

Prescribing Information

Pr **VISUDYNE***

Verteporfin for Injection 15 mg / vial

For Intravenous Use

Photosensitizing Agent for Photodynamic Therapy of Choroidal Neovascularization

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Date of Preparation:
May 31, 2000

Date of Revision:
January 9, 2008

Submission Control No: 116250

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VISUDYNE*

VERTEPORFIN FOR INJECTION

HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|-------------------------|---|---|
| Intravenous infusion | Lyophilized powder for injection containing 15 mg verteporfin per vial. | Ascorbyl palmitate, butylated hydroxytoluene, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, lactose. This is a complete listing. |

INDICATIONS AND CLINICAL USE

Visudyne Therapy is indicated for the treatment of predominantly classic subfoveal choroidal neovascularization in patients with:

- age-related macular degeneration (AMD),
- pathologic myopia,
- presumed ocular histoplasmosis.

Pediatrics: No data is available.

Geriatrics: 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.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Porphyria.
- Severe hepatic impairment.

WARNINGS AND PRECAUTIONS

VISUDYNE (verteporfin) is a drug to be used in Visudyne Therapy. Visudyne Therapy is a two-stage process requiring administration of both verteporfin for injection and nonthermal red light.

CAUTION: Visudyne Therapy should only be used by physicians trained in the treatment of predominantly classic subfoveal choroidal neovascularization using photodynamic therapy with verteporfin for injection and specified lasers. Following VISUDYNE injection, residual photosensitivity for 48 hours or more may result in erythema and blistering of the skin when exposed to sunlight or brightly focused indoor light.

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.

Appropriate facilities and personnel must be available to treat any complications of the procedure, as well as for the emergency treatment of allergic reactions to the agent itself (see 'Cardiovascular' and 'Immune').

General

Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 2 days. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

Extravasation of VISUDYNE, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling or discoloration at the injection site.

If extravasation does occur, the 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. The relief of pain may require analgesic treatment.

Standard precautions should be taken during infusion of VISUDYNE to avoid extravasation. Examples of standard precautions include, but are not limited to the following:

- a free-flowing intravenous (IV) line should be established before starting VISUDYNE infusion and the line should be carefully monitored,
- due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection,

- small veins in the back of the hand should be avoided.

Carcinogenesis and Mutagenesis

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

Verteporfin was not mutagenic, in the absence or presence of light, when studied in microbial mutagenicity, unscheduled DNA synthesis, mammalian point mutation, chromosome aberration, and mouse micronucleus assays.

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 therapeutic 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, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

No effect on male or female reproduction 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). Males were dosed 28 days prior to and during mating until necropsy (approximately 60 days). Females were dosed for 14 days prior to and during mating until Gestation Day 7.

Cardiovascular

Chest pain, vaso-vagal reactions and hypersensitivity reactions, which on rare occasions can be severe, have been reported. Both vaso-vagal and hypersensitivity reactions are associated with general symptoms such as syncope, sweating, dizziness, rash, dyspnea, flushing, and changes in blood pressure and heart rate. This may be related to complement activation (see '**Immune**').

Hepatic/Biliary/Pancreatic

Visudyne Therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since there is no clinical experience with verteporfin in such patients.

Immune

VISUDYNE at >5 times the expected maximum plasma concentration in treated patients caused a low level of complement activation in human blood in vitro. VISUDYNE resulted

in a concentration-dependent increase in complement activation in human blood in vitro. At 10 µg/mL (approximately 5 times the expected plasma concentration in human patients), there was mild to moderate complement activation. At ≥ 100 µg/mL, there was significant complement activation. Signs (chest pain, syncope, dyspnea, and flushing, see the information under '**Cardiovascular**') consistent with complement activation have been observed in <1% of patients administered VISUDYNE. Patients should be supervised during VISUDYNE infusion and observed for at least 30 minutes after infusion.

Fluorescein Angiography: Standard precautions for fluorescein angiography should be observed. Certain medical conditions (such as pregnancy or allergy to fluorescein) may make the injection of fluorescein dye for a particular patient inadvisable in the opinion of the ophthalmologist. Approximately 1/225,000 patients may experience a severe reaction resulting in a heart attack, stroke, or death. Most reactions are mild, such as temporary nausea or vomiting in a few patients and a rash, hives, or wheezing in about 1%.

