CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-119

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-119 **SUPPL #** _____

Trade Name Visudyne **Generic Name** verteporfin for injection

Applicant Name QLT **HFD-** 550

Approval Date, if known April 12, 2000

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product. NA

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Signature
Title: Dep Div Director

4/3/00
Date

/S/

Signature of Division Director

4/3/00
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21119	**Trade Name:**	VISUDYNE (VERTEPORFIN)
Supplement Number:		**Generic Name:**	VERTEPORFIN
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AE	**Proposed Indication:**	the treatment of Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

not appropriate for use in children 1/7/00

pediatric waiver granted

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LORI GORSKI

/S/ 1/7/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21119	**Trade Name:**	VISUDYNE (VERTEPORFIN)
Supplement Number:		**Generic Name:**	VERTEPORFIN
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	treatment of age-related macular degeneration in patients with predominately classic subfoveal choroidal neovascularization

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

not appropriate for use in children

Pediatric waiver granted

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LORI GORSKI

/S/

Signature

April 3, 2000

Date

PATENT CERTIFICATION

NDA NUMBER: 21-119

Applicant: QLT PhotoTherapeutics Inc.*
c/o Scott L. Gelbrand, Attorney At Law
Perkins Coie, LLP
1201 Third Avenue, 40th Floor
Seattle, WA 98101-3099
U.S.A.

*a U.S. subsidiary of QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, British Columbia V5Z 4H5
Canada

Active Ingredient: verteporfin

Certification: The undersigned certifies, based on her information, advice and belief the following statements in regards to verteporfin and Verteporfin for Injection. This product is the subject of this application for which approval is being sought.

The above mentioned active ingredient, verteporfin, is the subject of composition claims in U.S. Patent Number 4,920,143 and U.S. Patent Number 5,095,030, both of which expire on April 24, 2007. Both patents are owned by the University of British Columbia, and are exclusively licensed by the Applicant.

The drug product, Verteporfin for Injection, is the subject of composition claims in:

- U.S. Patent Number 5,214,036, which expires on May 25, 2010, is owned by the University of British Columbia, and is exclusively licensed by the Applicant,
- U.S. Patent Number 5,707,608, which expires on August 02, 2015, and is owned by the Applicant, and
- Pending U.S. Patent Application Serial Number 08/489850, which is owned by the Applicant.

Methods directed to the use of the drug product in photodynamic therapeutic protocols for the treatment of age-related macular degeneration and related conditions involving unwanted neovasculature in the eye are claimed in:

- U.S. Patents Number 5,705,518 and Number 5,770,619, both of which expire on January 06, 2015 and are owned by the University of British Columbia, and are exclusively licensed by the Applicant,
- U.S. Patent Number 5,798,349 which expires on August 25, 2015 and is co-owned by the Applicant, The General Hospital Corporation (Boston, MA) and The Massachusetts Eye And Ear Infirmary (Boston, MA), and

- U.S. Patent Number 5,756,541 which expires on March 11, 2016, and is owned by the Applicant.

Date: August 4, 1999

Respectfully submitted,

QLT PhotoTherapeutics Inc.

Jennifer Kaufman-Shaw

Jennifer Kaufman-Shaw
Director, Intellectual Property

The University of British Columbia**
University-Industry Liaison Office
2194 Health Sciences Mall, Room 331
Vancouver, British Columbia V6T 1Z3
Canada

** U.S. representative: c/o Kate H. Murashige, Attorney At Law
Morrison & Foerster, LLP
2000 Pennsylvania Avenue, N.W.
Washington, DC 20006-1888
U.S.A.

The General Hospital Corporation
55 Fruit Street
Boston, MA 02114
U.S.A.

The Massachusetts Eye And Ear Infirmary
243 Charles Street
Boston, MA 02114
U.S.A.

QLT PhotoTherapeutics Inc.

520 West 6th Avenue
Vancouver British Columbia
Canada V5Z 4H5
Telephone 604 872 7999
Fax 604 875 0021

August 14, 1999

Reference: NDA 21-119 : VISUDYNE™ (verteporfin for injection)

Subject: Certification – Non-use of capacity or services of person debarred under Generic Drug Enforcement Act of 1992.

I, Alexandra D. J. Mancini, the Vice President, Regulatory Affairs, QLT PhotoTherapeutics Inc. (the "Applicant"), hereby certify as follows:

The Applicant did not and will not use in any capacity the services of any person debarred under 21 USC Section 335A (a) and (b), in connection with this NDA.

