DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 19 1999

QLT PhotoTherapeutics, Inc.
c/o Mr. Jonathan Kahan
Hogan & Hartson
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109

Re: P990049
Coherent Opal Photoactivator Diode Laser and LaserLink Adapter
Filed: August 20, 1999

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of your premarket approval application (PMA). We regret to inform you that on the basis of this review, we believe that the PMA lacks information needed by CDRH to effectively complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use. While the deficiencies outlined below do not preclude further review of your PMA, if left uncorrected, they may ultimately preclude approval.

Our review noted the following deficiencies and, in order to correct these deficiencies we request the responses as indicated:

1. The devices for which approval is being requested include the Coherent Opal Photoactivator and the modified Coherent LaserLink. Please revise your trade name section to include both of these names.

2. Please clarify if the output wavelength is a single value, for example [redacted] .n or is it a range such as 689 +/- 3 nm. Both forms have been used in various sections of the PMA application. The description of the output wavelength should be consistent throughout the application.

3. It is recommend that the diode materials be identified with full names when first identified and with abbreviations when used subsequently.

4. Under section 2.1.3, Calibration, it is stated that the laser power display is calibrated to indicate laser power delivered from the attached laser delivery system. Please clarify if this means at the slit lamp focal plane, as stated under Power to Tissue in the laser specifications, Table 1.

5. You can not use the generic term "equivalent" when describing either the compatible slit lamps or contact lenses. You should provide specific specifications for these compatible accessories.

6. The full indication for use statement should be used throughout the application. Using a shortened version could lead to confusion in terms of the patient population for which approval is being requested. Please revise your application to use only the full indications for use.

7. In the second paragraph in section 2.3, Properties of Device, you have stated that "Light and drug dose alone cause no damage." I believe this would be better stated as "Light or drug dose alone cause no damage." It is the combination of light and drug that provides the therapeutic benefit in this treatment.

8. In section 2.4.2 on page 27, Figure 1, "Opal Optical Schematic" is mentioned but has not been included in the document. Please clarify this apparent omission.

9. Please clarify item 5 in Preoperative Instructions Section of the Operator's Manual. Item 5 reminds user to verify the drug protocol parameters as described in the System Preferences section. What is meant by verification of the drug parameters, since the laser settings will vary according to treatment spot size?

10. Please clarify what is the "zoom lens" mentioned in Appendix 5.2, Section 3, Introduction. From the wording in this section, it would appear that the "zoom lens" is critical in obtaining the correct laser dose for activation of verteporfin. Review of the Operator's Manual for the Coherent Opal Photoactivator does not identify such a lens and no adjustment of a zoom lens is mentioned in the directions for use for the Coherent Opal Photoactivator.

11. Please certify whether or not your software is Y2K compatible.

This letter reflects the current progress of our review of your application. Please be advised that further substantive review of your application or any response to this letter may result in additional deficiencies.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any

amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

Information correcting the above deficiencies should be submitted in the form of an amendment. All correspondence regarding this PMA should be submitted in 3 copies in the form of a PMA amendment to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this deficiency letter, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours,

/S/

James E. Dillard III
Acting Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc:
NDA 21-119
HFD-550/Div Files

APPEARS THIS WAY
ON ORIGINAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

ORIG AMENDMENT
BC

November 24, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is our response to the fax received on November 23, 1999 with questions from the Review Chemist.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (letter only)
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (desk copy by fax)

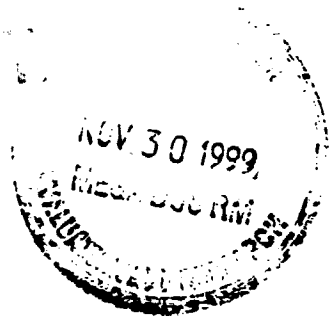
DUPLICATE

ORIG AMENDMENT

BL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

BEST POSSIBLE COPY



November 26, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Revisions to Labeling
Package Insert

Dear Dr. Chambers:

Enclosed please find three copies of an amendment to the VISUDYNE labeling. Edits by FDA to the draft (August 14, 1999) version of the Package Insert are accepted with the exception of the few revisions noted in strikeout and underlined text. Also provided are comments to support the proposed revisions. At your convenience, we wish to arrange for a teleconference to discuss these or any other changes to the labeling.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: Jonathan Kahan, U.S. Representative, Hogan & Hartson (letter only)
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER (complete copy via fax)
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA (complete copy via fax)

DUPLICATE

ORIG AMENDMENT
BC

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
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www.qltinc.com

November 29, 1999

NOV 30 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

BEST POSSIBLE COPY

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a response to a fax received on October 5, 1999 with a question from the Review Chemist.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

for

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (Desk Copy)

DUPLICATE

ORIG AMENDMENT

BP

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REC'D
DEC 01 1999
MEGA DOC RM
EVALUATION AND RESEARCH

November 29, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Pharmacology/Toxicology

Dear Dr. Chambers:

Attached is our response to the pharmacology/toxicology comments received by fax November 19, 1999 with questions from the Preclinical Reviewer.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: Jonathan Kahan, U.S. Representative, Hogan & Hartson (letter only)

DUPLICATE

QLT PhotoTherapeutics Inc. 520 West 6th Avenue Vancouver, BC Canada V5Z 4H5 t 604.872.7881 f 604.875.0001 www.qltinc.com

DRUG AMENDMENT

BP

November 30, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Pharmacology/Toxicology

Dear Dr. Chambers:

Enclosed is our response to the pharmacology/toxicology comments received by fax on October 20, 1999 with questions from the Preclinical Reviewer.

Also attached are the following:

1. Final report (Appendix 3 of this submission) to a draft report submitted in the preclinical Presubmission of May 28, 1999. The draft report is Reference 353 and is located in Presubmission Volume 53, Page 1.

