERDOSE

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Visudyne therapy is a two-stage process requiring administration of both verteporfin for injection and nonthermal red light. Verteporfin is used as a light-activated drug (photosensitiser). The regioisomers have been reported to have similar photodynamic properties. Treatment of diseases using photosensitisers and light activation is called photodynamic therapy (PDT).

Verteporfin is transported in the plasma primarily by lipoproteins. Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase (leukotriene) and cyclo-oxygenase (eicosanoids

such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction. Verteporfin appears to somewhat preferentially accumulate in neovasculature, including choroidal neovasculature. However, animal models indicate that the drug is also present in the retina. Therefore, there may be collateral damage to retinal structures following photoactivation including retinal pigment epithelium and outer nuclear layer of the retina. The temporary occlusion of choroidal neovascularisation (CNV) following Visudyne therapy has been confirmed in humans with fluorescein angiography.

Clinical trials

Age-Related Macular Degeneration (AMD)

AMD with predominantly classic subfoveal CNV: (Treatment of AMD with PDT; TAP studies BPD OCR 002 A&B):

Two adequate and well-controlled, double-masked, placebo-controlled, randomised studies were conducted in patients with classic-containing subfoveal CNV secondary to age-related macular degeneration (BPD OCR 002 A and B). A total of 609 patients (Visudyne 402, placebo 207) were enrolled in these two studies. A planned analysis of safety and efficacy was conducted at 1 year, with 94% of patients completing that portion of the study. A second analysis was planned at 2 years to establish durability of effect: 87% of patients completed 2 years of follow-up. During these studies, retreatment was allowed every 3 months if fluorescein angiograms showed any recurrence or persistence of leakage. The placebo control (sham treatment) consisted of intravenous administration of glucose 5% in water, followed by light application identical to that used for Visudyne therapy. 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 EDTRS chart) at 12 months relative to baseline.

The difference between treatment groups statistically favoured Visudyne at the 1-year and 2-year analyses for visual acuity endpoints.

The subgroup of patients with predominantly classic CNV lesions was more likely to exhibit a treatment benefit (N=242; Visudyne 159, placebo 83). Predominantly classic CNV lesions were defined as those in which the classic component comprised 50% or more of the area of the entire lesion. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of approximately 28% between treatment groups at both month 12 and 24 (67% for Visudyne patients compared to 40% for placebo patients, $p < 0.001$ at month 12; and 59% for Visudyne patients compared to 31% for placebo patients, $p < 0.001$ at month 24). Severe vision loss (≥ 6 lines of visual acuity from baseline) was experienced by only 12% of Visudyne-treated patients compared to 34% of placebo-treated patients at month 12, and by 15% of Visudyne-treated patients compared to 36% of placebo patients at month 24.

In patients followed from month 24 onwards and receiving Visudyne treatment as needed in an uncontrolled, open-label extension study (BPD OCR 002 A and B extension study), data suggest that vision outcomes at month 24 may be sustained for up to 60 months. No additional safety concerns were identified in the extension study.

In the BPD OCR 002 A and B extension 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 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.

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

(Verteporfin In Photodynamic Therapy of AMD; VIP-AMD study BPD OCR 003 AMD):

VIP-AMD was conducted in patients with AMD characterised by occult with no classic subfoveal CNV, or classic-containing CNV with a visual acuity score >73 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).

For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), a statistically significant difference of 12.9% in favour of Visudyne compared to placebo was observed at month 24 (46.2% i.e. 104 of 225 Visudyne patients, versus 33.3% i.e. 38 of 114 placebo patients, $p=0.023$). A group of patients who had occult with no classic lesions ($n=258$) showed a statistically significant difference in this same primary efficacy endpoint of 13.7% in favour of Visudyne compared to placebo (45.2% i.e. 75 of 166 Visudyne patients versus 31.5% i.e. 29 of 92 placebo patients, $p=0.032$).

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 letters) at baseline ($n=187$). In those patients, the responder rate difference was 26.2% in favour of Visudyne compared to placebo patients (51.2% i.e. 63 of 123 Visudyne patients versus 25% i.e. 16 of 64 placebo patients lost less than 3 lines of visual acuity at month 24, $p<0.001$).

(Visudyne In Occult Choroidal Neovascularization; VIO study BPD OCR 013):

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 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%, $p=0.150$; 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 safety and efficacy of Visudyne beyond 2 years have not been demonstrated.

Other Macular Diseases

Pathologic myopia:

(Verteporfin In Photodynamic Therapy of Pathologic Myopia; VIP-PM study BPD OCR 003 PM):

One adequate multicentre, double masked, placebo-controlled, randomised study (BPD OCR 003 PM) was conducted in patients with subfoveal CNV caused by pathologic 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. 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 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 ($p=0.003$).

At month 24, 79% Visudyne patients versus 72% placebo patients had lost less than 3 lines of visual acuity ($p=0.381$). The percentage of patients who lost less than 1.5 lines was 64% for Visudyne and 49% for placebo ($p=0.106$).

