PRODUCT MONOGRAPH

Pr**VISUDYNE***

Verteporfin for Injection

15 mg / vial

Manufacturer's Standard

Photosensitizing Agent

Valeant Canada LP
2150 St-Elzear Blvd., West
Laval, Quebec
Canada H7L 4A8

Date of Preparation:
January 27, 2016

Distributor:
Novartis Pharmaceuticals Canada Inc.
385 Bouchard Boulevard
Dorval, QC
H9S 1A9

Control number: 189192

*VISUDYNE is a registered trademark

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VISUDYNE*

VERTEPORFIN FOR INJECTION

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophylized 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 (verteporfin for injection) as part of photodynamic therapy (i.e., 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: VISUDYNE is not recommended for use in children or adolescents. The efficacy and safety of VISUDYNE has not been established in the pediatric population.

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 (see 'DOSAGE AND ADMINISTRATION' and 'DOSAGE FORMS, COMPOSITION AND PACKAGING').
- Porphyria.
- Severe hepatic impairment.

WARNINGS AND PRECAUTIONS

VISUDYNE is a drug to be used in Visudyne Therapy. Visudyne Therapy is a two-stage process requiring administration of both VISUDYNE 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 (see '**Skin**')**.**

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/m^2 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 related to VISUDYNE infusion, have been reported. Both vaso-vagal and hypersensitivity reactions are associated with general symptoms such as syncope, sweating, dizziness, rash, dyspnoea, flushing, and changes in blood pressure and heart rate. On rare occasions these reactions may be severe, and potentially include seizure. 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. Since verteporfin is excreted primarily via the biliary (hepatic) route, increased verteporfin exposure is possible (see '**ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**').

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 consistent with complement activation (e.g., chest pain, syncope, dyspnea, and flushing) (see '**Cardiovascular**') 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 (e.g., 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. During that period, patients should avoid exposure of unprotected eyes to direct sunlight or bright indoor light (see '**Skin**').

Peri-Operative Considerations

Caution should be exercised when Visudyne Therapy under general anesthesia is considered. There are 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 Therapy under general anesthesia is considered.

Sexual Function/Reproduction

No information is available about fertility in humans with verteporfin. 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/m^2 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. Patients should wear a wrist band to remind them to avoid direct sunlight for 2 days. 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: VISUDYNE is not recommended for use during pregnancy. The efficacy and safety of VISUDYNE has not been established in pregnant women. VISUDYNE use during pregnancy should only be considered if the expected benefit to mother outweighs the potential risk to the fetus.

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/m^2 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/m^2 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/m^2 based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

Nursing Women: VISUDYNE is not recommended for use in nursing women. Verteporfin and its diacid metabolite have been found in the breast milk of one woman after a 6 mg/m^2 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 for at least 48 hours. The effects of verteporfin and its metabolite on neonates are unknown. Nursing should be interrupted during Visudyne Therapy 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: VISUDYNE is not recommended for use in children or adolescents. The efficacy and safety of VISUDYNE has not been established in the pediatric population.

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 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 '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 ≥ 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)

	% of Patients				
	BPD OCR 002 A+B (AMD)		BPD OCR 003 (PM)		BPD OCR 004 (OHS)
BODY SYSTEM: Preferred Term	**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%

TABLE 1. Summary of Associated Treatment-Emergent Adverse Events Occurring with Incidence ≥ 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)

	% of Patients				
	BPD OCR 002 A+B (AMD)		BPD OCR 003 (PM)		BPD OCR 004 (OHS)
BODY SYSTEM: Preferred Term	**Visudyne (N=159)**	**Placebo (N=83)**	**Visudyne (N=81)**	**Placebo (N=39)**	**Visudyne (N=26)**
NERVOUS SYSTEM:					
Dizziness	1.3%	1.2%			
Hypesthesia	1.9%				
RESPIRATORY SYSTEM:					
Dyspnea	1.3%		1.2%		
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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 reactions (presyncope) and hypersensitivity reactions, related to Visudyne infusion have been reported. General symptoms can include headache, malaise, syncope, hyperhidrosis, dizziness, presyncope, rash, urticaria, pruritus, vesicles, dyspnea, flushing and changes in blood pressure or heart rate. On rare occasions these reactions may be severe, and potentially include seizure.

Rare cases of retinal pigment epithelial tear have been reported.
Rare cases of retinal tear, including complete retinal tear have been reported.

Retinal edema and macular edema have been reported.

DRUG INTERACTIONS

Overview

Drug interaction studies in humans have not been conducted with VISUDYNE.

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.

Drugs increasing verteporfin uptake in the vascular endothelium

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

Other photosensitizing 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, 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 antagonizing blood vessel occlusion

Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 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.
- 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 TRIALS, 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/m^2 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/m^2 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/cm^2 of neovascular lesion administered at an intensity of 600 mW/cm^2. 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 after aseptic reconstitution and dilution. 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Verteporfin, also referred to as benzoporphyrin derivative monoacids A ring (BPD-MA), consists of a 1:1 mixture of the equally active regioisomers BPD-MA_C and BPD-MA_D. It is used as a light-activated drug (photosensitiser). The regioisomers have been reported to have similar photodynamic properties.