2. Amendment (Appendix 4 of this submission) to a final toxicology study report. This amendment was the result of a comment received from FDA by fax on October 4, 1999. Our response of October 12 indicated this amendment to the report would be forthcoming. The report that is being amended is Reference 330, located in Presubmission Volume 41, Page 11.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: Jonathan Kahan, U.S. Representative, Hogan & Hartson (letter only)

DUPLICATE

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ORIG AMENDMENT
SU

December 1, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

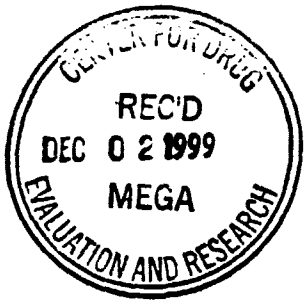
NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
4-Month Safety Update

Dear Dr. Chambers:

Enclosed find three copies of the 4-month safety update. Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.



David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (letter only)

Jonathan Kahan, U.S. Representative, Hogan & Hartson
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

QLT PhotoTherapeutics Inc.
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December 10, 1999

BP

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Pharmacology/Toxicology

Dear Dr. Chambers:

Enclosed is our response to the pharmacology/toxicology comments received by fax on December 9, 1999.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

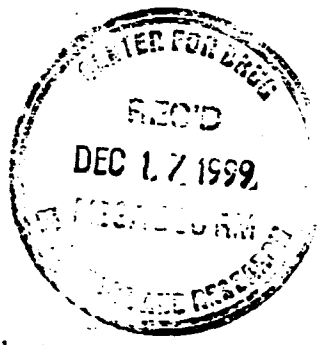
QLT PHOTOTHERAPEUTICS INC.

DUPLICATE

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: Jonathan Kahan, U.S. Representative, Hogan & Hartson (letter only)

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com



December 14, 1999

NDA DRUG AMENDMENT

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

BI

BEST POSSIBLE COPY

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
CMC/Microbiology

Dear Dr. Chambers:

Enclosed please find 3 copies of 2 volumes each, containing information requested by Dr. Carole Vincent regarding the validation of sterilizing equipment used in the manufacture of VISUDYNE™ at Parkedale Pharmaceuticals Inc, Rochester Michigan.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

Elizabeth M. Waterfield, B.Sc.
Manager, Regulatory Affairs

ORIGINAL

cc: Jonathan Kahan, U.S. Representative, Hogan & Hartson (letter only)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

DGRD GSOB

DEC 17 1999

Mr. Martin A. Kaufman
Director, Regulatory Affairs - Devices
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5

Re: P990048 – Zeiss VISULAS 690s and VISULINK PDT

Mr. Kaufman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance (OC) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the Quality System (QS)/GMP regulation.

The Division of Enforcement II (DOE) of the OC has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a QS/GMP inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. This letter is independent of correspondence you have received or will receive from ODE regarding the status of the review of the entire PMA. **Please be aware that a QS/GMP inspection will not be scheduled until an adequate response to this deficiency letter is received by CDRH and your PMA is filed by ODE.** In addition, you should be aware that your response to this deficiency letter does not affect the status of the ODE review (i.e., the filing decision). We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OC review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment **AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OC REQUEST IN YOUR REFERENCE BLOCK.** FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44 (g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted.

If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: Field Programs Branch, OC
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd., Room #120
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter may result in additional deficiencies being identified.

If you have any questions concerning this deficiency letter, please contact either Vertleen Covington at (301) 594-4695 or Allen T. Wynn at (301) 594-4695.

Sincerely yours,

/S/

Kathy Poneleit
Director
Premarket Approval
Application Program
Office of Device Evaluation
Center for Devices and
Radiological Health

APPEARS THIS WAY
ON ORIGINAL

DEFICIENCY LIST

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has completed a review of your response to a Deficiency Letter dated October 12, 1999, concerning your PMA P990048. Please address the following and provide the requested documentation, where applicable:

Your firm was asked to supply the verification and/or validation protocols used in the manufacturing process for the Zeiss VISULAS 690s Laser and VISULINK PDT [redacted] Adaptors and the documentation to show you had completed the verification or validation processes. You provided a Validation Plan that covered system integration/Final Testing and also referenced related documents covering acceptance testing and final testing. You also supplied a Validation Report. However, your report primarily consisted of signature blocks for assessments of specifications contained in the validation plan that have been signed off as compliant with the current process. No actual documentation was submitted to show you had done any validation processes. Since this is a modular PMA submission, we are not sure that you have actually manufactured product yet. If you have manufactured product and gone through validation or verification processes, please provide the documentation (data) to show that this has been done.

When your firm is inspected, our investigator will want to look at the data for your installation and qualification of your manufacturing equipment. The documents you supplied certified that the equipment met your test requirements, but did not show the actual test results.

They will also want to examine the documentation for training of employees more closely. You explained in your response that German and European law did not permit the submission of training records that identified your employees.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA 21-119

December 22, 1999

Review of P990048 and Amendment 4

Submitted by QLT PhotoTherapeutics, Inc.
For Carl Zeiss, Inc.

Reviewed by Richard P. Felten, DGRD, GSDB
/S/

The devices described in this PMA and Amendments include the Zeiss VISULAS 690s [redacted] Laser and the VISULINK PDT adapter. The original submittal also included the [redacted] adapter which was withdrawn from consideration for approval in Amendment 1 dated October 18, 1999. In addition, Amendment 2, dated November 2, 1999 was provided by company to specifically state that the [redacted] adapter was not used in any of the clinical trials supporting this application and therefore withdrawal of this device does not affect clinical data review.

The VISULAS 690s diode laser and the VISULINK PDT adapter are used in combination with appropriate slit lamps and contact lenses to deliver 689 +/- 3nm laser light to retina for the activation of the drug verteporfin. This combination drug/device system is used for the treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV).

