CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-119

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-119

REVIEW # 1 **DATE REVIEWED:** 08-DEC-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	16-AUG-99	17-AUG-99	18-AUG-99
AMENDMENT	23-SEP-99	27-SEP-99	12-OCT-99
	06-OCT-99	08-OCT-99	18-OCT-99
	14-OCT-99	18-OCT-99	26-OCT-99
	18-OCT-99	20-OCT-99	03-NOV-99
	26-OCT-99	27-OCT-99	03-NOV-99
	01-NOV-99	03-NOV-99	09-NOV-99
	03-NOV-99	04-NOV-99	10-NOV-99
	09-NOV-99	10-NOV-99	19-NOV-99
	10-NOV-99	15-NOV-99	19-NOV-99
	24-NOV-99	29-NOV-99	09-DEC-99
	29-NOV-99	30-NOV-99	09-DEC-99

NAME & ADDRESS OF APPLICANT: QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, British Columbia
Canada V5Z 4H5

DRUG PRODUCT NAME:

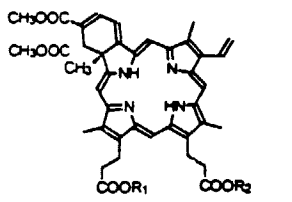
Proprietary: VISUDYNE™ (verteporfin for injection)
Established: Verteporfin
Code Name/#: CAS 129497-78-5
Chem.Type/Ther.Class: 1P

PHARMACOL. CATEGORY: Photodynamic therapy for age-related macular degeneration

DOSAGE FORM: Sterile, lyophilized powder for injection (liposomal formulation)
STRENGTHS: 15 mg/vial
ROUTE OF ADMINISTRATION: Intravenous infusion
DISPENSED: _X_ Rx __ OTC

By physician: At time of use, reconstitute lyophilized powder with 7.0 mL sterile water.
Determine desired dose based on need to administer 6 mg/m^2 body surface area.
Withdraw desired amount of reconstituted VISUDYNE and bring to final volume of 30 mL using 5% Dextrose for Injection.
Infuse intravenously over 10 min at rate of 3 mL/min.
Treatment of the second eye using this same regimen can begin as early as 1 week after treating the first eye.
Approximately 3 months later, both eyes can be evaluated and, if indicated, a second round of treatment can be initiated.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



BPD-MA$_C$ $R_1 = CH_3$, $R_2 = H$

BPD-MA$_D$ $R_1 = H$, $R_2 = CH_3$

$C_{41}H_{42}N_4O_8$
M.W.: 718.81

9-Methyl and 13-Methyl trans-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoate

or

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*-

VERTEPORFIN (a 1:1 mixture of BPD-MA$_C$ and BPD-MA$_D$)

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:
Chemistry Reviews of

CONSULT REVIEWS:
Review of Tradenames (CDER Labeling and Nomenclature Committee, Consult #)
Sterility Assurance Report (C. Vincent, HFD-160)

REMARKS: A number of concerns were identified in the course of reviewing this submission. The following issues, in contrast to those cited below, have been satisfactorily addressed by the applicant. The use of porcine blood from European slaughterhouses raised concern about contamination with bovine blood and the possible introduction of the infectious agent for the transmissible spongiform encephalopathies (Creutzfeldt-Jacob disease and "mad cow disease"). However, the Dutch manufacturer has made changes in process controls and batch record content

REMARKS: (continued)
that eliminate these concerns. Likewise, only blood from pigs slaughtered before June 1998 has been used to manufacture all clinical and commercial batches of VISUDYNE, sparing concern about the presence in the product of dioxin/PCBs from European cattle contaminated with these materials during the first 6 months of 1999. The removal of the considerable impurities associated with the process starting material from one supplier has been documented through the purification of subsequent synthetic steps. Confusion in the presentation of information on structure elucidation by [redacted] techniques has been corrected. The liposomal material from the original process and incorporated into the VISUDYNE used in the bulk of studies to date has been demonstrated to be equivalent to the material derived from the large-scale commercial process. The issue of the presence of free and aggregated verteporfin in the liposomal preparations has been laid to rest by persuasive evidence that indicates that complete incorporation of verteporfin in the liposome-based formulation is an intrinsic property of VISUDYNE. The stability of the lyophilized product at 25 °C has been adequately established to approve a 24-month expiry period. The stability of the reconstituted product (even from lyophilized product after prolonged storage) is consistent with the Package Insert direction to use within 4 hours of reconstitution.

CONCLUSIONS & RECOMMENDATIONS:

The manufacture of the drug product—VISUDYNE or Verteporfin for Injection [VFI]—originates with blood-derived hemin from Dutch pigs. Conversion of hemin to the starting material requires material transfer from this supplier to other manufacturers in Europe, Japan, and Canada. This pattern of international shipping continues with the transfer of the labile verteporfin API from the Canadian manufacturer to the Japanese manufacture of the labile liposomal Verteporfin Presome, which in turn is shipped to the US manufacturer of the sterile, lyophilized final product, VFI. The applicant has not provided for all of these material transfers satisfactory information on the shipping/handling conditions and the testing, especially the acceptance testing. These omissions give rise to serious concerns about product safety and quality. In addition, inconsistencies and omissions have been noted in the specifications for verteporfin API and VFI which could compromise product quality. The Package Insert description for handling the reconstituted VISUDYNE is sufficiently ambiguous to permit product mishandling and jeopardize its safe use before being administered to the patient. The related cGMP and product-specific inspections of the manufacturing and testing facilities have not been completed. Until these various issues are addressed satisfactorily, the recommendation for this submission is APPROVABLE. Please see the chemist's draft letter for details.