IN WITNESS WHEREOF, the undersigned has signed this certificate on behalf of QLT PhotoTherapeutics Inc. on the 14th day of August 1999.

QLT PHOTOTHERAPEUTICS INC.

By: Alexandra Mancini

Name: Alexandra D. J. Mancini, M.Sc.

Title: Vice President, Regulatory Affairs

QLT PhotoTherapeutics Inc.

520 West 6th Avenue
Vancouver British Columbia
Canada V5Z 4H5
Telephone 604 872 7881
Fax 604 875 0001

August 9, 1999

VIA FAX : 665-3140

[redacted]

Dear Sir / Madam :

Please arrange for a wire transfer payment on August 10, 1999. Details are as follows :

Beneficiary : Food & Drug Administration

Destination Branch : [redacted]

Amount of Wire Transfer: [redacted]

Re : User ID # 3757
NDA # 21-119

Please debit our Account No. [redacted] directly, including service charges. Your assistance in this matter is appreciated.

Sincerely yours,

QLT PhotoTherapeutics Inc.

ANNA WONG
Manager, Financial Services

Per : _____
David Swetlow, C.A.
Controller

Meeting Minutes

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

QLT , IND[redacted]
February 22, 1999
Unmask Phase 3 Data

FDA Attendees

Wiley Chambers, Deputy Director
William Boyd, Medical Officer
Jennifer Dunbar, Medical Officer
Joanne, Holmes, Clinical Reviewer
Raphael Rodriguez, Project Manager
Lori Gorski, Project Manager
Andrea Weir, Pharmacology Team Leader
Susan Wilson Pharmacology Reviewer
Anthony Zeccola, Chief, Project Manager
Lillian Patrician, Statstician
Richard Felten, Device Reviewer

QLT Attendees

Mohammad Azab, Vice President, Clinical Research and Medical Affairs
Ed Levy, Vice President, Corporate Development
Julia Levy, President and Chief Executive Officer
Alexandra Mancini, Vice President, Regulatory Affairs
David Mitchell, Manager, Regulatory Affairs
Andrew Strong, Director, Clinical Research
Yong Hao, Director, Biometrics & Data Evaluation
Gusti Huber, Project Leader, Ciba Vision
John Koester, Head, Biostatistics & Data Management, Ciba Vision
Larry Mandt, Director, Regulatory Affairs , Ciba Vision
Al Reaves, Head, Clinical Project Management, Ciba Vision
Jeannie Skinner, Manager, Regulatory Submissions, Ciba Vision
Neil Bressler, Professor of Ophthalmology, Johns Hopkins Hospital

Discussion of Questions for the FDA

1. Based on the statistical significance of the primary endpoint in both TAP studies, does the Agency agree that verteporfin therapy is efficacious in the reduction of vision loss at the 12-month assessment?

A complete NDA review is necessary to answer this question.

2. Based on the safety data provided, does the Agency agree that verteporfin therapy is safe up to the 12-month assessment in the TAP studies population?

A complete NDA review is necessary to answer this question.

3. If both eyes are eligible in a patient, does the Agency have a concern about light activation being administered to both eyes following a single injection?

Yes. Agency would need to evaluate proposed selection criteria and proposed treatment plan to address these concerns. It was recommended that a new protocol could be used to collect data for new sites to work out timing of dosing

4. Does the Agency agree that the proposed eligibility criteria define an appropriate patient population for an expanded-access program?

Yes.

5. As detailed in Section 4.3, we intend to request cost recovery that will be in the range of , depending on the number of sites initiated and the final cost estimates. Can the Agency provide comment on the rationale supporting the cost-recovery level identified and on the likelihood that we will be granted such permission?

Sponsor does not provide specific enough details (i.e. expenses) in the meeting packet to comment on the cost-recovery level.

6. We cannot make a decision on the scope of the expanded use program until we know the costs. Therefore, can the Agency confirm that we would receive concurrent responses on the IND for treatment use and on the request for cost recovery?