Verteporfin 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/m^2

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: In a study of patients with mild hepatic impairment (defined as having two abnormal hepatic function tests at enrolment), AUC and C_{max} were not significantly different from the control group, half-life however was significantly increased by approximately 20%.

Renal: No studies on the pharmacokinetics of verteporfin in patients with renal impairment have been reported. Elimination is by the fecal route, with less than 0.01% of the dose recovered in urine, thus clinically significant changes in verteporfin exposure in patients with renal impairment are unlikely.

STORAGE AND STABILITY

Store VISUDYNE between 20 and 25°C (68-77°F) (see 'DOSAGE AND ADMINISTRATION, **Reconstitution'** for handling instructions once reconstituted).

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 AND PRECAUTIONS').

DOSAGE FORMS, COMPOSITION AND PACKAGING

VISUDYNE 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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

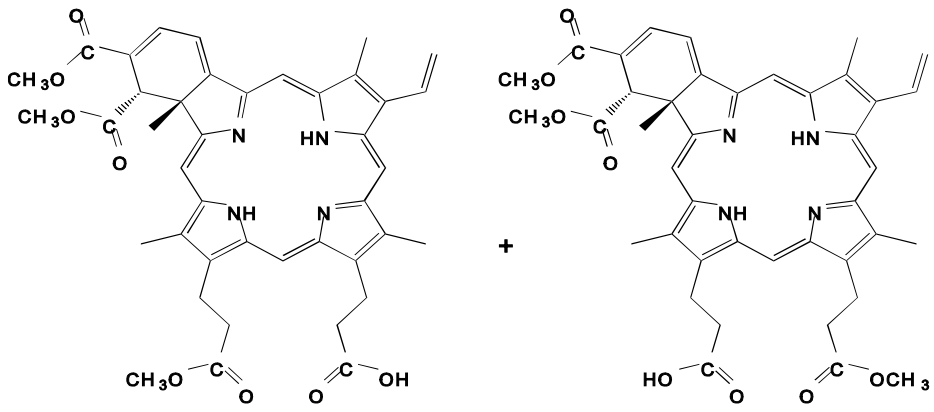
Proper name: Verteporfin

Chemical name: The chemical names for the verteporfin regioisomers are:

23*H*,25*H*-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-monomethyl ester, *trans*-

Molecular formula and molecular mass: $C_{41}H_{42}N_40_8$, 718.8

Structural formula:



Physicochemical properties: Verteporfin is a dark green to black solid. Verteporfin is soluble in benzyl alcohol, dichloromethane, dimethylacetamide, dimethyl sulfoxide, PEG-300S, PEG-400 and tetrahydrofuran.

CLINICAL TRIALS

Clinical Studies

Age-Related Macular Degeneration

Two adequate and well-controlled, double-masked, placebo-controlled, randomized studies (BPD OCR 002 (TAP A + B)) were conducted in North America and Europe in patients with classic-containing subfoveal CNV secondary to age-related macular degeneration. A total of 609 patients (VISUDYNE [n=402], placebo [n=207]) were enrolled in these two studies. Treatment was delivered as a 10-minute intravenous infusion of VISUDYNE (6 mg/m^2) or placebo (5% dextrose) followed by light application 15 minutes after the start of infusion. A light dose of 50 J/cm^2 was applied using a fluence rate of 600 mW/cm^2 over 83 seconds. During these studies, retreatment was allowed every 3 months if fluorescein angiograms showed any recurrence or persistence of leakage. The primary efficacy endpoint was the percentage of patients who lost fewer than 15 letters (3 lines) of visual acuity from baseline at 1 year. Durability of effect was established at 2 years.

The difference between treatment groups statistically favoured VISUDYNE at the 1-year and 2-year analyses for visual acuity endpoints. The magnitude of benefit was maintained at the 2-year timepoint. Table 3 shows results for the primary efficacy variable.

TABLE 3. Classic-Containing Subfoveal CNV: Percentage of Responders, Both Studies Combined, ITT with LOCF

	Number (%) of Patients			
Timepoint	VISUDYNE N=402	Placebo N=207	Difference (VISUDYNE-placebo)	P value
Month 12	246 (61.2)	96 (46.4)	(14.8)	<.001
Month 24	213 (53.0)	78 (37.7)	(15.3)	<.001

Responders: defined as patients who lost fewer than 15 letters (3 lines) of visual acuity from baseline.
ITT: Intent-To-Treat population, which included data for all randomized patients.
LOCF: missing efficacy values were imputed by the method of Last Observation Carried Forward.
Placebo control (sham treatment): IV Dextrose 5% in Water, followed by light application identical to that used for Visudyne Therapy.
94% and 87% of patients completed 1 and 2 years of study, respectively.

Subgroups of older patients (≥75 years), patients with dark irides, patients with occult lesions, or patients with less than 50% classic CNV were less likely to benefit from Visudyne Therapy.

The subgroup of patients with predominantly classic CNV lesions was more likely to exhibit a large treatment benefit (N=242; VISUDYNE [n=159], placebo [n=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 which may have included occult CNV, blood, and other components that blocked fluorescence. Table 4 shows results for the primary efficacy variable for the subgroup of patients with predominantly classic CNV.