cc:
Orig. NDA 21-119
HFD-550/Division File
HFD-550/CHEM/A.Fenselau
HFD-550/CSO/L.Gorski

/S/ 12/9/99
Allan Fenselau, Review Chemist, HFD-550

/S/ 12/10/99
Linda Ng, Chemistry Team Leader HFD-550

37 ***pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.***

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-119

REVIEW # 2 **DATE REVIEWED:** 16-MAR-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	16-AUG-99	17-AUG-99	18-AUG-99
AMENDMENT	28-JAN-00	31-JAN-00	24-FEB-00
AMENDMENT	06-MAR-00	08-MAR-00	13-MAR-00

NAME & ADDRESS OF APPLICANT: QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, British Columbia
Canada V5Z 4H5

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Proprietary: VISUDYNE™ (verteporfin for injection)
Established: Verteporfin
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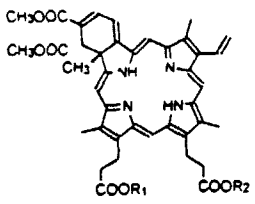
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



BPD-MA$_C$ $R_1 = CH_3$, $R_2 = H$
BPD-MA$_D$ $R_1 = H$, $R_2 = CH_3$

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M.W.: 718.81

9-Methyl and 13-Methyl trans-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoate

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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*-

VERTEPORFIN (a 1:1 mixture of BPD-MA$_C$ and BPD-MA$_D$)

[redacted]

CONCLUSIONS & RECOMMENDATIONS: Deficiencies concerning specifications for the starting material [redacted] in the synthesis of the API verteporfin need to be corrected. A commitment has been made to provide, by no later than 01-SEP-00, the following: a) copies of the "optimized and validated" HPLC assays used to analyse [redacted] for the presence and amounts [redacted] b) the method validation reports for these procedures, c) the acceptance criteria for these two classes of impurities. The recommendation for this submission is APPROVAL, pending approval of all remaining sites for cGMP compliance.

/S/ 4/4/00

Allan Fenselau, Review Chemist, HFD-550

/S/ 4/4/00

Linda Ng, Chemistry Team Leader HFD-550

cc:
Orig. NDA 21-119
HFD-550/Division File
HFD-550/CSO/L.Gorski
HFD-550/CHEM/A.Fenselau
HFD-550/CHEM/TeamLdr/L.Ng
HFD-550/Div.Dep.Dir/W.Chambers
HFD-830/Dir.DNDCIII/C-w.Chen

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21119/000**
Priority: **1P** Org Code: **550**
Stamp: **16-AUG-1999** Regulatory Due: **22-AUG-2000**
Action Goal: District Goal: **18-DEC-1999**
Applicant: **QLT**
C/O BOGLE & GATES
60 UNION ST 2 UNION SQUARE
SEATTLE, WA 981012346
Brand Name: **VISUDYNE (VERTEPORFIN)**
Established Name:
Generic Name: **VERTEPORFIN**
Dosage Form: **FIJ (FOR INJECTION)**
Strength: **15 MG PER VIAL**

FDA Contacts:

L. GORSKI	**(HFD-550)**	**301-827-2090**	**, Project Manager**
A. FENSELAU	**(HFD-550)**	**301-827-2503**	**, Review Chemist**
L. NG	**(HFD-830)**	**301-827-2511**	**, Team Leader**

Overall Recommendation:

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **INTERMEDIATE MANUFACTURER**

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment: [redacted]
CIBA VISION OPHTHALMICS
11460 JOHNS CREEK PKY
DULUTH, GA 30097
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CEX** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

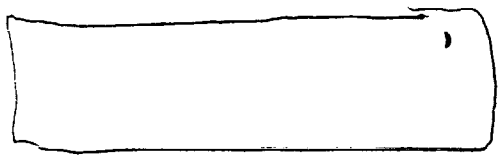
Profile: **CSN** OAI Status: **POTENTIAL OAI**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date: **10-FEB-2000**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: [redacted]

DMF No: [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

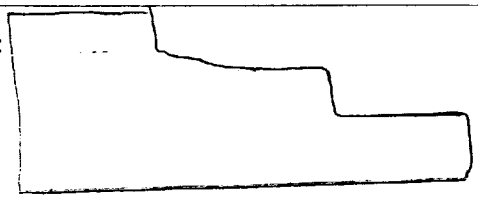


AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date: **10-FEB-2000**

Responsibilities: **INTERMEDIATE MANUFACTURER**

Establishment:

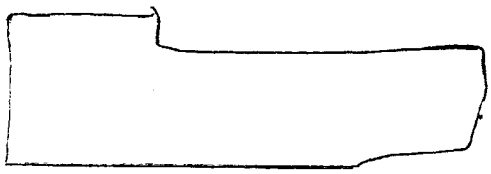


DMF No:
AADA No:

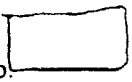
Profile: **CTL** OAI Status: **NONE**
Last Milestone: **INSPECTION SCHEDULED**
Milestone Date: **24-FEB-2000**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment:



DMF No:
AADA No:



Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

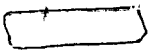
QLT PHOTOTHERAPEUTICS INC
520 WEST 6TH AVENUE
VANCOUVER, BRITISH COLUMBIA,

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date: **14-MAR-2000**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE RELEASE TESTER
INTERMEDIATE RELEASE TESTER

Establishment:



DMF No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

[redacted]

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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