The Zeiss VISULAS 690s diode laser is designed to have an output power of up to 193 mW, this output when combined with the VISULINK PDT adapter and appropriate slit lamp and contact lens will be capable of generating power densities of 600 mW/cm^2 or a treatment dose of 600 J/cm^2 . This energy can be delivered to spot sizes up to 6400 microns.

The devices described in this PMA are modifications of the clinical trial devices with the changes made being based on physician feedback. For the VISULAS 690s diode laser these changes included increase in treatment spot size to 6400 microns, increase in power to 193 mW, and the addition of the dye timer. For the VISULINK PDT adapter the only change was in the coating used on the physician safety filter to improve safety. None of these changes alter the ability of the devices to activate the drug verteporfin. The modified devices have been tested and Zeiss has provided this test data. The data does establish that the modified system does perform identically to the system used in the clinical trial producing the identical wavelength and the corresponding required power for treatment.

Our initial review of this application did identify a number of deficiencies requiring clarification or additional information. These deficiencies were conveyed to company in our deficiency letter dated November 18, 1999. Company has responded to this letter with Amendment 4 dated December 9, 1999. Company has specffically stated that their laser/adapter system is limited to use with Zeiss slit lamps and cannot be used with

[redacted] Company has clarified that the actual output wavelength is more correctly identified as 689 +/- 3 nm. Finally company has clarified a number of statements contained in their application and have agreed to expand the section referencing use of a "zoom lens" by identifying this as the "zoom system" and clearly identifying the adjustment which produces this effect. Company has also provided a revised schematic of Figure 7 of the Operator Manual which better shows the integration of the VISULINK PDT adapter with the VISULAS laser. All of these responses are acceptable and this Amendment adequately addresses our deficiency concerns. In terms of non-manufacturing issues, the information contained in the PMA application is complete and acceptable.

Review of the manufacturing sections of this PMA were performed by Office of Compliance. The initial review of the Zeiss manufacturing sections resulted in a deficiency letter dated October 12, 1999. The response to this letter was dated November 12, 1999 and received in our Document Mail Center on November 15, 1999. A review of these responses has been completed and a second manufacturing deficiency letter was sent the company dated December 17, 1999. A copy of the remaining deficiency is attached to this review. The major item still to be addressed is the company's failure to provide the actual test data supporting their validation and verification of the manufacturing process for their system.

At this time, from an Office of Device Evaluation stand point, this PMA is Approvable dependent on satisfactory responses to the manufacturing deficiencies and completion, if necessary, of a GMP inspection.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEFICIENCY LIST

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has completed a review of your response to a Deficiency Letter dated October 12, 1999, concerning your PMA P990048. Please address the following and provide the requested documentation, where applicable:

Your firm was asked to supply the verification and/or validation protocols used in the manufacturing process for the Zeiss VISULAS 690s Laser and VISULINK PDT or [redacted] Adaptors and the documentation to show you had completed the verification or validation processes. You provided a Validation Plan that covered system integration/Final Testing and also referenced related documents covering acceptance testing and final testing. You also supplied a Validation Report. However, your report primarily consisted of signature blocks for assessments of specifications contained in the validation plan that have been signed off as compliant with the current process. No actual documentation was submitted to show you had done any validation processes. Since this is a modular PMA submission, we are not sure that you have actually manufactured product yet. If you have manufactured product and gone through validation or verification processes, please provide the documentation (data) to show that this has been done.

When your firm is inspected, our investigator will want to look at the data for your installation and qualification of your manufacturing equipment. The documents you supplied certified that the equipment met your test requirements, but did not show the actual test results.

They will also want to examine the documentation for training of employees more closely. You explained in your response that German and European law did not permit the submission of training records that identified your employees.

cc:
NDA 21-119
HFD-550 Div Files

APPEARS THIS WAY
ON ORIGINAL

NDA 21-119

December 22, 1999

Review of P990049 and Amendment 2

Submitted by QLT PhotoTherapeutics, Inc.
For Coherent Medical

Reviewed by Richard P. Felten, DGRD, GSDB
/S/

The devices described in this application include the Coherent Opal Photoactivator diode laser and the modified Coherent LaserLink adapter. These devices in combination with the appropriate slit lamps and contact lenses are used to deliver 689 +/- 3 nm light to the retina for the activation of the drug verteporfin. This combination drug/device system is used for the treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV).

The Opal Photoactivator diode laser uses [redacted] to generate the 689 +/- 3 nm wavelength. The laser has a maximum output of 0.3 Watts thus insuring that the minimum of 200 mW is available for therapy. The laser in combination with the LaserLink adapter, slit lamps and contact lenses is capable of generating a power density up to 600 mW/cm^2 or a treatment dose of up to 600 J/cm^2. This device system is capable of treating retinal spots of up to 6400 microns.

The device which is the subject of this application, the Opal Photoactivator and the modified Coherent LaserLink adapter are modification of the devices used in the Phase I/II and Phase III clinical trials. In terms of the laser system, the Opal Photoactivator diode laser is a diode laser having the same output wavelength as the system used in the clinical trials. Coherent has provided test data establishing the output characteristics of both systems and the identity of the Opal system compared to the system used in the clinical trials. Other modifications made to the laser system were:

1. the use of microprocessor to control and perform all start-up functional and safety tests,
2. addition of a second diode thermistor to eliminate the single point failure of one thermistor,
3. addition of a lens size display/entry on console to simplify user interface,
4. add an infusion timer for user convenience,
5. preset treatment parameters again to simplify user interface, and
6. use of an intermittent aiming beam.

All of these changes have been tested and documented. The information provided has established that the Opal Photoactivator does generate the identical wavelength and energies as were used in the clinical trials.