TABLE 4. Predominantly Classic Subfoveal CNV Subgroup: Percentage of Responders, Both Studies Combined, ITT with LOCF

	Number (%) of Patients			
Timepoint	**VISUDYNE N=159**	**Placebo N=83**	**Difference (VISUDYNE-placebo)**	**P value**
Month 12	107 (67.3)	33 (39.8)	(27.5)	<.001
Month 24	94 (59.1)	26 (31.3)	(27.8)	<.001

Responders: defined as patients who lost fewer than 15 letters (3 lines) of visual acuity from baseline.
ITT: Intent-To-Treat population, which included data for all randomized patients.
LOCF: missing efficacy values were imputed by the method of Last Observation Carried Forward.
Placebo control (sham treatment): IV Dextrose 5% in Water, followed by light application identical to that used for Visudyne Therapy.

Patients with predominantly classic CNV lesions that did not contain occult CNV exhibited the greatest benefit (N=134; VISUDYNE [n=90], placebo [n=44]). At 1 year, these patients demonstrated a 49% difference between treatment groups when assessed by the <3 lines-lost definition (77% vs. 27%).

Severe vision loss (≥6 lines of visual acuity from baseline) was experienced by only 12% of VISUDYNE-treated patients compared to 33% of placebo-treated patients at Month 12, and by 15% of VISUDYNE-treated patients compared to 36% of placebo-treated patients at Month 24.

At one year, 38% of VISUDYNE patients in this population, compared to 20% of placebo patients, showed evidence of stable (<1 line lost) or improved vision.

The lesions in the VISUDYNE group were less likely to show progression of classic CNV beyond the baseline area (57% vs. 82%) and were less likely to be >6 disc areas (40% vs. 74%) in size.

In the long-term open-label TAP study extension, all patients reaching the Month 24 or a subsequent visit were eligible for treatment in the study eye if they had: evidence of fluorescein leakage from CNV in the absence of serious ocular adverse events, or, a potential for benefit from verteporfin treatment in the absence of leakage unless the absence was due to end-stage disease (based on the Investigator's assessment)

The extension study enrolled 320 of the 402 verteporfin-treated patients; 124 had predominantly classic lesions, and 198 completed the study. Follow-up was conducted at 3 month intervals for up to 48 months, with a final visit at 60 months. Re-treatment was performed on evidence of CNV fluorescein leakage.

Table 5 summarizes the visual acuity (VA) outcomes in verteporfin-treated patients at the end of the 24-month controlled portion of the TAP A+B study and the end of the 60-month long-term open-label extension.

TABLE 5. TAP A+B Vision Results: Month 24 ITT with LOCF, Compared With Month 60

	Verteporfin-Treated Patients							
	All				Predominantly Classic			
Vision Variable	Month 24 (N=402)		Month 60 (N=193)*		Month 24 (N=159)		Month 60 (N=77)	
	n	%	n	%	n	%	n	%
<15 letters (3 lines) loss	213	(53)	105	(54)	94	(59)	50	(65)
<30 letters (6 lines) loss	329	(82)	159	(82)	135	(85)	70	(91)

ITT: Intent-To-Treat population, which included data for all randomized patients
LOCF: missing efficacy values were imputed by the method of Last Observation Carried Forward.
*193 patients had a visual acuity assessment at Month 60.

For both verteporfin-treated populations (all, and predominantly classic lesions), the Month 60 vision outcomes were similar to or slightly better than those at the end of the controlled phase (Month 24).

Figure 1 presents the proportion of treatment responders (patients losing less than 3 lines of visual acuity from baseline) during the extension for all long-term verteporfin-treated patients with predominantly classic CNV, with 95% confidence intervals (CI).

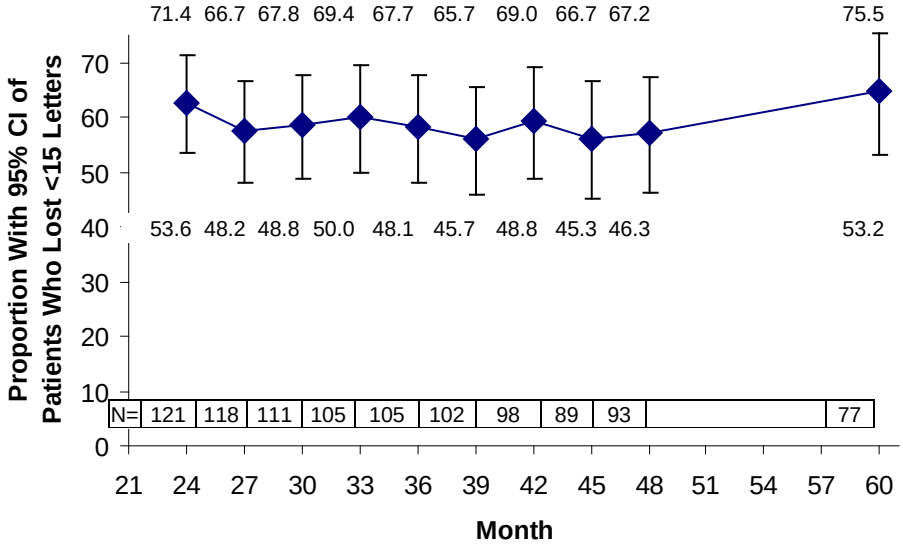


Figure 1. Proportion of Patients Who Lost <15 Letters of VA From Baseline (Month 0) During the TAP A+B Extension (Months 24-60): Long-Term Verteporfin-Treated Patients With Predominantly Classic CNV