A response to the request for cost recovery will be received by the date the IND becomes active.

cc: HFD-550/Div Files
HFD-550/DepDir/Chambers 4/3/99
HFD-550/MO/Boyd
HFD-550/MO/Dunbar
HFD-550/Clin/Holmes 3/10/99
HFD-550/PM/Gorski 3/23/99
HFD-550/PM/Rodriguez
HFD-550/P/T TL /Weir
HFD-550/P/T/Wilson
HFD-725/Stat/Patrician
HFZ-410/DGRD/Felten

c:/lori/minutes

Meeting Minutes QLT PhotoThreapeutics
July 20, 1998

QLT PhotoTherapeutics	
Mohammad Azab	VP, Clinical Research and Medical Affairs
Ed Levy	VP, Corporate Development
Alexandra Mancini	VP, Regulatory Affairs
David Mitchell	Manager, Regulatory Affairs
Andrew Strong	Director, Clinical Research
CIBAVision	
Gusti Huber	Project Leader
Larry Mandt	Director, Regulatory Affairs
Al Reaves	Director, Clinical Research
John Koester	Head Biostatistics
Covance	
Catherine Michel	Director, Regulatory Affairs
Participating Ophthalmologist	
Neil Bressler	Johns Hopkins
FDA	
Lori Gorski	Project Manager
Wiley Chambers	Deputy Division Director
Joanne Holmes	Clinical Reviewer
Elizabeth Ludwig	Medical Officer
Raphael Rodriguez	Project Manager
Lillian Patrician	Statistician
Richard Felten	Device Reviewer

1. Does the Agency agree with our general position that expanded use should be implemented in the event that the data from the TAP studies demonstrate a sufficient level of patient benefit?

   FDA Response: *The decision to request expanded use is an option of the sponsor of an IND. The agency will review any request.*

2. Given that a minimum of 18 months of fully masked comparative data would be available from the TAP studies as of March 1999, does the Agency agree that if the 1-year data demonstrate adequate efficacy and safety, the Phase 3 studies should be unmasked and treatment made available to all qualifying patients?

   FDA Response: *No. The Agency has previously recommended 24 month studies and no information has been submitted which suggests that it is not an appropriate time frame for evaluation. The VIP studies are a separate indication and should not be considered with the TAP studies.*

3. Does the Agency agree that a treatment-use submission as per 21 CFR §312.34 and §812.36, when applied to this program and indication, may be in the form of a single submission to the existing IND, and that it cover both drug and device aspects for this therapy?

   FDA Response: *Yes.*

4. Does the Agency agree that the proposed data would be adequate to fulfill the efficacy and safety data requirements of a submission requesting treatment use?

FDA Response: *Without reviewing the data, it is not possible to determine. A line listing and summary of all adverse experiences should be included in addition to the other items proposed for inclusion.*

5. We believe the listed costs are valid components of a cost recovery request. Does the Agency agree with our interpretation of the regulations as applied to this program? Can the Agency provide clarification on the research and development costs allowed for recovery?

FDA Response: *Although an initial review is made at the Division level, the final decision will be made at the Office or Center level. The proposal to charge should be a price which is not larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.*

6. Does the Agency agree to meet in January to discuss the data and make decisions about expanded access, including the criteria for eligibility?

FDA Response: *Provided the request is made at least 30 days in advance and the full briefing materials are received by the agency at least two weeks in advance of the meeting.*

- Would the Agency encourage the participation of some members of the DSMC in this meeting?

FDA Response: *The inclusion of some members of the DSMC is not necessary. The choice of participants is entirely the IND sponsor's choice.*

- How quickly would the Agency be able to respond to the request for a treatment-use protocol? What about the request for permission to obtain cost recovery?

FDA Response: *New INDs, including Treatment INDs are permitted to proceed automatically 30 days after receipt by the FDA unless the sponsor is notified to the contrary. Authorization for charging under a Treatment IND goes into effect automatically 30 days after receipt by the FDA unless the sponsor is notified to the contrary.*

- Would the Advisory Committee likely be requested to participate in a decision to allow treatment use? What about the request for permission to obtain cost recovery?

FDA Response: *The full Advisory Committee is unlikely to be requested to participate in the decision to allow treatment use or cost recovery. Individual members of the Advisory Committee may be requested to assist in the decision.*

6. What is the expected timing of the NDA/PMA reviews?

FDA Response: *If the application is given a priority status, the Division will attempt to have reviews completed prior to the 6 month FDAMA User Fee clock.*

7. The company understands there are discussions planned for this summer within the Agency on the topic of treatment use. Will additional guidance and/or clarification on treatment use be made available soon? Will agreements reached today need to be revisited prior to submission of a request for treatment use?