In terms of the modified Coherent LaserLink, the device described in this application has been modified from the device used in the clinical trials. As with the Opal laser, these modifications were suggested by users and are designed to improve both safety and user interface. The modifications made to the LaserLink adapter were addition of a spot size sensor to measure spot size as the slit lamp focal plane and the addition of a broken fiber sensor which measures fiber transmission and has built in limits that would detect a broken fiber based on loss of transmission. Again these changes have been described and tested.

The initial review of this application identified a number of deficiencies in the Operator Manual and in the information provided describing the use of the Opal Photoactivator and modified Coherent LaserLink adapter. These deficiencies were conveyed to the company by letter dated November 19, 1999. Amendment 2 to this PMA contains the responses to these deficiencies. Coherent has clarified issues regarding output wavelength, use of the term "zoom lens", and the statement in the Operator's Manual to verify drug parameters. In addition company has agreed to drop the term "equivalence" when used with slit lamps or contact lenses, has agreed to use the full indication for use statement, and has agreed to add the full name of the diode system. Company has also added the requested Opal Optical Schematic and has verified that their software is Y2K compatible. All of the responses are acceptable and satisfy the issues raised in the deficiency letter. In terms of non-manufacturing issues, the information contained in the PMA application is complete and acceptable.

Review of the manufacturing sections of this PMA were performed by Office of Compliance. The initial review of this material resulted in a deficiency letter, dated October 12, 1999. Coherent, through QLT, has responded to this letter and their response was on December 10, 1999. At this time the response is still under review. A copy of the manufacturing deficiencies is attached to this review.

At this time, from an Office of Device Evaluation stand point, this PMA is Approvable dependent on satisfactory responses to the manufacturing deficiencies and completion, if necessary, of a GMP inspection.

APPEARS THIS WAY
ON ORIGINAL

DEFICIENCY LIST

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your original combined drug-device application part II, for the Coherent Opal Photoactivator Laser Console and LaserLink Adapter (P990049), dated August 15, 1999. Please address the following and provide the requested documentation, where applicable:

1. On page 85 of volume 2, your application indicates that product performance and product reliability complaints should not be considered "safety complaints". These types of complaints could be malfunctions that could impact patient safety. Please provide your logic in not considering these to impact patient safety.

2. On pages 368-370 of volume 2, your firm provided documentation of some of its software validation test plan. Several items have the notation, "will test on next version". Why were they not tested on this version? Were they ever tested and where is the documentation to show this?

3. On pages 385-386 of volume 2, your firm provides a list of anomalies or design features noted during validation of the OPAL system that you state could result in user error and system misuse. However, there is a handwritten comment, "NOTE: None of the anomalies listed will cause any harm or injury to the patient." There is no explanation why you believe this. There is no proof to show that these features will not cause problems. You need to explain why you believe these features will not cause problems.

4. Pages 117-123 of volume 3, provide lists of employees and their training status for other laser models manufactured by your firm. Some of the training is listed as "C", certified, and some as "N", training not complete. I'm not sure what you are trying to show here. Have any employees been trained on the Coherent Opal Photactivator Laser Console? Does some of the training regarding other laser models relate to the Opal? If this is true, you need to specify which types of training are relevant to the Opal. Also, the meaning of "N" is not clear. When is the training expected to be complete?

5. Page 232 of volume 3 provides a flowchart for electrostatic discharge control. It indicates that employees are required to document testing wrist straps when used, but are not required to document testing of heel straps prior to entering the work area? Why the discrepancy?

6. Page 234 of volume 3 contains the Coherent Opal Photoactivator Installation Procedure. In it, the dimensions of the device are only listed as L, H and W and the weight as XX. Yet further in the application (i.e., Page 236), there are known measurements applied to these designations. Why were these omitted from the installation procedure?

7. Page 264 of volume 3 contains the Opal Label sheet. There are some hand-written comments that are not clear. Under the console labels, there is a note "Human Use only Side

of ?" and there is another note that says "CE Label Removed ?" What do these notes mean and why they are there?

8. Appendix 97 contains service statistics for other models of lasers manufactured by QLT. No statistics for the Opal Photoactivator Laser Console or LaserLink Adapter are included. I'm not sure why you included this information in this application. It doesn't seem relevant.

cc:
NDA 21-119
HFD-550-Div Files

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

FINAL EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: January 10, 2000

NDA 21-119
HFD-550
SPONSOR: QLT PhotoTherapeutics Inc,
Product Visudyne
Chemical Type: 1
Potential: P
Indications : Treatment of Choroidal Neovascularization (CNV)
Project Manager: Lori Gorski
Medical Officer: Wiley Chambers

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-119 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, CRFs , and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between division medical officer, Dr. Wiley Chambers and DSI reviewer, Dr. Jose Carreras.

NAME	CITY	Protocol	CL
[redacted]	Miami, Florida	[redacted]	NAI
[redacted]	Baltimore, Maryland	[redacted]	NAI

Key to Classifications
NAI = No deviation from regulations
VAI = Minor Deviation(s) from regulations

BEST POSSIBLE COPY

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver, BC Canada V5T 4T5
t 604.872.7881 f 604.875.0001 www.qlt.nc.com

NC

January 31, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Financial Disclosure

Dear Dr. Chambers:

As agreed on January 28, 2000 with Linda Carter from the Office of Drug Evaluation I (Tel: 301.594.6758), below is additional information required to describe the nature of the financial disclosure information provided in the NDA (Section 8.1.3, Volume 63, Pages 14-21). The eight investigators for whom this information is provided are listed below and the FDA Disclosure Form 3455 included in the NDA are again provided in this amendment. We apologize for neglecting to include this required information in the original NDA submission.

[redacted] - for who the significant-payments box is checked (refer to the attached form).
[redacted] is a consultant for QLT and received approximately [redacted] of his base salary through this arrangement, a total of approximately [redacted] per year during conduct of the study.