The 15-letter responder rate was stable between Months 24 and 60. The lowest responder rate, 51% (at Month 39), had a 95% CI that overlaps all other data points. Bearing in mind the nature of the TAP study extension, the data suggests that Month-24 vision outcomes may be sustained for up to 5 years.

In long-term verteporfin-treated patients, the mean number of verteporfin treatments in the study eye per year decreased consistently, over 5 years (Table 6). These data, coupled with visual acuity outcomes are indicative of a defined, finite course of therapy.

TABLE 6. TAP A+B: Mean Number of Verteporfin Courses in the Study Eye

Study Period	Lesion type	
	All N=320	Predominantly Classic N=124
First year	3.5	3.5
Second year	2.4	2.3
1st year of extension	1.3	1.1
2nd year of extension	0.4	0.4
3rd year of extension	0.1	0.1

Pathologic Myopia

One adequate and well-controlled, double-masked, placebo-controlled, randomized study (BPD OCR 003 (VIP-PM)) was conducted in North America and Europe in patients with subfoveal CNV secondary to pathologic myopia. A total of 120 patients (VISUDYNE [n=81], placebo [n=39]) were enrolled in the study. The treatment dosing and retreatments were the same as in the AMD studies. The primary efficacy endpoint was the percentage of patients who lost fewer than 15 letters (3 lines) of visual acuity from baseline at 1 year. The difference between treatment groups statistically favoured VISUDYNE at the 1-year analysis for visual acuity variables, but not at the 2-year analysis. Table 7 shows results for the primary efficacy variable.

TABLE 7. Pathologic Myopia: Percentage of Responders, ITT with LOCF

Timepoint	Number (%) of Patients			
	VISUDYNE N=81	Placebo N=39	Difference (VISUDYNE-placebo)	P value
Month 12	70 (86.4)	26 (66.7)	(19.8)	0.011
Month 24	64 (79.0)	28 (71.8)	(7.2)	0.381

Responders: defined as patients who lost fewer than 15 letters (3 lines) of visual acuity from baseline.
LOCF: missing efficacy values were imputed by the method of Last Observation Carried Forward.
ITT: Intent-To-Treat population, which included data for all randomized patients.
Placebo control (sham treatment): IV Dextrose 5% in Water, followed by light application identical to that used for Visudyne Therapy.
96% and 94% of patients completed 1 and 2 years of study, respectively.

In the long-term VIP-PM study extension, all patients reaching the Month 24 visit were eligible for treatment in the study eye if in the investigator's opinion, there was potential for benefit, even if there was no CNV leakage at the time.

Eligible patients could have been retreated every 3 months from the Month 24 extension study visit to Month 48 with a final visit at Month 60. Re-treatment was performed on evidence of CNV fluorescein leakage.

Of the 81 verteporfin-treated patients who participated in the VIP-PM controlled study, 67 enrolled in the extension; 52 completed the study.

Table 8 presents visual acuity outcomes observed at the ends of the controlled portion of the study (Month 24) and the study extension (Month 60).

TABLE 8. Pathologic Myopia (VIP PM) Vision Results: Month 24 ITT with LOCF Compared with Month 60

Vision Variable	Verteporfin-Treated Patients			
	Month 24 (N=81)		Month 60 (N=52)*	
	n	%	n	%
<15 letter loss (3 lines) loss	64	(79)	40	(77)

ITT: Intent-To-Treat population, which included data for all randomized patients
LOCF: missing efficacy values were imputed by the method of Last Observation Carried Forward
* visual acuity observations for 52 patients were available at Month 60

For all long-term verteporfin-treated patients, vision outcomes were similar between the extension's end (Month 60) and the controlled portion's end (Month 24).

Figure 2 presents the proportion of patients who lost less than 15 letters of visual acuity (VA) from baseline (Month 0) during the extension portion of the study.