FDA Response: *The Division is unaware of the referenced discussions. The Division intends to honor agreements reached in any meeting, but cannot speak for the Office, Center or Agency without prior discussions with these levels.*

cc: [redacted]

HFD-550/CSO/Gorsk.
HFD-550/DepDir/Chambers 5/13/93
HFD-550/MO/Ludwig
HFD-550/Clin Rev/Holmes
HFD-550/CSO/Rodriguez
HFD-725/Stat/Patrician
HFZ-410/DGRG/Richard Felten

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

RECORD OF A MEETING

Date: August 7, 1996
IND [redacted]
Subject: CMC issues
Drug: BPD-MA (verteporfin)
Indication: Closure of (ocular) choroidal neovascularization
Sponsor: QLT Therapeutics

Between members of QLT: Julia Levy, David Dolphin, Louis Gura, Yau-Kwan Ho, Iman Karmadi, Alexandra Mancini, Dev Singh, Simon Wallis

and CibaVision Ophthalmics: Richard Bergstroem, Gustave Huber, Larry Mandt

and FDA: Wiley Chambers, Jonca Bull, Elizabeth Ludwig, Bart Ho, Hasmukh Patel, Eric Sheinin, Joanne Holmes

The meeting addressed CMC issues presented in the July 23, 1996, briefing document.

1a. The Division agreed that the BPD-1,3-diene CD ester A-ring can be considered the key intermediate.

1b. [redacted]

2a. Additional data are needed before the division can comment on whether the proposed methods are adequate for characterization of the drug substance and drug product. However, there are no additional tests the division would suggest at this time. Related compounds are within the acceptable range at 3%, although they should be characterized. A consistent regulatory specification should be chosen, e.g., for shelf life. Another ID test, in addition to retention time, should be chosen and data provided. It is acceptable for QLT to fill the bottles with lyophilized powder under nitrogen. While the drug substance is stable in the presence of oxygen, nitrogen is used due to the liposomes.

2b. While there were no objections to the proposed analytical comparisons being sufficient to demonstrate equivalence of the 2 processes, QLT was reminded that data were necessary for an absolute confirmation.

3. At some point, QLT should attempt to obtain data on the individual regioisomers and enantiomers, but it is not a priority at this time.

Joanne M. Holmes

Meeting Minutes

FDA/QLT PhotoTherapeutics Inc./CibaVision

BPD-MA (verteporfin), CMC Issues

August 7, 1996

See Agency Minutes. 5/20/97

A meeting was held on August 7, 1996 between representatives of the FDA's Opthalmology group, QLT PhotoTherapeutics and CibaVision Ophthalmics. The agenda centered around discussion of Chemistry, Manufacturing and Control Issues as outlined in a background/information package sent to the agency on July 23, 1996. Copies of the overheads used in the presentations are attached.

The following individuals attended:

QLT PhotoTherapeutics

Dr. David Dolphin	Vice President, Technology Development
Mr. Louis Gura	Director, Drug Development
Dr. Yau- Kwan Ho	Director, Analytical Services
Mr. Iman Karmadi	Sr. Director, Technical Operations
Dr. Julia Levy	President and CEO
Ms. Alexandra Mancini	Vice President, Regulatory Affairs
Dr. Dev Singh	Manager, Formulation Development
Mr. Simon Wallis	Director, Pharmaceutical Development
Ms. Elizabeth Waterfield	Associate, Regulatory Affairs

CibaVision Ophthalmics

Mr. Richard Bergstroem	Head, Central Drug Regulatory Affairs
Dr. Gustave Huber	Vice President, Project Leader PDT
Mr. Larry Mandt	Director, Regulatory Affairs

FDA Opthalmology Group

Dr. Jonca Bull	Medical Officer
Dr. Wiley Chambers	Acting Division Director
Ms. Joanne Holmes	Project Manager
Dr. Bart Ho	Review Chemist
Dr. Rashmikant Patel	Chemistry Team Leader
Dr. Eric Sheinin	Director, DNDC III
Dr. Elizabeth Ludwig	Medical Officer

The discussion centered on the following issues :

- process validation
- drug substance and drug product test methods and specifications
- equivalence of drug product prepared by different evaporation techniques
- regioisomers and enantiomers

Dr. David Dolphin presented the BPD-MA synthetic process and the rationale for QLT's proposal to designate the [redacted]CD diester as the key intermediate, and to validate Step 4 of the process.

The following questions were asked of the Agency:

1. Does the Agency agree that BPD [redacted]CD diester A- ring can be considered the key intermediate?
2. Does the Agency agree that process validation can begin at Step 4?