[redacted] - for who the proprietary-interest box is checked (refer to the attached form).
[redacted] is named on a US patent submitted for use of verteporfin to angiographically diagnose choroidal neovascularization (CNV). This technology is not in use and the patent has not been issued.

[redacted] - for who the proprietary-interest box is checked (refer to the attached form).
[redacted] is named on a US patent issued for use of any green dye, including verteporfin, for photodynamic therapy (PDT) of CNV secondary to age-related macular degeneration (AMD).

[redacted] - for who the significant-equity-interest box is checked (refer to the attached form).
[redacted] purchased significant QLT stock [redacted] during the conduct of the masked portion of the pivotal Phase III studies.

.../p.2

[redacted]- for who the proprietary-interest box is checked (refer to the attached form).
[redacted]s named on the two patents identified above: the US patent submitted for use of verteporfin to angiographically diagnose CNV and the US patent issued for use of any green dye, including verteporfin, for PDT of CNV secondary to AMD.

[redacted]- for who the significant-equity-interest box is checked (refer to the attached form).
[redacted]purchased significant QLT stock prior to the initiation of the pivotal Phase III studies.

[redacted] - for who the proprietary-interest box is checked (refer to the attached form).
[redacted]is named on the US patent issued for use of any green dye, including verteporfin, for PDT of CNV secondary to AMD.

[redacted] for who the significant-equity-interest box is checked (refer to the attached form).
[redacted]purchased significant QLT stock during the conduct of the masked portion of the pivotal Phase III studies.

The above disclosed arrangements or interests are not expected to have biased the clinical results since 1) there was no evidence during the conduct of the pivotal Phase III studies that investigators were unmasked and 2) the analysis of covariance that was used to evaluate the continuous variable of visual acuity change from baseline included a treatment-by-center interaction term to test for homogeneity of response among the centers. This interaction term was not significant.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver, BC Canada V5T 4T5
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f 604.875.0001
www.qltinc.com

February 1, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Draft Promotional Material

Dear Dr. Chambers:

Enclosed please find a single copy of the draft promotional material for VISUDYNE™ as requested in your fax of January 13, 2000. Two complete copies have been forwarded directly to DDMAC.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 4 2000

[redacted]
John Hopkins University
The Wilmer Ophthalmological Institute
600 N. Wolfe Street, Maumenee 713
Baltimore, Maryland 21287-9275

Dear Dr.[redacted]

Between November 15 and 19, 1999, Ms. Lynette P. Salisbury, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study [redacted] of the investigational drug Visudyne (verteporfin), performed for QLT PhotoTherapeutics Inc, This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report and your November 24, 1999, written response to the items listed on the Form FDA 483. We note that you acknowledged mistakes were made and promised you will exercise more care to ensure that the problems noted will not recur in future studies.

We appreciate the cooperation shown Investigator Salisbury during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN: 3002829539

Field Classification: VAI

Headquarters Classification:
__ _1) NAI
__x_2)VAI-no response required
____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
____ inadequate consent form
____ inadequate drug accountability records
__X_ failure to adhere to protocol
_____ inadequate records
_____ failure to report ADRS in the case report form
__X__ Other (specify) Administered study drug to subject not enrolled in the study

cc:
HFA-224
HFD-550 Review Div. Dir.
HFD-550/ MO/Chambers
HFD-550/ PM/Gorski
HFD-550/Doc. Rm. NDA # 21-119
HFD-45 r/f
HFD-47 c/r/s GCP file# 09940
HFD-47/Carreras
HFD-47/Currier
HFR-CE250/Draper
HFR-CE250/Glascow
HER-CE250/Salisbury

Note to Rev. Div. M.O.

This investigator enrolled 39 subjects in the study. One subject refused treatment and was terminated. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

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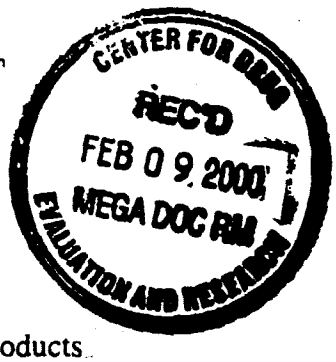

February 8, 2000

BL

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Revised Package Insert

Dear Dr. Chambers:

Enclosed please find three copies of the revised Package Insert for VISUDYNE™ (verteporfin for injection) per our discussion of February 7, 2000.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

D. Mitchell

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (complete copy)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

MEMORANDUM

FROM: Andrea B. Weir, Ph.D., HFD-550, Pharmacology Team Leader

/S/ 2-14-00
2/18/00

TO: Wiley Chambers, MD, HFD-550, Deputy Director
Mary Jane Walling, ODE V, Associate Director for Regulatory Affairs

SUBJECT: NDA 21-119/Response to Administrative Review of Action Package

---

The following is the Pharmacology/Toxicology response to Abby Jacobs' comments on the labeling of Visudyne. The paragraph numbers used in this memorandum correspond to the paragraph numbers that Dr. Jacobs used in her memorandum. A copy of Dr. Jacobs' memorandum is attached for reference.

I. Pharmacology/Toxicology concurs that the route of administration for the reproductive toxicity studies, intravenous, should be included in the labeling.

II. The comments regarding the clinical pharmacology/clinical studies are noted; however, Pharmacology/Toxicology does not recommend any labeling changes based upon these comments.

III. The comments regarding information for patients are noted; however, Pharmacology/Toxicology does not recommend any labeling changes based upon these comments.

IV. The comments regarding adverse reactions reported more frequently with Visudyne are noted; however, Pharmacology/Toxicology does not recommend any labeling changes based upon these comments.

V. The comments regarding the dosage and administration are noted; however, Pharmacology/Toxicology does not recommend any labeling changes based upon these comments.