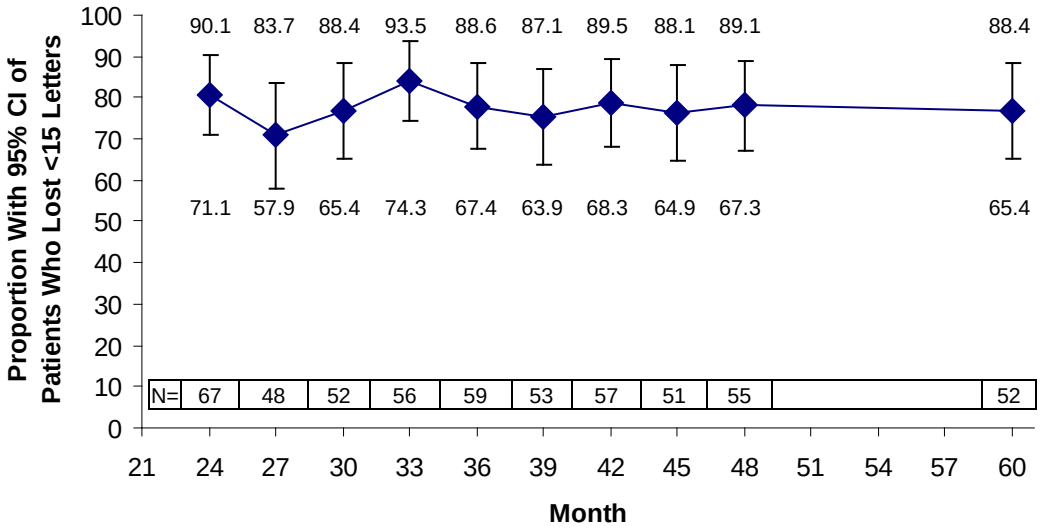


Figure 2. Proportion of Patients Who Lost <15 Letters of VA From Baseline (Month 0) During the VIP PM Extension (Months 24-60)

For long-term verteporfin-treated patients, the proportion of patients who lost less than 15 letters of visual acuity from baseline was 81% at Month 24. This proportion varied modestly (71% to 84%) over the extension period with the 95% CI intervals overlapping. Bearing in mind the nature of the VIP-PM study extension, the data suggests that Month-24 vision outcomes may be sustained for up to 5 years. In long-term verteporfin-treated patients, the mean number of verteporfin treatments in the study eye per year decreased consistently, over 5 years (Table 9). These data, coupled with visual acuity outcomes are indicative of a defined, finite course of therapy.

TABLE 9. VIP-PM: Mean Number of Verteporfin Courses in the Study Eye (N=67)

Study Period	Mean treatments
First year	3.5
Second year	1.8
1st year of extension	0.4
2nd year of extension	0.2
3rd year of extension	<0.1

Presumed Ocular Histoplasmosis

One open-label study (BPD OCR 004 (VOH)) was conducted in North America and Europe in patients with subfoveal CNV secondary to presumed ocular histoplasmosis. A total of 26 patients were enrolled in the study and treated with VISUDYNE. Most patients enrolled had predominantly classic CNV lesions (73% of patients) and lesion size #3 disc areas (85% of patients). The treatment dosing and retreatments were the same as in the AMD studies.

Table 10 shows the visual acuity results.

TABLE 10. Presumed Ocular Histoplasmosis: Results of Visual Function Variables

	VISUDYNE	
	Month 12 N=25	**Month 24 N=22**
Percentage of patients who gained 7 letters or more of visual acuity from baseline	56%	45%
Percentage of patients who lost fewer than 8 letters of visual acuity from baseline	84%	82%
Percentage of patients who lost fewer than 15 letters of visual acuity from baseline	92%	91%

96% and 85% of patients completed 1 and 2 years of study, respectively.

VISUDYNE-treated patients compare favourably with historical control data demonstrating a reduction in the number of episodes of severe visual acuity loss (>6 lines of loss).

The VOH Extension study included 17 of the 26 patients included in the VOH 24-month open-label study; 15 completed through Month 48. Patients could have been retreated every 3 months from Month 24 to the final Month 48 visit.

Over 24 months, patients exhibited clinically relevant gains in visual acuity (VA) after treatment with verteporfin. Table 11 presents visual acuity outcomes at the end of the initial study (24 months) and at the end of the extension (48 months).

TABLE 11. Ocular Histoplasmosis Vision Results: Month 24 ITT LOCF Compared with Month 48

Vision Variable	Verteporfin-Treated Patients			
	Month 24 (N=22) [a]		Month 48 (N=15) [b]	
	n	%	n	%
≥7 letter gain	10	(46)	9	(60)
<8 letter loss	18	(82)	14	(93)
<15 letter loss	20	(91)	14	(93)

ITT: Intent-To-Treat population, which included data for all randomized patients
LOCF: missing efficacy values were imputed by the method of Last Observation Carried Forward
[a] Number of patients in Month 24 ITT group=22
[b]Visual acuity observations for 15 patients' were available at Month 48

At Month 48 there were higher proportions of responders and larger increases from baseline in visual acuity than at Month 24. At Month 48, almost all patients had lost fewer than 8 letters of visual acuity from baseline (14 of 15 patients assessed) and many patients had gained 7 or more letters (9 of 15 patients assessed). These data demonstrate that the treatment benefits of verteporfin in patients with OHS are still present at Month 48.

Based on the 17 verteporfin treated patients completing VOH extension study, 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.

DETAILED PHARMACOLOGY

Pharmacokinetics

Verteporfin as a lipid-based formulation is rapidly taken up by circulating lipoproteins, with limited (approximately 5-7%) binding to albumin.