Ophthalmologic

Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Following Visudyne Therapy, 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 be advised to not drive or use machines as long as these symptoms persist.

Patients will become temporarily photosensitive for 2 days after the infusion should avoid exposure of unprotected eyes to direct sunlight or bright indoor light. See the information under '**Skin**'.

Peri-Operative Considerations

Caution should be exercised when Visudyne Treatment under general anesthesia is considered. There is no clinical data related to the use of VISUDYNE in anesthetized patients. At a >10-fold higher dose given by bolus injection to sedated or anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious non-sedated pigs or in any other species, whether conscious or under general anesthesia. Caution should be exercised when Visudyne Treatment under general anesthesia is considered.

Sexual Function/Reproduction

No effect on male or female reproduction 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).

Males were dosed 28 days prior to and during mating until necropsy (approximately 60 days). Females were dosed for 14 days prior to and during mating until Gestation Day 7.

Skin

Patients who receive VISUDYNE will become temporarily photosensitive for 2 days 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. This includes, but is not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental 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 treated patients must go outdoors in daylight during the first 2 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. VISUDYNE should be used during pregnancy only if the benefit justifies the potential risk to the fetus

Teratogenic Effects: Rat fetuses of dams administered verteporfin for injection intravenously at ≥ 10 mg/kg/day during organogenesis (approximately 40-fold the human exposure at 6 mg/m² based on AUC_{inf} in female rats) exhibit an increase in the incidence of anophthalmia/microphthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125-fold the human exposure at 6 mg/m² based on AUC_{inf} in female rats) had an increased incidence of wavy ribs and fetal alterations.

In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at 10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7-fold the human exposure at 6 mg/m² based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

Nursing Women: Verteporfin and its diacid metabolite have been found in the breast milk of one woman after a 6 mg/m² infusion. The verteporfin breast milk levels were up to 66% of the corresponding plasma levels and declined below the limit of quantification (2 ng/mL) within 24 hours. The diacid metabolite had lower peak concentrations but persisted up to at least 48 hours. Because the effects of verteporfin and its metabolite on neonates are unknown, either nursing should be interrupted or treatment postponed, taking into account

the risks of delayed treatment to the mother. Women should not nurse for 96 hours after Visudyne Therapy.

Pediatrics: Safety and effectiveness in pediatric patients have not been established.

Geriatrics: 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In randomized clinical trials in choroidal neovascularization, mainly in patients with age-related macular degeneration (AMD), the most frequently reported adverse events to VISUDYNE (verteporfin for injection) are injection site reactions (including pain, edema, inflammation, extravasation, rashes, and less commonly, hemorrhage and discoloration) and visual disturbances (including blurred vision, flashes of light, decreased visual acuity and visual field defects such as grey or dark haloes, scotoma and black spots). These events occurred in approximately 10-30% of AMD patients.

Severe vision decrease, equivalent of 4 lines or more, within 7 days has been reported in approximately 1-5% of AMD patients. At least partial recovery of vision, defined as more than one line improvement of vision following the event, occurred in most patients (approximately 75% of patients).

Photosensitivity reactions usually occurred in the form of skin sunburn following exposure to sunlight during the first 2 days after treatment usually within 24 hours of VISUDYNE infusion. The higher incidence of back pain in the VISUDYNE group occurred primarily during infusion and was not associated with any evidence of hemolysis or allergic reaction and usually resolved by the end of the infusion.

Vaso-vagal and hypersensitivity reactions can occur, which on rare occasions can be severe. See information under '**Warnings and Precautions, 'Cardiovascular', and, 'Immune'**'.

Clinical Trial Adverse Drug Reactions (ADRs)

Table 1 describes adverse events associated with treatment (Adverse Drug Reactions) that occurred with a frequency equal to or greater than 1 percent, in the pivotal 24-month study populations supporting the three indications (see CLINICAL TRIALS).

