CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-119/S-001

PHARMACOLOGY REVIEW

Review and evaluation of Pharmacology and Toxicology Data

Division of Analgesics, Anti-inflammatory, and Ophthalmic Drug Products
HFD-550
Reviewer: Susan D. Wilson, D.V.M., Ph.D.

NDA Number: N21-119

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Information to Sponsor: Yes(X)

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Sponsor or Agent:

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Manufacturer (if different) for drug substance:

Drug Name:

1° - VISUDYNE™
2° - verteporfin
3° - BPD-MA
4° - benzoporphyrin derivative monoacid ring A
5° - CL 318,952

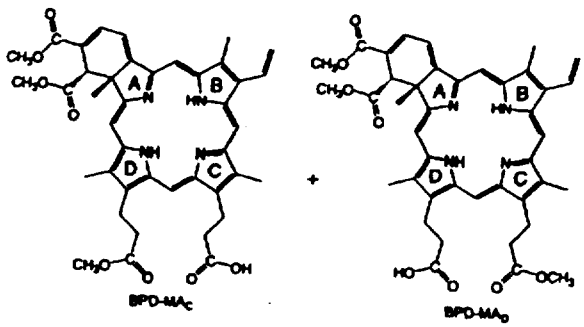
Chemical Name: 1:1 mixture of the following regioisomers

BPD-MA_C - 9-methyl trans-(±)-18-etheneyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl –23*H*, 25*H*-benzo(b)porphine-9,13-dipropanoate

BPD-MA_D - 13-methyl trans-(±)-18-etheneyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl –23*H*, 25*H*-benzo(b)porphine-9,13-dipropanoate

CAS Number (if provided by sponsor): Not provided

Structure: $C_{41}H_{42}N_4O_8$



Molecular Weight: 718.814

Relevant IND/NDA/DMF: INDs [redacted]

Drug Class: Photodynamic therapeutic agent

Indication: For the treatment of choroidal neovascularization associated with age-related macular degeneration

Clinical Formulation (and components): [redacted]

Components/Excipients	Concentration (mg/vial)
Verteporfin – active ingredient	15
Butylated hydroxytoluene	
Ascorbyl palmitate	
Egg phosphatidylglycerol (IV)	
Dimyristoyl phosphatidylcholine (IV)	
Lactose monohydrate (NF)	

Route of Administration: intravenous infusion

Proposed Clinical Protocol: No new protocol submitted

Studies Reviewed within this submission:

Report No.	Report Date	Study Title	Test Material Lot
		SAFETY PHARMACOLOGY	
PH-00013	Jul. 24, 2000	Complement activation inhuman blood and serum *in vitro* by ' QLT0074 and verteporfin in lipid-based formulations [Vol. 1.2; pp. 2-15]	ID # - CX08-136 and -139
PH-00016	Jul. 24, 2000	Hemodynamic and pulmonary effects observed in pigs following injection of QLT7004 or verteporfin in lipid-based formulations [Vol. 1.2; pp. 16-34]]	TC0631 and TC1019

Disclaimer (Use of sponsor's material): Sponsor submitted information was utilized in the preparation of this review.

Introduction/Drug History: Age-related macular degeneration [ARMD] is a leading cause of irreversible vision loss in individuals ≥65 years. ARMD presents as either a "dry" or "nonvascular" form or a "wet" or "vascular" form. The choroidal neovascularization observed with the wet form of this disease is characterized by [1] immature, fragile, and leaky vessels; [2] infiltration of fibrocytes and fibrocellular tissue between the retinal pigmented epithelium (RPE) and photoreceptors; [3] RPE detachment; and [4] subretinal fibrosis. The normal architecture is disrupted, eventually leading to a loss of photoreceptors, RPE, destruction of the macula, and associated vision loss.

The current treatment for neovascular ARMD, photocoagulation, can result in retinal damage, atrophic scarring, and development of visual scotoma, and is essentially nonselective. The Sponsor proposes that BPD-MA plus photoactivation [e.g. photodynamic therapy] is an alternative treatment modality that theoretically results in closure of the choroidal neovasculature [CNV] while minimizing the damage to the overlying neurosensory retina and normal tissues. Although, this treatment would not repair irreversibly diseased tissue, it is predicted that it will prevent the progression of the disease. The Sponsor indicates that BPD-MA tissue concentration at various time points following drug infusion is greater in the CNV than in surrounding normal tissue. Therefore, this treatment potentially results in greater selectivity than photocoagulation, if properly timed. The mechanism of action is similar to that described for other photodynamic therapies. Following photoactivation of BPD-MA, there is the generation of singlet oxygen and other radicals. These moieties perturb cellular structures, including cellular membranes, and result in cytotoxicity. Damage to endothelial cells is also associated with platelet aggregation, degranulation, and thrombus formation, which appears to be a major mechanism for the development of vascular occlusion.

Previous Clinical Experience: The medical officer, Dr. Wiley Chambers, has reviewed the clinical trials conducted in association with this NDA.

Pharmacology: - No new studies submitted

II. Safety Pharmacology

A. Complement Activation

a. *In Vitro*

i. Title: Complement activation inhuman blood and serum *in vitro* by QLT0074 and verteporfin in lipid-based formulations [Vol. 1.2; pp. 2-15]
Study Identification: PH-00013
Site: [redacted]
Study Dates: June 17 – June 30, 1999
Formulation and Lot No.: Verteporfin for Injection [VFI]; ID # - CX08-136 and –139
Vehicle: Drug vehicle
[**Note:** Another formulation was evaluated. Since this formulation is not clinically relevant, the results will not be presented for this test article.]
Certificate Analysis: No [X]
Final Report: Yes [X] July 24, 2000
GLP and QA Statements Signed: No [X]
Objective: "To compare the degree of complement activation in serum or blood by ... verteporfin and [its] vehicle control".