Tissue distribution was studied in mice. Highest concentrations of radioactivity were observed in the gall bladder and liver. Relatively small concentrations were found in the skin. Studies in rabbits indicate the highest verteporfin concentrations in the eye are found in the retina and choroid 30 minutes after IV injection. Placental transfer studies in rats showed limited transfer to the fetus.

Only one metabolite, the diacid hydrolysis product of both regioisomers of verteporfin, can be detected in the plasma of mice, rats, and pigs. The concentration of diacid present in the circulation is limited, never exceeding 10% of verteporfin. Metabolism to the diacid is mediated by liver and plasma esterases whereas NADPH-dependent enzymes do not participate to any measurable extent.

In rats and dogs, verteporfin exhibits dose-proportional exposure and does not accumulate upon multiple daily dosing. The plasma clearance of both regioisomers is rapid and the half-life for doses up to 2 mg/kg in the rat, dog, and monkey do not exceed 5 hours.

The major route of elimination in rats was in feces (approximately 90%) with a small amount (less than 1%) in urine.

TOXICOLOGY

Acute Toxicity

In acute toxicity studies in rats and dogs, verteporfin for injection was administered IV followed by treatment of the hindlimb skin with filtered red light. Effects without light were also assessed. Acute toxicity was dependent upon light activation and produced localized deep-tissue damage which was dose-related to both drug and light. There was no significant systemic toxicity observed in these acute studies in animals that received the lipid formulation, either with or without verteporfin. Rats were dosed up to 100 mg/kg and dogs up to 20 mg/kg of verteporfin.

Multiple-Dose Toxicity

Toxicity was evaluated in multiple-dose studies in rats and dogs not exposed to light. Rats given intravenous verteporfin for injection at 25 or 50 mg/kg/day daily for 2 weeks, exhibited mild extravascular hemolysis. Hematopoietic responses were seen in the bone marrow, spleen and liver. Similar effects were seen in animals given the lipid formulation without verteporfin. There were no treatment-related effects at 2 or 10 mg/kg/day. In a 28-day study in rats, verteporfin was associated with transient losses in body weight and mild dose-related anemia associated with changes in the hematopoietic system at doses of 2, 10, or 25 mg/kg/day. Vascular irritation at the injection site was also observed at these doses. In dogs given 10 mg/kg/day every day for 2 weeks, microscopic changes that correlated with a decrease in erythrocyte parameters were observed in the liver, spleen and bone marrow. No treatment-related effects were seen at 5 mg/kg/day, a repeated daily dose 33 times greater than used as a single dose for AMD treatment.

Special Toxicity

Skin Toxicity

Verteporfin was evaluated in mice exposed to 5 minutes of whole-body simulated sunlight to assess the duration of skin photosensitivity. No skin photoreactivity was detected in mice dosed at 2 mg/kg and exposed to light 3, 24 or 48 hours after dosing. At a dose of 10 mg/kg, severe changes to the skin resulting in the formation of large eschars were observed in mice exposed to light 3 hours after drug administration.

Ocular Toxicity

The effect of verteporfin for injection and direct administration of light into the eye of normal rabbits and monkeys was investigated in single- and multiple-dose dose-ranging studies. Levels of ocular toxicity, particularly to the retina/choroid, were dependent on the drug dose, the light dose and the period of time between drug and light administration. Data indicated that, with light exposure 15 minutes after the start of a 10-minute drug infusion, doses of drug and light comparable to those used in clinical investigations are well tolerated.

A study of ocular sensitivity to ambient light was performed in normal dogs to determine the effects of exposure to strong sunlight 24 hours after intravenous administration of verteporfin. Although significant skin toxicity was observed, no ocular toxicity (as assessed by histopathology) was observed at the highest dose of drug tested that was approximately 130 times the dose used for AMD treatment.

Hepatoxicity

Mild to moderate effects on the liver in vivo were observed in studies with high doses of verteporfin. These are considered to be a result of hemolysis. Hepatotoxicity in human liver slices was studied in vitro and cellular viability parameters showed no change over time when tissues were incubated with clinically relevant doses of verteporfin.

In Vitro Blood Compatibility

Verteporfin was assessed for compatibility with human blood. No evidence of hemolysis or protein flocculation was observed at concentrations 167-fold greater than that expected in humans following the dose of 0.15 mg/kg (6 mg/m^2) that has been used for the treatment of AMD.

Immunotoxicity

Verteporfin was not found to be immunogenic to humoral (antibody) or cellular (T cell) arms of the immune system. No antigenicity as determined by passive cutaneous anaphylaxis and active systemic anaphylaxis in guinea pigs was observed.

Irritation Potential

Verteporfin is not an ocular or dermal irritant in the absence of light. Vascular irritation at the injection site was observed after 28 daily intravenous administrations in rats at doses of 2 mg/kg/day or greater.

Reproductive Studies

Fertility/Early Development

In a fertility and early embryonic development study, rats administered verteporfin exhibited no changes in male or female reproduction or male reproduction assessments. The no-observed-effect-level (NOEL) for parental toxicity was 1 mg/kg/day for both sexes. The NOEL for reproductive performance of both sexes and early development was determined to be at least 10 mg/kg/day, the highest dose tested and representing a repeated daily dose 67 times higher than used as a single dose for AMD treatment.