TABLE 1. Summary of Associated Treatment-Emergent Adverse Events Occurring with Incidence \geq 1% (Predominantly Classic CNV due to AMD from the TAP Studies, CNV due to PM from the VIP PM Study, and CNV due to OHS from the VOH Study)

| BODY SYSTEM: Preferred Term | % of Patients | | | | |
|--------------------------------------|-----------------------|-------------------|--------------------|-------------------|--------------------|
| | BPD OCR 002 A+B (AMD) | | BPD OCR 003 (PM) | | BPD OCR 004 (OHS) |
| | Visudyne (N=159) | Placebo (N=83) | Visudyne (N=81) | Placebo (N=39) | Visudyne (N=26) |
| ANY ASSOCIATED EVENT | 49.1% | 37.3% | 30.9% | 33.3% | 34.6% |
| BODY AS A WHOLE: | | | | | |
| Allergic reaction | | | 1.2% | | |
| Asthenia | 2.5% | | 4.9% | | |
| Body odor | | | 1.2% | | |
| Fever | 1.3% | | | | |
| Headache | 5.7% | 10.8% | 4.9% | 7.7% | 3.8% |
| Infusion related back pain | 3.1% | | 1.2% | | |
| Injection site discoloration | 1.3% | | 1.2% | | |
| Injection site edema | 8.2% | | 2.5% | | 3.8% |
| Injection site extravasation | 8.2% | 4.8% | 2.5% | 2.6% | 11.5% |
| Injection site hemorrhage | 2.5% | | 1.2% | | |
| Injection site hypersensitivity | 1.3% | | | | |
| Injection site inflammation | 3.8% | | 2.5% | | 7.7% |
| Injection site pain | 9.4% | | 6.2% | 2.6% | 11.5% |
| Injection site reaction | | | | | 3.8% |
| Pain | 3.1% | | | | 3.8% |
| Photosensitivity reaction | 2.5% | | 3.7% | | |
| CARDIOVASCULAR SYSTEM: | | | | | |
| Hypertension | 1.9% | | 1.2% | | |
| Syncope | | | | | 3.8% |
| DIGESTIVE SYSTEM: | | | | | |
| Constipation | 1.9% | | | | |
| Nausea | 1.9% | 2.4% | 1.2% | | |
| HEMIC AND LYMPHATIC SYSTEM: | | | | | |
| Anemia | 1.3% | 1.2% | | | |
| Eosinophilia | 1.3% | | | | |
| METABOLIC AND NUTRITIONAL DISORDERS: | | | | | |
| Creatinine increased | 1.3% | 1.2% | | | |
| Glycosuria | 1.9% | | | | |
| Hypercholesteremia | 1.9% | | | | |
| Ketosis | 1.3% | 2.4% | | | |
| MUSCULOSKELETAL SYSTEM: | | | | | |
| Arthralgia | | | | | 3.8% |
| NERVOUS SYSTEM: | | | | | |
| Dizziness | 1.3% | 1.2% | | | |
| Hypesthesia | 1.9% | | | | |
| RESPIRATORY SYSTEM: | | | | | |
| Dyspnea | 1.3% | | 1.2% | | |

TABLE 1. Summary of Associated Treatment-Emergent Adverse Events Occurring with Incidence \geq 1% (Predominantly Classic CNV due to AMD from the TAP Studies, CNV due to PM from the VIP PM Study, and CNV due to OHS from the VOH Study)

| BODY SYSTEM: Preferred Term | % of Patients | | | | |
|-------------------------------------|-----------------------|-------------------|--------------------|-------------------|--------------------|
| | BPD OCR 002 A+B (AMD) | | BPD OCR 003 (PM) | | BPD OCR 004 (OHS) |
| | Visudyne (N=159) | Placebo (N=83) | Visudyne (N=81) | Placebo (N=39) | Visudyne (N=26) |
| SKIN AND APPENDAGES: | | | | | |
| Pruritus | | | 2.5% | 2.6% | 3.8% |
| Rash | 1.3% | | | | |
| Skin disorder | | | 1.2% | | |
| Urticaria | | | 1.2% | | |
| SPECIAL SENSES: ^a | | | | | |
| Eye disorder | | | 1.2% | | |
| Photophobia | | | 2.5% | | |
| Vision abnormal | | | 1.2% | | |
| Vision decreased | | | 1.2% | | |
| TREATMENT SITE OCULAR: ^b | | | | | |
| Cataract | 1.3% | | | | |
| Conjunctivitis | 2.5% | 3.6% | 2.5% | | |
| Dry eyes | | | 1.2% | | |
| Eye disorder | | | 1.2% | | |
| Eye pain | 3.8% | 2.4% | | | |
| Face edema | | | 1.2% | 2.6% | |
| Photophobia | 1.3% | 1.2% | 2.5% | | |
| Retinal disorder | | | | | 3.8% |
| Vision abnormal | 3.1% | 3.6% | 3.7% | | 7.7% |
| Vision decreased | 5.0% | 1.2% | 11.1% | 10.3% | 3.8% |
| Visual field defect | 4.4% | 1.2% | 3.7% | 5.1% | 3.8% |

^a Special Senses includes events in the untreated ("other") eye.