Attachment

cc:

Gorski/HFD-550	NDA 21-119
Wilson/HFD-550	HFD-550/Div Files
	HFD-105/ODEV/DeLap
	HFD-550/DD/Midthun

Comments on the labeling of NDA21-119 Visudyne Verteprofin 1/19/00
From A. Jacobs

***I think the clinical experimental design/protocol does not allow one to conclude that Visudyne (a benzoporphyrin-laser treatment) is beneficial for macular degeneration. The placebo arm of the study is not an appropriate placebo. It may be necessary to have an untreated arm to conclude that laser plus dye is beneficial for the condition. No improvement was seen in the drug treated group, only less deterioration (12%) than laser alone (33%) (which may have been harmful relative to no treatment). An untreated arm was not included. If laser treatment alone is harmful, then drug treatment is ameliorating an iatrogenic effect, by absorbing the laser light. I also found a June 1999 paper that reported that eyes treated by macular photocoagulation with a green-light laser (Visudyne used a red-light laser) did less well than NO treatment at all. One could conclude that the so-called placebo (sham-light-treated) group was not a placebo to be compared against, since the light doses that the eyes in the two groups received were not at all similar. See II. A. below.

I. Pharm tox portion of labeling:

A. Pregnancy: 1st paragraph, line 1. The route of administration should be added -- intravenously administered?

B. Pregnancy: 2nd paragraph, line 1. The route of administration should be added -- intravenously administered?

II. Clinical pharmacology/clinical studies

A. p. 8 It was noted in the pharm/tox review that the verteprofin protected cells from light in a dose-related manner. Thus, one explanation for the placebo (sham-light -only treated) persons (eyes) doing more poorly than verteporfin-treated persons (eyes) (greater severe vision loss) is that the light dose at 689 nm, which the eyes of the sham-treated persons are receiving, is greater than that for those receiving drug. Without a totally untreated group, from the clinical studies reported, one could just as appropriately conclude that verteporfin is protecting eyes from induced laser light damage, as much as having anything to do with macular degeneration. The studies conducted in normal monkeys or monkeys in which CNV was induced were not reassuring. The studies in normal monkeys did not have any untreated controls and histopathologic changes after 2, 3 and 5 weeks with light alone were attributed to postmortem processing. Furthermore, the studies in monkeys did not measure visual acuity or anything else after one year. Monkeys in which CNV was induced with an argon laser, might not be sensitive to further damage by laser alone.

III. Information for patients

A. p. 10 What is the basis for advising patients to expose their skin to ambient indoor light? Perhaps the data supporting this are somewhere in the package, but I could not find them. Photobleaching may or may not result in major breakdown of the drug or more rapid elimination of the drug. I could not find any information on identity or excretion of photobleached products of verteprofin. The possible photobleaching products would depend on the wavelength and intensity of the light. Some photobleached products may still absorb light and generate free radicals, albeit at lower efficiency. Each chemical structure has its own set of photobleaching products and one cannot extrapolate from other chemicals or drugs. At the same time the drug is being photobleached, the skin is being exposed to the free radicals generated in the skin. Just because the skin is not red does not mean that damage is not being produced. Damage may be cumulative. Without any demonstrated benefit, there is an added risk.

IV. Adverse reactions reported more frequently with Visudyne

A. p. 12 Ocular treatment site: Why is severe vision loss listed here-isn't this the primary endpoint? If true, it is in conflict with clinical studies on page 8 that reported 33% severe vision loss with placebo (sham with light) and 12% with Visudyne.

V. Dosage and administration

A. Visudyne administration p. 14. 1st paragraph. It is recommended that reconstituted Visudyne be inspected visually for particulate matter and discoloration prior to administration. It also says that the reconstituted Visudyne material is an opaque dark green solution. Is it possible to examine an opaque dark green solution for either particulate matter or discoloration?

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

AMENDMENT

SU

QLT PhotoTherapeutics Inc.
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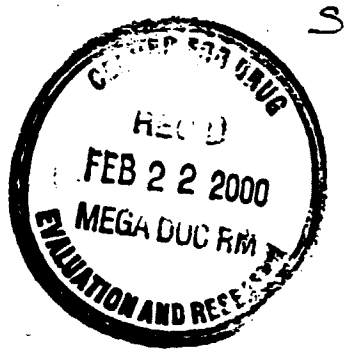

February 18, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Updated Safety and Efficacy Data

Dear Dr. Chambers:

Enclosed please find three copies of an amendment to this application in response to the approvable letter issued by the Agency on February 11, 2000. This amendment addresses the request for updated safety and efficacy information. Responses to all application deficiencies noted were addressed in the amendment submitted January 28, 2000, including revised labeling. The labeling was again revised and submitted February 8, 2000.

Based on the new information submitted herein, we have made a few more revisions to the Package Insert. We have updated the strikeout version submitted February 8 (maintaining the strikeouts from February 8) and this is included in this submission.

We also acknowledge receipt of the Chemistry Reviewer's fax of February 15, 2000 regarding the analysis of impurities in [redacted] We hereby commit to providing the requested information by September 1, 2000.

Draft promotional materials for VISUDYNE therapy were submitted on February 1, 2000 to both the reviewing division application and to DDMAC as requested in the approvable letter.

.../p.2

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver. BC Canada V5T 4T5
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March 2, 2000

NDA ORIG AMENDMENT

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

BM

MAR 0 3 2000

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment

Dear Dr. Chambers:

Attached is our response to the Agency's fax dated February 28, 2000 concerning the final report for Study TX-98008.