Embryo/Fetal Development

Developmental toxicity studies in rats and rabbits were conducted in which verteporfin was intravenously administered during the period of major organogenesis (10 or 13 consecutive days) at maternally toxic doses as high as 10 mg/kg/day (approximately 40-fold the human exposure at 6 mg/m^2 based on AUC_{inf} in female rats). No adverse effects on embryo-fetal viability, weight or morphology were observed. Rat fetuses of dams given 25 mg/kg/day (approximately 125-fold the human exposure at 6 mg/m^2 based on AUC_{inf} in female rats) for 10 consecutive days had increased incidences of anophthalmia / microphthalmia and wavy ribs. Two mg/kg/day was the NOEL for both maternal and developmental toxicity in rats. The NOEL for maternal toxicity in rabbits was 3 mg/kg/day and for developmental toxicity, 10 mg/kg/day. No teratogenicity was observed, even at doses that were maternally toxic. A placental study in rats showed limited transfer of verteporfin to the fetus (ratio of AUC of 0.007:1 for fetus:mother, respectively).

Pre and Postnatal Development

In a pre and postnatal study in rats, no effect of verteporfin was observed on reproductive performance during gestation, parturition or lactation. No effect was seen on survival, physical development, behavior and reproductive performance of the F_1 generation or on the survival and development of the F_2 generation. Maternal toxicity of the F_0 generation females was observed at 1, 3 and 10 mg/kg/day and consisted of changes in red blood cell parameters. The NOEL for F_1 and F_2 generation development toxicity was 10 mg/kg/day.

Mutagenicity

The mutagenic potential of verteporfin in the absence and presence of light was studied in five in vitro studies and one in vivo study. Negative results were obtained in all studies. Microbial mutation assays were conducted with and without metabolic activation (S9) at concentrations up to 1540 µg/plate. Mammalian point mutation assays were conducted using Chinese hamster ovary cells (CHO) with and without S9, at concentrations of 0.1 µg/mL and light up to 630 J/m^2. Similar assays were performed without light at concentrations up to 100 µg/mL without S9 and at concentrations up to 200 µg/mL with S9. In vitro cytogenetics, chromosome aberration in CHO cells, was carried out without S9 at a concentration of 0.09 µg/mL and light up to 360 J/m^2, and with S9 at a concentration of 3.7 µg/mL and light up to 300 J/m^2. Unscheduled DNA synthesis was performed using rat hepatocytes and 0.01 µg/mL with light up to 5000 J/m^2. An in vivo mouse micronucleus assay was carried out with up to 10 mg/kg and light at 48 J/cm^2.

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PART III: CONSUMER INFORMATION

IMPORTANT: PLEASE READ

[Pr]VISUDYNE [*]
Verteporfin for Injection

This leaflet is Part III of a three-part 'Product Monograph' and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Visudyne. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
VISUDYNE is a light-activated drug used in photodynamic therapy.

VISUDYNE is used to treat the wet form of age-related macular degeneration (AMD), pathologic myopia (a severe form of nearsightedness) and presumed ocular histoplasmosis (a fungal infection of the eye). These diseases lead to vision loss because of damage to the macula, the part of the retina responsible for acute vision. Damage is caused by an ingrowth of abnormal blood vessels, called choroidal neovascularisation (CNV). These vessels leak blood and fluids (hence the term 'wet') and cause scarring. There are several patterns of leakage that can be identified in CNV, including the classic (rapidly leaking) and occult (slower leaking) patterns. VISUDYNE is used to treat the predominantly classic form of CNV.

What it does:
VISUDYNE therapy can:

- **slow vision loss,**
- **slow or stop the growth of the CNV area,**
- **reduce or stop leakage.**

VISUDYNE is injected into a vein, usually in the arm, and travels to the abnormal blood vessels in the eye. After a few minutes, the doctor shines a non-thermal laser on the affected area of the eye to activate VISUDYNE. This starts a chemical process that destroys the abnormal vessels growing in the macula.

When it should not be used:
Do not use VISUDYNE if you:

- **have porphyria, a metabolic disorder that disrupts the production of heme from precursor molecules called porphyrins, causing them to accumulate abnormally in tissues and blood. (Heme is part of hemoglobin, the protein in red blood cells that carries oxygen).**
- **are hypersensitive (allergic) to verteporfin or any of the other ingredients of VISUDYNE (see 'What the nonmedicinal ingredients are'),**
- **have severe liver impairment.**

What the medicinal ingredient is:
The active ingredient in VISUDYNE is verteporfin.

What the nonmedicinal ingredients are:
Ascorbyl palmitate, butylated hydroxytoluene, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, lactose.

What dosage form it comes in:
VISUDYNE is supplied in a glass vial with a gray stopper with an aluminium flip-off cap. It holds a powder cake which contains 15 mg verteporfin. When used, the product is made into a solution that is injected intravenously by a qualified health professional only.