^b Treatment Site -Ocular includes ocular treatment site (study eye) events.

Less Common Clinical Trial Adverse Drug Reactions (ADR) (<1%)

The following describes adverse events associated with treatment (Adverse Drug Reactions) that occurred with a frequency of less than one percent, in the pivotal 24-Month study predominantly classic study population. No ADRs <1% occurred in patients with pathologic myopia and ocular histoplasmosis. The ADRs with an asterisk (*) are those that also occurred in patients who received placebo.

In patients with AMD treated with Visudyne, systemic ADRs that occurred in one patient only (<1%) were abdominal pain*, accidental injury, chest pain, chills, chills and fever, flu syndrome*, abnormal lab test*, tachycardia, diarrhea*, dyspepsia*, gastrointestinal carcinoma, hepatomegaly, stomach ulcer hemorrhage, tongue disorder, hypothyroidism, basophilia, blood dyscrasia, leukocytosis, leukopenia, lymphocytosis, diabetes mellitus, gout, hyperglycemia*, hypoglycemia, hypokalemia*, arthralgia*, depression*, hypertonia,

neuralgia, vertigo, increased cough*, pharyngitis*, eczema, skin discoloration, dysuria, metrorrhagia, and frequent urination.

ADRs <1% occurring in the ocular treatment site were AMD progression*, dry eyes*, lacrimation disorder, subretinal hemorrhage, and vitreous disorder.

ADRs <1% occurring in the other eye were cataract, lacrimation disorder, photophobia*, and decreased vision.

The following have also been reported in other clinical trials: retinal detachment (nonrhegmatogenous), retinal or choroidal vessel nonperfusion, severe vision decrease with or without subretinal or vitreous hemorrhage, and severe vision decrease with retinal hemorrhage.

Clinical Trial Adverse Events (AEs)

Table 2 describes all adverse events, whether or not considered related to the treatment that occurred with a frequency equal to or greater than one percent, in the pooled pivotal 24-month study populations.

TABLE 2. Summary of Not Associated Treatment-Emergent Adverse Events Occurring with Incidence \geq 1% (Predominantly Classic CNV due to AMD from the TAP Studies, CNV due to PM from the VIP PM Study, and CNV due to OHS from the VOH Study)

| BODY SYSTEM: Preferred Term | Visudyne (N=266) | Placebo (N=122) |
|--|-----------------------------|----------------------------|
| ANY NOT ASSOCIATED EVENT | 84.2% | 81.1% |
| BODY AS A WHOLE: | | |
| Infection | 12.8% | 9.0% |
| Flu syndrome | 10.2% | 2.5% |
| Pain | 8.6% | 6.6% |
| Accidental injury | 7.5% | 10.7% |
| Headache | 5.6% | 11.5% |
| Back pain | 4.9% | 6.6% |
| Chest pain | 3.8% | 2.5% |
| Abdominal pain | 3.4% | 4.1% |
| Asthenia | 3.0% | 2.5% |
| Allergic reaction | 2.6% | 4.1% |
| Fever | 2.6% | 1.6% |
| Viral infection | 1.5% | 0.8% |
| Cyst | 1.1% | |
| Hernia | 1.1% | 1.6% |
| CARDIOVASCULAR SYSTEM: | | |
| Hypertension | 7.1% | 8.2% |
| Cardiovascular disorder | 2.6% | 0.8% |
| Syncope | 2.3% | |
| Myocardial infarct | 1.9% | 1.6% |
| Angina pectoris | 1.5% | 1.6% |
| Arrhythmia | 1.5% | 0.8% |