In patients followed from month 24 onwards (67 patients) and receiving Visudyne treatment as needed in an uncontrolled, open-label, extension study (BPD OCR 003 PM extension study), data suggest that vision outcomes at month 24 may be sustained for up to 60 months. Other than 8 Visudyne-treated patients gaining more than 3 lines of vision after 60 months there were no significant changes in vision in either the treated or placebo group. No additional safety concerns were identified in the extension study.

In the BPD OCR 003 study in pathological myopia, the average number of treatments per year was 3.5 in the first year after diagnosis, 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.

Ocular histoplasmosis:

(Verteporfin in Ocular Histoplasmosis; VOH study BPD OCR 004):

One open-label study (BPD OCR 004) was conducted in patients with ocular histoplasmosis syndrome. A total of 26 patients were treated with Visudyne in the study. The posology and retreatments 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.

In patients followed from month 24 onward (17 patients) and receiving Visudyne treatment as needed in an uncontrolled, open-label extension study (BPD OCR 004 extension study), data suggest that vision outcomes at month 24 may be sustained for up to 48 months. No additional safety concerns were identified in the extension study.

In the VOH study in presumed ocular histoplasmosis the average number of treatments per year was 2.9 in the first year after diagnosis, 1.2 in the second, 0.2 in the third and 0.1 in the fourth year.

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:

Visudyne exhibits a simple and predictable pharmacokinetic profile. C_{max} after a 10 minute infusion of 6 and 12 mg/m² body surface area in the target population is approximately 1.58 and 3.24 microgram/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 the end of the infusion) and at the time of light administration was found for each Visudyne dose administered. C_{max} and area under the curve (AUC) values were linearly proportional to dose.

Plasma elimination half-life mean values ranged from 5-6 hours and were similar for both structural isomers.

The mean half-life of verteporfin in subjects with mild hepatic dysfunction was approximately 6.5 hours, while that of normal subjects was close to 4.7 hours. The mean AUC values 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 for patients with mild hepatic impairment.

Protein binding:

In whole human blood, 90% of verteporfin is associated with plasma and 10% associated with blood cells, of which very little is membrane associated. 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 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 enzymes.

Excretion:

In rats, approximately 90% of the intravenous dose of ¹⁴C-BPD-MA was excreted in the faeces in 7 days, mainly by excretion in the bile. Less than 1% of the radioactivity was excreted in the urine. Only negligible amounts of verteporfin or BPD-DA are recovered in human urine, confirming a biliary excretion. The total body clearance in healthy volunteers was 105 mL/hour/kg and urinary excretion was less than 0.01% of the dose, as verteporfin and BPD-DA.

Special populations:***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.

5.3 PRECLINICAL SAFETY DATA**Genotoxicity**

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. In addition, other photodynamic therapy agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, to increase mutations and DNA-protein cross-linking in mouse L5178 cells, and to increase DNA-strand breaks in malignant human cervical carcinoma cells but not in normal cells. Verteporfin was not evaluated in these systems. In other assays verteporfin, with or without metabolic activation (hepatic S9 fraction), and with or without irradiation using white (full spectrum) fluorescent light, showed no evidence of genotoxicity in assays of gene mutation (bacterial and mammalian (CHO) cells) or clastogenic activity (CHO cells *in vitro* and an *in vivo* mouse micronucleus test). Verteporfin, with or without irradiation, was also negative in an assay of unscheduled DNA synthesis in rat hepatocytes. It is not known how the potential for DNA damage with PDT agents translates into human risk.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose, dimyristoylphatidylcholine, egg phosphatidylglycerol sodium, ascorbyl palmitate, butylated hydroxytoluene.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

4 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep vial in the outer carton in order to protect from light.

After reconstitution and dilution protect from light until used and use within a maximum of 4 hours (see section 4.2). From a microbiological point of view, the product should be used immediately.

6.5 NATURE AND CONTENTS OF CONTAINER

Visudyne (verteporfin) is a sterile powder for intravenous infusion.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

6.7 PHYSICOCHEMICAL PROPERTIES

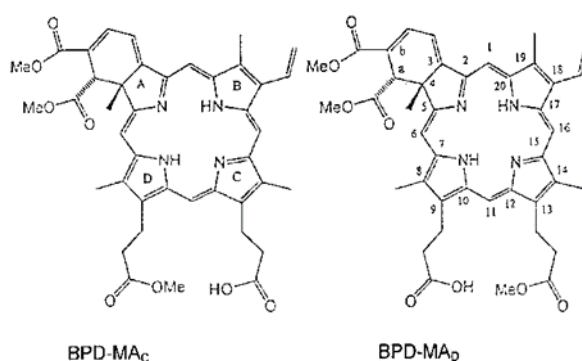


FIGURE 1. Structure of BPD-MA_c and BPD-MA_p

Molecular formula: C₄₁H₄₂N₄O₈

Molecular weight: 718

CAS No: 129497-78-5

Chemical name: (±)-trans-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-benzo[b]porphine-9,13-dipropanoic acid monomethyl esters

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30th November 2000

10 DATE OF REVISION

1st November 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Data sheet converted to new Medsafe format (SmPC style) and editorial updates.
4.4	Addition of anaphylactic reactions as a precaution.
4.8	Immune System Disorders and Anaphylactic reactions added.
8	Update to sponsor details due to change in product sponsor.