[redacted]

Dr. Dev Singh presented a brief description of the formulation process, and outlined the proposed test methods and specifications for drug substance and drug product.

The following question was asked of the Agency:

Are the proposed methods adequate for characterization of the drug substance and the drug product?

The Agency agreed that the proposed test methods for analysis of drug substance were adequate, with the exception of the ID test, in which the HPLC retention time of the sample must correspond to that of a known standard of BPD-MA. A specific ID

test is required. QLT proposed, and the Agency agreed, that the UV/VIS absorption spectrum of the sample would provide sufficient information.

The Agency stated that a related compound specification of 3% was within the acceptable range. It is not necessary to include specifications for synthetic process impurities in the drug product specifications, however, specifications for those compounds which are degradation products, if detected, should be included.

Dr. Singh presented an overview of the formulation of BPD-MA (verteporfin) for Injection, and described the proposed change in evaporation techniques. He outlined the analytical methods to be used to demonstrate the equivalence of the finished product prepared by the current (thin film) and proposed [redacted] methods.

The following question was asked of the Agency:

Will the proposed analytical comparisons be sufficient to demonstrate equivalence of the two evaporation techniques?

The Agency agreed that the proposed methods were acceptable. The proposed scale up of the formulation process afforded by the [redacted] method (5x) was also acceptable.

Dr. Julia Levy presented an overview of the pharmacology and toxicology studies that have been carried out on the regioisomers and enantiomers of BPD-MA.

The following question was asked of the Agency:
Will any additional testing be required on the individual regioisomers and the enantiomers?

The Agency had no immediate requirements for additional studies, however it was felt that some pharmacokinetic data on the enantiomers would be useful.

The Agency agreed that batches of 15 mg vials containing drug product prepared by the thin-film process would be acceptable as primary stability batches for the NDA.

QLT agreed that reconstituted product stability studies will be carried out to support labeling.

As EPG has not previously been used in an approved drug product, the Agency suggested that this ingredient should be treated as a new chemical entity. QLT informed the Agency that the precursor to EPG (Egg phosphatidyl choline, EPC) has been used in an approved product (Intralipid), and will provide the Agency with the relevant information for the Agency's consideration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

*FOR FDA USE ONLY

APPLICATION NUMBER
NDA 21-119

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
QLT PhotoTherapeutics Inc.	August 14, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
604-872-7881	604-707-7373

APPLICANT ADDRESS *(Number, Street, City, State, Country, and ZIP Code or Mail Code, and US License number if previously issued):*

c/o Scott L. Gelbrand, Attorney
Perkins Coie, LLP
1201 Third Avenue, 40th Floor
Seattle, WA 98101-3099

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, State, and ZIP Code telephone & FAX number)* IF APPLICABLE

Mr. Jonathan S. Kahan
Hogan & Hartson
555 Thirteenth Street, N.W.
Washington, DC, USA 20004-1109
tel: (202) 637-5794 fax (202) 637-5910

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
verteporfin	VISUDYNE™

CHEMICAL/BIOCHEMICAL NAME *(If any)*	CODE NAME *(If any)*
benzoporphyrin derivative monoacids A ring	CL 318,952

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
sterile lyophilized cake	15 mg	intravenous

PROPOSED INDICATIONS FOR USE:
Treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV)

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGIC APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 255 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicated whether the site is ready for inspection or, if not, when it will be ready.

See attachment following Page 2 of this form.

Cross References (list related License Application, INDs, NDAs, PMAs 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See attachment following Page 3 of this form.

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
X	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) 2 PreMarket Applications – part of 3-part combination product

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Jonathan Kahan	Jonathan Kahan, Hogan & Hartson	8/15/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
555 Thirteenth Street, N.W., Washington, DC, USA 20004-1109	(202) 637-5794

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
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APPLICATION NUMBER

NDA 21-119

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TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
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Perkins Coie, LLP
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NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Verteporfin	VISUDYNE™

CHEMICAL/BIOCHEMICAL NAME *(If any)*	CODE NAME *(If any)*
benzoporphyrin derivative monoacids A ring	CL 318,952

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
sterile lyophilized cake	15 mg	Intravenous

PROPOSED INDICATIONS FOR USE:

Treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV)

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
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☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

Amendment to Financial Disclosure (NDA Section 8.1.3)

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NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Washington, DC 20201

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