Study Design – Complement activation was determined on whole blood and serum from 3 donors using commercially available assays. The complement activation ELISA [CAE] assay "measures the amount of functional complement activity in a sample". [**Note:** The second assay was a C3a ELISA and was used only for a single sample. The results were not consistent with previous results and with the CAE assay. Therefore, these data were considered an artifact.] Samples were incubated with [redacted] and vehicle for 30 minutes prior to performing the assay.

Results and Conclusions – There was a dose-dependent activation with complement with minimal activation at 10 µg/ml and significant at ≥100 µg/ml. Complement activation in serum samples was more readily detected at the low concentration. Activation in blood samples was also observed with the VH, but the magnitude was less than that for the formulation containing drug substance. In general, there was no apparent activation in serum samples incubated with vehicle. The table below outlines the individual and mean results for VFI.

Sample	CAE UNIT [percentage of control]							
Concentration	Individual Serum			Individual Blood			Mean	Mean
[µg/ml]	1	2	3	1	2	3	Serum	Blood
[redacted]							35	15
							21.8 [62%]	9.6 [64%]
							6.7 [19%]	2.8 [20%]
							0.87 [2%]	0.2 [1.5%]

These results are consistent with the literature in which liposomal formulations have been shown to activate complement. Results should be interpreted cautiously because of the small N.

B. Cardiovascular and Pulmonary Effects

a. Pigs

i. Title: Hemodynamic and pulmonary effects observed in pigs following injection of QLT7004 or verteporfin in lipid-based formulations [Vol. 1.2; pp. 16-34]]
Study Identification: PH-00016
Site: [redacted]
Study Dates: June – July, 1999
Formulation and Lot No.: VFI; Lot Nos. TC0631 and TC1019
Certificate Analysis: No [X]
Final Report: Yes [] July 24, 2000
GLP and QA Statements Signed: No [X]
Objective:

Study Design – Four female Landrace-Yorkshire cross pigs [7-12 weeks; app. 30 kg] were administered 2 mg/kg of VFI by iv injection following sedation with the dissociative anesthetic, ketamine, at 20 mg/kg im and atropine 1 mg. Sedation was maintained by additional ketamine administration as needed. Concentration and rate of injection were varied. Endpoints included clinical observations, heart rate, and respiratory rate.

Results and Conclusions – Signs of anaphylactic/anaphylactoid reactions were induced in 1/2 pigs administered VFI at a concentration of 1 mg/ml and a rate of approximately 0.04 mg/kg/min. and 1/1 pig administered VFI at a concentration of 0.3 mg/ml and a rate of approximately 0.2 mg/kg/min. These signs included "patchy red skin, decreased and weakened heartbeat, and problems breathing culminating in apnea". Treatment with an antihistamine [Benadryl] abrogated the reactions. This phenomenon was observed in studies submitted in the original NDA. No signs developed in 2/2 pigs administered VFI at a concentration of 0.25-0.3 mg/ml and a rate of approximately 0.04 mg/kg/min. Occurrence and severity of the reaction appeared to be concentration and injection rate dependent.

III. Pharmacokinetics/Toxicokinetics: No new studies submitted

[redacted]: No new studies submitted

[redacted]: None submitted

[redacted]: No new studies submitted

[redacted]: No new studies submitted

[redacted]: No new studies submitted

Overall Summary - These studies are consistent with the results of studies submitted in the original NDA. Anaphylactic/anaphylactoid reactions developed in sedated/anesthetized pigs apparently as a result of histamine release induced by complement activation. The relevance to humans is unclear.

Recommendations:

a. **Internal Comments:** See Labeling recommendations
b. **External Recommendations:** See Labeling recommendations

Labeling Review: The Sponsor proposes the following changes to the label. The original label is indicated in black type. The proposed changes are in red type. The Reviewer's recommendations are indicated by black bold italicized type and strikeouts.

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 nonsedated pigs. 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.***[1]

Signs [chest pain, syncope, dyspnea, and flushing] consistent with complement activation have been observed in <1% of patients administered VISUDYNE.[2] Patients should be supervised during VISUDYNE infusion.

[1]At the 10 µg/ml concentration, the CAE units ranged from [redacted] of control values in whole blood and plasma, respectively. At 100 and 1000 µg/ml, the CAE units ranged from approximately [redacted] of control values, respectively for both whole blood and plasma.
[2]According to the Sponsor, preliminary *in vivo* study in humans indicated that C3a was not increased and that the increase in complement activation in individuals with antiphospholipid antibodies was variable. However, in the Safety Update [p. 26, Vol. 1.1], the Sponsor describes an AE [less frequent/rare] that would be consistent with an anaphylactic/anaphylactoid reaction and potentially complement activation. Therefore, this finding supercedes the study evaluating complement activation. [**Note:** This response has been described in response to the administration of liposomes in humans.]

/S/

Reviewer's Signature:

Susan D. Wilson, D.V.M., Ph.D.

26 Sept 2000

Date

/S/

Team Leader Concurrence:

Robert E. Osterberg, RPh, PhD

9/26/00

Date