If you have any questions about this submission please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell
Senior Manager, Regulatory Affairs

DUPLICATE

cc: (cover letter)
Jonathan Kahan, US Representative, Hogan & Hartson
Richard Felten, Senior Reviewer, ODEI, CDRH, FDA
Lori Gorski, CDER Division of Analgesics,
Anti-inflammatory and Ophthalmic Drug Products

QLT PhotoTherapeutics Inc.
887 Great Northern Way
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March 3, 2000

NEW CORRESP

NC

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Draft Promotional Material

Dear Dr. Chambers:

Enclosed please find a single copy of revised draft promotional material for VISUDYNE™ in response to DDMAC's letter of February 17, 2000. Two complete copies have been forwarded directly to DDMAC.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

ORIGINAL

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NC

March 6, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment

Dear Dr. Chambers:

Enclosed please find three copies of the reply to the Chemistry Reviewer fax of February 15, 2000.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl, Ph.D.
Senior Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (letter only)
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (desk copy by fax)

QLT PhotoTherapeutics Inc.
887 Great Northern Way
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www.qltinc.com

March 7 2000

NEW CORRESP

NC

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Draft Promotional Material

Dear Dr. Chambers:

Enclosed please find a single copy of revised draft promotional material for VISUDYNE in response to DDMAC's letter of February 17, 2000. Two complete copies have been forwarded directly to DDMAC.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

ORIGINAL

PHARMACOLOGY/TOXICOLOGY REVIEW
PHARM/TOX AMENDMENT - March 3, 2000

MAR 15 2000

TO:	**Lori Gorski**	/S/
FROM:	**Susan Wilson**	
THROUGH:	**Andrea Weir**	/S/
DATE:	**March 14, 2000**	15 Mar 00
RE:	**N21-119** **Visudyne; QLT Phototherapeutics Inc.**	
ACTION ITEM:	**No action indicated at this time**	

4/4 2000

This amendment addresses a request faxed to the Sponsor on February 28, 2000. The request [in bold-face] and the response are provided below.

1. **The Sponsor will be asked to provide a statement that indicates whether or not there were any changes from the draft report to the final for study TX-98008 [Test for chemical induction of gene mutation at the HGPRT locus in cultured Chinese Hamster ovary (CHO) cells with and without metabolic activation with a confirmatory assay].**

Response: Although there were changes in the final report [e.g. signature pages, addition of test article purity, dosing solution analysis, etc.], the Sponsor indicates that no changes were made which impacted the study conclusions.

Reviewer's Comment - This response is adequate.

cc:
NDA 21-119
HFD-550:DivFiles
HFD-550:DivDir/KMidthun
HFD-550:DepDir/MO/WChambers
HFD-550:PT/SWilson
HFD-550:CSO/LGorski

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

TO:	**Lori Gorski** /S/ 14 Mar 2000
FROM:	**Susan Wilson**
THROUGH:	**Andrea Weir** /S/ 3-15-00
DATE:	**March 14, 2000**
RE:	**N21-119 Label – Approvable Letter – February 11, 2000 Visudyne; QLT Phototherapeutics Inc.**
ACTION ITEM:	**Revisions to be incorporated into the label**

The following revisions should be incorporated into the proposed labeling.

p. 11, paragraph 2 – Carcinogenesis, Mutagenesis, Impairment of Fertility - Replace [redacted] with **verteporfin for injection**– Sentence should read "No effect on male or female fertility has been observed in rats following intravenous administration of [redacted] **verteporfin for injection"**

p. 11, paragraph 3 - Pregnancy category: Teratogenic Effects- line 1 – Replace VISUDYNE with **verteporfin for injection** and insert **intravenously** – Sentence should read "Rat fetuses of dams administered [redacted] **verteporfin for injection intravenously** at ≥10 mg/kg/day during organogenesis"

p. 11, paragraph 4 - Pregnancy category: Teratogenic Effects- line 2 - Replace VISUDYNE with **verteporfin for injection** and insert **intravenously** – Sentence should read "In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received [redacted] **verteporfin for injection intravenously** at ≥10 mg/kg/day during organogenesis."

cc:
NDA21-119
HFD-550:DivFiles
HFD-550:DivDir/KMidthun
HFD-550:DepDir/MO/WChambers
HFD-550:PT/SWilson
HFD-550:CSO/LGorski

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 2 1

[redacted]
Bascom Palmer Eye Institute
900 N.W. 17th Street
Miami, Florida 33136

Dear Dr. [redacted]

Between November 15 and 18, 1999, Mr. Roy R. Rinc, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study [redacted] of the investigational drug Visudyne (verteporfin), performed for QLT PhotoTherapeutics Inc,. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Rinc during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN: 3002830203

Field Classification: NAI

Headquarters Classification:
__X_1) NAI
____2)VAI-no response required
____3)VAI-response requested

cc:
HFA-224
HFD-550 Review Div. Dir.
HFD-550/ MO/Chambers
HFD-550/ PM/Gorski
HFD-550/Doc. Rm. NDA # 21-119
HFD-45 r/f
HFD-47 c/r/s
HFD-47/Carreras
HFD-47/Currier
HFR-SE250/Chappell
HFR-SE2585/Torres
HER-SE2575/Rinc

f:c:mb:3/20/00

Note to Rev. Div. M.O.

This investigator enrolled 39 subjects in the study. One subject was discontinued due to old age and one subject for a severe adverse drug event. The field investigator examined six subjects' records.

Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

March 23, 2000

Review of P990048 and P990049

Submitted by QLT PhotoTherapeutics, Inc.

Reviewed by Richard P. Felten, DGRD, GSDB

/S/

These PMA's are the device section of the NDA submitted by QLT PhotoTherapeutics for their combination drug/device system for the treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV). The photosensitive drug to be used in this therapy has the trade name VISUDYNE. The laser systems, including slit lamp adapters, which are described in these PMA's are intended to provide the activating light needed for drug activation to provide the intended therapeutic effect.

P990048 is for the Zeiss VISULAS 690s diode laser and the VISULINK PDT slit lamp adapter.

P990049 is for the Coherent Opal Photoactivator diode laser system and the Coherent Opal LaserLink slit lamp adapter.