TABLE 2. Summary of Not Associated Treatment-Emergent Adverse Events Occurring with Incidence \geq 1% (Predominantly Classic CNV due to AMD from the TAP Studies, CNV due to PM from the VIP PM Study, and CNV due to OHS from the VOH Study)

| BODY SYSTEM: Preferred Term | Visudyne (N=266) | Placebo (N=122) |
|---|-----------------------------|----------------------------|
| Arteriosclerosis | 1.5% | 1.6% |
| Coronary artery disorder | 1.5% | 1.6% |
| Peripheral vascular disorder | 1.5% | 0.8% |
| Pulmonary embolus | 1.1% | |
| DIGESTIVE SYSTEM: | | |
| Nausea | 3.8% | 5.7% |
| Gastrointestinal disorder | 2.6% | 3.3% |
| Diarrhea | 2.3% | 3.3% |
| Cholecystitis | 1.9% | 0.8% |
| Gastrointestinal carcinoma | 1.5% | |
| Cholelithiasis | 1.1% | |
| Constipation | 1.1% | |
| Gastroenteritis | 1.1% | 1.6% |
| Tooth disorder | 1.1% | 0.8% |
| ENDOCRINE SYSTEM: | | |
| Hypothyroidism | 1.9% | 0.8% |
| Hyperthyroidism | 1.1% | 0.8% |
| METABOLIC AND NUTRITIONAL DISORDERS: | | |
| Hypercholesteremia | 6.4% | 7.4% |
| Creatinine increased | 3.4% | 1.6% |
| Peripheral edema | 3.4% | 4.1% |
| Glycosuria | 2.6% | 1.6% |
| Albuminuria | 2.3% | 1.6% |
| Ketosis | 1.9% | 4.1% |
| SGOT increased | 1.5% | |
| Alkaline phosphatase increased | 1.1% | 2.5% |
| Hyperkalemia | 1.1% | 0.8% |
| MUSCULOSKELETAL SYSTEM: | | |
| Arthritis | 4.5% | 4.9% |
| Arthralgia | 3.0% | 6.6% |
| Myalgia | 1.9% | 3.3% |
| Arthrosis | 1.1% | 1.6% |
| Bone disorder | 1.1% | 2.5% |
| NERVOUS SYSTEM: | | |
| Depression | 4.9% | 3.3% |
| Dizziness | 4.5% | 3.3% |
| Insomnia | 2.6% | 0.8% |
| Anxiety | 2.3% | 0.8% |
| Sleep disorder | 2.3% | |
| Vertigo | 1.5% | 1.6% |
| Cerebrovascular accident | 1.1% | 0.8% |

TABLE 2. Summary of Not Associated Treatment-Emergent Adverse Events Occurring with Incidence \geq 1% (Predominantly Classic CNV due to AMD from the TAP Studies, CNV due to PM from the VIP PM Study, and CNV due to OHS from the VOH Study)

| BODY SYSTEM: Preferred Term | Visudyne (N=266) | Placebo (N=122) |
|--|-----------------------------|----------------------------|
| RESPIRATORY SYSTEM: | | |
| Bronchitis | 6.8% | 3.3% |
| Sinusitis | 4.9% | 4.9% |
| Pharyngitis | 4.5% | 3.3% |
| Cough increased | 4.1% | 1.6% |
| Rhinitis | 3.4% | 2.5% |
| Dyspnea | 1.9% | 2.5% |
| Lung disorder | 1.9% | 1.6% |
| Pneumonia | 1.9% | 1.6% |
| Emphysema | 1.1% | 1.6% |
| SKIN AND APPENDAGES: | | |
| Rash | 3.8% | 0.8% |
| Skin ulcer | 1.5% | 1.6% |
| Skin disorder | 1.1% | 0.8% |
| Sweating | 1.1% | |
| SPECIAL SENSES: ^a | | |
| Conjunctivitis | 6.4% | 4.1% |
| Cataract | 5.6% | 4.9% |
| Vision decreased | 4.1% | 0.8% |
| AMD progression | 3.4% | 7.4% |
| Vision abnormal | 3.0% | 3.3% |
| Corneal lesion | 2.3% | 0.8% |
| Eye disorder | 2.3% | 2.5% |
| Eye pain | 2.3% | |
| Glaucoma | 2.3% | 4.1% |
| Dry eyes | 1.9% | 0.8% |
| Eye itching | 1.9% | 0.8% |
| Blepharitis | 1.5% | 1.6% |
| Otitis media | 1.5% | 1.6% |
| Corneal opacity | 1.1% | |
| Diplopia | 1.1% | |
| Vitreous disorder | 1.1% | 0.8% |

TABLE 2. Summary of Not Associated Treatment-Emergent Adverse Events Occurring with Incidence \geq 1% (Predominantly Classic CNV due to AMD from the TAP Studies, CNV due to PM from the VIP PM Study, and CNV due to OHS from the VOH Study)

| BODY SYSTEM: Preferred Term | Visudyne (N=266) | Placebo (N=122) |
|---|-----------------------------|----------------------------|
| TREATMENT SITE OCULAR:^b | | |
| Cataract | 12.0% | 9.0% |
| Vision abnormal | 8.6% | 7.4% |
| Vision decreased | 5.6% | 4.9% |
| Conjunctivitis | 5.3% | 4.1% |
| Corneal lesion | 3.4% | 0.8% |
| Visual field defect | 3.0% | 1.6% |
| Eye itching | 2.6% | 0.8% |
| Eye pain | 2.3% | 1.6% |
| Glaucoma | 2.3% | 3.3% |
| Blepharitis | 1.9% | 1.6% |
| Dry eyes | 1.9% | 0.8% |
| Vitreous disorder | 1.9% | 1.6% |
| Eye disorder | 1.5% | 0.8% |
| AMD progression | 1.1% | |
| Keratitis | 1.1% | |
| Lacrimation disorder | 1.1% | 2.5% |
| UROGENITAL SYSTEM: | | |
| Cystitis | 3.8% | 1.6% |
| Prostatic disorder | 3.8% | 0.8% |
| Prostatic carcinoma | 1.1% | |
| Prostatic specific antigen increase | 1.1% | |
| Urinary tract infection | 1.1% | 6.6% |
| Vaginal hemorrhage | 1.1% | 0.8% |

^a Special Senses includes events in the untreated ("other") eye.

^b Treatment Site -Ocular includes ocular treatment site (study eye) events.

Based on long-term experience in patients receiving open-label Visudyne treatment beyond the 24-month placebo-controlled phase (TAP 60-Months extension study, see 'Clinical Trials'), no additional safety concern was identified.

Based on long-term experience in patients receiving open-label Visudyne treatment beyond the 24-month placebo-controlled phase for pathologic myopia (VIP-60-Month extension study where 54 of 67 patients completed the study, (see 'Clinical Trials') or presumed ocular histoplasmosis (VOH 48-Month extension study where 15 of 17 patients completed the study, see 'Clinical Trials'), no additional safety concern was identified.

Post-Market Adverse Drug Reactions

Other adverse drug reactions that have been reported include chest and back pain (which may radiate to other areas including but not limited to pelvis, shoulder girdle or rib cage) and other musculoskeletal pain during infusion.

Vaso-vagal and hypersensitivity reactions have occurred, which on rare occasions have been severe. General symptoms can include headache, malaise, syncope, sweating, dizziness, rash, urticaria, pruritus, dyspnea, flushing and changes in blood pressure or heart rate.

Rare cases of retinal pigment epithelial tear have been reported.

Rare cases of complete retinal tear have been reported.

DRUG INTERACTIONS

Overview

Drug interaction studies in humans have not been conducted with VISUDYNE (verteporfin for injection).

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.

Drug-Drug Interactions

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of Visudyne Therapy. Possible examples include the following: calcium channel blockers, polymyxin B or radiation therapy. These could enhance the rate of VISUDYNE uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β -carotene, ethanol, formate and mannitol, would be expected to decrease VISUDYNE activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A₂ inhibitors, could also decrease the efficacy of Visudyne Therapy.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing and Treatment Considerations

- A course of Visudyne Therapy is a two-step process requiring administration of both drug and light.
- The first step is the intravenous infusion of VISUDYNE (verteporfin for injection).
- The second step is the activation of VISUDYNE with light from a nonthermal diode laser.
- The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.
- The average number of treatments needed declines over time (see 'Clinical Pharmacology, Age-related Macular Degeneration, Pathologic Myopia and Presumed Ocular Histoplasmosis').

Concurrent Bilateral Treatment

The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous Visudyne Therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior Visudyne Therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues were identified, the second eye can be treated using the same treatment regimen after a second VISUDYNE infusion. Approximately 3 months later, both eyes can be evaluated and concurrent treatment following a new VISUDYNE infusion can be started if both lesions still show evidence of leakage.

Lesion Size Determination

The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

Spot Size Determination

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve. For treatment of lesions that are larger than the maximum treatment spot size, apply the light to the greatest possible area of active lesion.

Recommended Dose

The Visudyne dose is 6 mg/m² body surface area, diluted in 30 ml infusion solution, given by a 10-minute intravenous infusion.

Administration

Drug Administration

VISUDYNE should be reconstituted according to the directions given under '**Reconstitution**'.

The volume of reconstituted VISUDYNE required to achieve the desired dose of 6 mg/m² body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump and in-line filter. The clinical studies were conducted using a standard infusion line filter of 1.2 microns.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (see '**Warnings and Precautions, General**').

Light Administration

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10-minute infusion with VISUDYNE.

Photoactivation of VISUDYNE is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm² of neovascular lesion administered at an intensity of 600 mW/cm². This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation.

The laser system must be acceptable for the delivery of a stable power output at a wavelength of 689±3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

The following laser systems have been tested for compatibility with VISUDYNE and are acceptable for the delivery of a stable power output at a wavelength of 689±3 nm:

- Lumenis Opal Photoactivator laser console and modified LaserLink adapter, distributed by Coherent-AMT, 15-550 Trillium Drive, Kitchener, Ontario, Canada N2R 1K3,
- Zeiss VISULAS 690s laser and VISULINK PDT adapter, distributed by Carl Zeiss Canada Ltd., 45 Valleybrook Drive, Toronto, Ontario M3B 2S6.

Reconstitution:

Parenteral Products:

| Vial Size | Volume of Diluent to be Added to Vial | Approximate Available Volume | Nominal Concentration per mL |
|-----------|---------------------------------------|------------------------------|------------------------------|
| 15 mg | Sterile Water for Injection, 7.0 mL | 7.5 mL | 2 mg/mL |

Reconstituted VISUDYNE must be stored at 20-25°C, protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution. Discard the unused portion.

Incompatibilities

VISUDYNE should only be reconstituted with sterile Water for Injection. Do not mix VISUDYNE in the same solution with other drugs. VISUDYNE may precipitate in saline solutions. Do not use normal saline or other parenteral solutions.

Dilution for Intravenous Infusion

Once reconstituted VISUDYNE is diluted with 5% Dextrose Injection, it should preferably be used immediately, but not exceeding 4 hours. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration, or leakage should not be used

OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

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 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 the retinal pigmented epithelium and outer nuclear layer of the retina. The temporary occlusion of choroidal neovascularization (CNV) following Visudyne Therapy has been confirmed in humans by fluorescein angiography.

Pharmacokinetics

Following intravenous infusion, verteporfin exhibits bi-exponential elimination with a terminal elimination half-life of approximately 5-6 hours. The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m²

Metabolism: Verteporfin is metabolized to a small extent to its diacid metabolite by liver and plasma esterases. NADPH dependent liver enzyme systems (including the cytochrome P450 isozymes) do not appear to play a role in the metabolism of verteporfin.

Excretion: Elimination is by the fecal route, with less than 0.01% of the dose recovered in urine.

Special Populations and Conditions

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

Hepatic Insufficiency: In a study of patients with mild hepatic insufficiency (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 Insufficiency: No data is available. Elimination is by the fecal route, with less than 0.01% of the dose recovered in urine.

STORAGE AND STABILITY

Store VISUDYNE between 20 and 25°C (68-77°F).

SPECIAL HANDLING INSTRUCTIONS

Spills and Disposal

Spills of VISUDYNE should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is recommended. All materials should be disposed of properly.

Accidental Exposure

Because of the potential to induce photosensitivity reactions, it is important to avoid contact with the eyes and skin during preparation and administration of VISUDYNE. Any exposed person must be protected from bright light (see Warnings).

DOSAGE FORMS, COMPOSITION AND PACKAGING

VISUDYNE (verteporfin) is supplied in a single-use glass vial with a gray bromobutyl stopper and aluminium flip-off cap. It contains a lyophilized cake with 15 mg verteporfin. The product is intended for intravenous injection only.

Each mL of reconstituted VISUDYNE contains:

ACTIVE: Verteporfin, 2 mg

INACTIVES: Ascorbyl palmitate, butylated hydroxytoluene, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, lactose

RG-040037(2)
VISUDYNE (verteporfin for injection)
Canadian Prescribing Information