WARNINGS AND PRECAUTIONS

Before using VISUDYNE, tell your doctor if you:

- **are pregnant or planning to become pregnant. Fetal malformations were seen in animal studies for one species (rat) when VISUDYNE was administered during pregnancy. Your doctor will decide with you whether the product should be used.**
- **are breastfeeding or intend to breastfeed. Visudyne appears in human breast milk. You and your doctor should discuss whether nursing should be interrupted or treatment postponed. You should not nurse for at least 96 hours after VISUDYNE administration.**
- **have liver or gall bladder problems.**
- **are using any other medications (see 'Interactions with this medication').**

Patients receiving VISUDYNE will become temporarily sensitive to light for 2 days. Therefore you must:

- **protect all parts of your skin and eyes from direct sunlight and bright indoor light. This includes tanning salons, bright halogen lighting, high power lighting used in surgical operating rooms and dental offices, and light-emitting medical devices.**
- **wear protective clothing and dark sunglasses when going outdoors. UV sunscreens are NOT effective in protecting against light sensitivity.**
- **wear a temporary wristband to remind yourself and others that you are light sensitive.**

However, you should not stay in the dark, but you should expose your skin to normal indoor lighting, because this helps break down the drug in the skin.

Accidental spills of VISUDYNE (e.g., on skin) should be wiped up immediately to avoid later photosensitivity reactions when this tissue is exposed to light. Contact with the skin and eyes should be avoided.

Following VISUDYNE therapy, you may develop a short-

term disturbance in your vision. You should not attempt to drive or use machines until it goes away.

INTERACTIONS WITH THIS MEDICATION

Some drugs increase light sensitivity and could increase the potential for skin reactions or affect Visudyne activity. These include some antibiotics (tetracyclines, sulfonamides, polymyxin B) and antifungals (griseofulvin), oral diabetes drugs (sulfonylurea antihyperglycemic drugs), and drugs for mental disorders (phenothiazines).

Other drugs that may interact with VISUDYNE include drugs for heart or circulation conditions (calcium channel blockers, blood thinners or anti-clotting drugs, diuretics).

Antioxidant such as beta-carotene or drugs that scavenge free radicals (such as dimethylsulfoxide (DMSO), formate, mannitol, and alcohol) may interact with VISUDYNE.

Radiation therapy may also interact with VISUDYNE.

Make sure your doctor knows all the medications you are taking before starting VISUDYNE therapy.

PROPER USE OF THIS MEDICATION

<u>Usual adult dose:</u>
Your doctor will calculate the correct dose to give you, based on your body surface area. VISUDYNE should only be administered by a qualified health professional in an ophthalmology practice.

<u>Overdose</u>:

If your doctor tells you that you've had an overdose, you will have to protect your skin and eyes from bright light for a longer time than normal. Follow your doctor's instructions.
If you feel you have been given an overdose, consult with your doctor or healthcare practitioner administering the product immediately following the procedure, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Changes in vision (including blurring, decreased sharpness, flashes of light and gaps or 'spider webs' in vision) were among the most frequently reported side effects. If these occur, or if 'floaters' or persistent changes in visual field appear, contact your doctor (see Table). These may be signs of a serious condition.

Temporary musculoskeletal pain commonly occurs, during or after infusion, often as chest and back pain which can radiate to other areas including the pelvis, shoulder girdle or ribs.

Other common side effects include weakness, nausea, constipation, hypertension, elevated blood cholesterol or urinary glucose, dry, itchy or painful eyes, aversion to light, decrease in pain or touch sensitivity, sunburn or increased sensitivity to the sun.

Injection site reactions (e.g. pain, swelling, blisters and discolouration) may occur, and can be serious (see next section).

This is not a complete list of side effects. For any unexpected effects while taking VISUDYNE, contact your doctor or emergency care provider.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Side effect	What happens	What to do
Severe vision decrease	In clinical trials, about 1-5% of patients experienced such decreases within the first 7 days of treatment. Some patients achieved partial recovery.	Contact your doctor immediately if you have vision loss.
Changes in the visual field	Loss of vision (often sudden), appearance of light flashes, floaters.	Contact your doctor.
Hyper-sensitivity (allergic) reactions	You feel sweaty, hot or flushed, dizzy, itchy, short of breath, have a headache, hives, difficulty swallowing or feel like you are about to faint during or after receiving VISUDYNE. On rare occasions, these allergic reactions may be severe and could include seizures.	Get medical assistance immediately. Contact your doctor.
Injection site reactions	Discomfort, pain swelling, bleeding, leakage or discolouration occurs at the injection site. Light exposure can cause a painful or tissue damaging reaction.	Cover the site for as long as it is discoloured. Oral pain relievers can be taken. BE SURE to contact your doctor.

HOW TO STORE IT

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

IMPORTANT: PLEASE READ

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Before contacting* Canada Vigilance*, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
or
http:// www.novartis.ca
or by contacting the sponsors.

Valeant Canada LP
2150 St-Elzear, Blvd., West
Laval, Quebec
Canada H7L 4A8
1-800-361-4261

Distributor:
Novartis Ophthalmics
Novartis Pharmaceuticals Canada Inc.
385 Bouchard Boulevard
Dorval, QC
H9S 1A9

1.800.363.8883

This leaflet was prepared by Valeant Canada LP

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Last revised: January 27, 2016