Review of these PMA's did identify minor deficiencies which were communicated to the company by letters dated November 18, 1999 for the Zeiss PMA and November 19, 1999 for the Coherent PMA. These deficiencies were addressed in Amendment 4 to P990048 and Amendment 2 to P990049.

The Zeiss PMA, P990048 describes their diode laser and slit lamp adapter. The Zeiss VISULAS 690s diode laser is a modification of the Zeiss laser system used during the clinical trials. The modifications were based on recommendations from the physicians. These modifications included expanded treatment spot size to 6400 microns, increase output power to 193 mW, and the addition of a dye timer. None of these modifications affect the output characteristics of the diode wavelength and all of these modifications have been documented as providing adequate light exposure for drug activation.

In terms of deficiencies identified for P990048, company has clarified the laser output wavelength, has stated that their adapter is limited to Zeiss slit lamps, and has clarified use of the term "zoom lens". The operator manual provided for the Zeiss systems is acceptable with the labeling being correct and the directions for use being clear for this specific indication for use. At this time there are no outstanding issues needing response for P990048.

The Coherent PMA, P990049 describes the Opal diode laser and adapter systems. The Coherent LaserLink adapter permits connection of the Coherent Opal diode laser to both Zeiss and [redacted] slit lamps. The Coherent Opal Photoactivator diode laser is a

modification of the Coherent laser used in clinical trials and the modification were based, in part, on physician recommendations. The modifications made include use of microprocessor controls for start-up and safety functions; addition of dye timer; use of intermittent aiming beam; adding lens size display to console; and use of preset treatment parameters. Coherent has also clarified the use of the term 'zoom lens". The operator manual provide is acceptable, adequately describing connection of adapter to slit lamp and providing the appropriate directions for use for the indication for use. At this time there are no outstanding issues needing response for P990049.

Both P990048 and P990049 are complete and acceptable. In addition all manufacturing issues for both PMA's have been addressed and site inspections have been scheduled. At this time. P990048 and P990049 are complete and these devices can be approved for use in activation of the drug VISUDYNE for the intend use of this drug.

cc: NDA 21-119
HFD-550/Div Files
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

QLT PhotoTherapeutics Inc.
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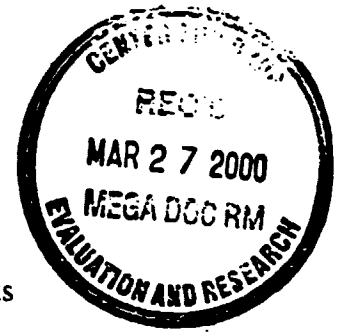

March 24, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

NDA ~~ORIG~~ AMENDMENT

BP SU

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Draft Press Release
1-year Results of VIP Study

Dear Dr. Chambers:

Enclosed please find three copies of an amendment to this application comprised of information in an upcoming press release as well as summary tables of 1-year results from the VIP study for the treatment of occult CNV in AMD patients and CNV in patients with pathologic myopia.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

ORIGINAL

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

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March 24, 2000

NDA ORIG AMENDMENT

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

XR

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Revised Patent Information

Dear Dr. Chambers:

Enclosed please find three copies of an amendment to the patent information for verteporfin submitted in the original application.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

DUPLICATE

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver, BC Canada V5T 4T5
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March 30, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

[redacted]
Verteporfin for Injection
[redacted]
Information Amendment - Clinical
Draft Press Release
1-year Results of VIP Study

Dear Dr. Chambers:

Enclosed please find three copies of safety and efficacy results from preliminary analysis of the data gathered in the first year from the VIP study [redacted] conducted for the treatment of CNV resulting from early-stage AMD or pathologic myopia.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the above number.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER
Richard Felten, Senior Reviewer, ODEI, CDRH, FDA

QLT PhotoTherapeutics Inc.
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March 31, 2000

NDA ORIG AMENDMENT

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

BI

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Microbiology Amendment

Dear Dr. Chambers:

Attached is microbiology information requested by Dr. Carol Vincent in a phone conversation on March 30, 2000.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

DUPLICATE

Caroline Stokl, Ph.D.
Sr. Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver, BC Canada V5T 4T5
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April 3, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Request for Exclusivity

Dear Dr. Chambers:

We hereby request five years exclusivity for the new molecular entity verteporfin for injection.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER

TOTAL P.02

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver, BC Canada V5T 4T5
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www.qltinc.com

April 3, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Final Draft Labeling

Dear Dr. Chambers:

We accept the draft labeling for VISUDYNE received from FDA by fax on March 24, 2000. Enclosed please find three copies of this labeling which is dated for today, plus a disc copy in Word format.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
(full submission)
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER

QLT PhotoTherapeutics Inc. 887 Great Northern Way Vancouver, BC Canada V5T 4T5
t 604.872.7881
f 604.875.0001
www.qltinc.com

April 5, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Draft Promotional Material

Dear Dr. Chambers:

Enclosed please find a single copy of four new draft promotional pieces for VISUDYNE: three direct-to-consumer advertisements and a listing of frequently asked questions and associated answers that will be posted on the VISUDYNE website. Two complete copies have been forwarded directly to DDMAC.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER

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CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 10 2000
MEGA DOC RM

April 7, 2000

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

NDA C[illegible]ENT

Attention: Document Control Room

BL

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Information Amendment
Final Draft Labeling

Dear Dr. Chambers:

Enclosed please find three copies of the final draft labeling for VISUDYNE™ (verteporfin for injection) per the revisions received from FDA today by fax, together with a disc copy in Word format.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at the number above.

Yours sincerely,

D Mitchell

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

DUPLICATE

cc: (cover letter only)
Jonathan Kahan, U.S. Representative, Hogan & Hartson
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
(one complete copy)
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER