DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

P940012

Date: DEC 27 1995

From: Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject: Premarket Approval of QLT Phototherapeutics, Inc.
c/o Hogan & Hartson
OPTIGUIDE Fiber Optic Diffuser DCYL Series
Coherent Lambda Plus PDL1 and PDL2
Photodynamic Lasers
600 Series Dye Modules (Models 630 and 630 XP) and
Series 700 and 800 KTP/532 and KTP/YAG
Surgical Lasers

To: The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA's.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) premarket approval orders for the above referenced medical devices (Tab B); and

(2) the availability of summaries of safety and effectiveness data for the devices (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Richard P. Felten, CDRH, HFZ-410, December 21, 1995, 594-1307

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

BARD Diagnostic Sciences, Inc.; Premarket Approval of BARD® BTA® Test.

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by BARD Diagnostic Sciences, Inc., Redmond, WA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of BARD® BTA® Test. After reviewing the recommendation of the Immunology Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on DEC 27 1995, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim, Ph.D.

Center for Devices and Radiological Health (HFZ-440)

Food and Drug Administration

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2098 Gaither Road

Rockville, MD 20850

301-594-1293.

SUPPLEMENTARY INFORMATION: On June 6, 1994, BARD Diagnostic Sciences, Inc., Redmond, WA, 98052, submitted to CDRH an application for premarket approval of BARD® BTA® Test. The BARD® BTA® rapid latex agglutination test is an in vitro device intended for the qualitative measurement of Bladder Tumor Associated Analytes in human urine to aid in the management of bladder cancer patients.

On September 21, 1995, the Immunology Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application.

On DEC 27 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. This notice is issued under the Federal Food, Drug, and Cosmetic Act section 520(h), 90 Stat. 554-555, 571 (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

_____
D. Bruce Burlington, M.D.
Director
Center for Devices and
Radiological Health

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20856

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

DEC 27 1995

Re: P940012
600 Series Dye Modules (Models 630 and 630 XP) and Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers
Filed: April 13, 1994
Amended: February 16, February 23 and November 13 and 17, 1995

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the 600 Series Dye Modules (Models 630 and 630 XP) and Series 700 and 800 KTP/532 and KTP/YAG (operating at 532 nm) Surgical Lasers. These devices are indicated for use in Photodynamic Therapy with PHOTOFRIN porfimer sodium as sources of activation of PHOTOFRIN for palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who, in the opinion of their physician cannot be satisfactorily treated with Nd:YAG laser therapy. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should 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 approval order, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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SUMMARY OF SAFETY AND EFFECTIVENESS DATA
Model 630 and 630 XP Dye Modules
Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers

3.1 Introduction

This is a combination product consisting of a drug (PHOTOFRIN®), the OPTIGUIDE™ Fiber Optic Diffuser, and specified lasers which activate the drug.

3.1.1 Device Generic Names: Dye Laser Modules, KTP/532, KTP/YAG Surgical Lasers

3.1.2 Device Trade Names: 600 Series Dye Modules (Models 630 and 630 XP) Series 700 and 800 KTP/532, KTP/YAG Surgical Lasers

3.1.3 Applicants Name and Address:

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

* a US subsidiary of Quadra Logic Technologies Inc., Vancouver, BC, V5Z 4H5 Canada

Laser Manufacturer: Laserscope
Name and Address: Laserscope
3052 Orchard Drive
San Jose, CA 95134-2011

3.1.4 PMA Number: P940012

3.1.5 Panel Recommendation: September 12, 1994

3.1.6 Date of Notice to Applicant:

3.2 Indications for Use

The 630 and 630 XP Dye Modules with dye optically pumped by either a Series 700 or 800 KTP/532 or KTP/YAG (operating at 532 nm) Surgical Laser, are intended for use in Photodynamic Therapy (PDT) as sources for the photoactivation of PHOTOFRIN® for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser.

3.3 Device Descriptions

The 630 and 630 XP Dye Modules provide a guaranteed power output of 3.2 watts (7.0 watts XP) of 630 +/- 3 nm light. They are designed for use with either the Series 700 and 800 KTP/532 or KTP/YAG (operating at 532 mn) Surgical Lasers. They have a built-in wavelength verification meter and an integrating sphere power meter. Dosimetry limits are selected by the operator and these are displayed on the control panel.

The Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers are quasi-continuous wave lasers. A potassium (chemical symbol K) titanyl phosphate (KTP) crystal is used to cause the laser to emit light at 532 nm. The laser has a 25kHz repetition rate with a 400 to 600 nsec full width at half maximum (FWHM) pulse width, resulting in a quasi-continuous wave laser. The 532 nm light is in turn used to optically stimulate the dye in the 630 and 630 XP Dye Modules, causing them to emit light at 630 nm as noted above.

All Laserscope systems conform to the requirements of 21 CFR 1040 Performance Standards for Light-Emitting Products.

3.4 Alternative Practices and Procedures

Esophageal cancer often blocks the esophagus and this prevents swallowing by the patient. Most treatments are palliative and focus on surgical methods of maintaining the lumen.

Surgical lasers, such as the Nd:YAG surgical laser, have reportedly become the routine treatment for esophageal cancer. These lasers are used to ablate or otherwise remove cancerous tissue to maintain a lumen.

Because of the high laser energies delivered by Nd:YAG surgical lasers, they also create steam and smoke (laser plume) and tissue charring. This can require smoke evacuators to reduce the potential risks reportedly associated with the plume as well as to minimize odors.

3.5 Marketing History

The 630 and 630 XP Dye Modules have not been marketed for human use in the United States but have been used in clinical investigations of photodynamic therapy. In these settings, the devices have been used under Investigational New Drug (IND) exemptions in order to gather information on safety and effectiveness as provided by the regulations.

The 630 and 630 XP Dye Modules require a high energy source to optically pump the dye molecules to the high levels necessary for them to emit light at 630 nm. Either the 700 or 800 Series KTP/532 or KTP/YAG (operating at 532 mn) Surgical Lasers can serve as this high energy source.

The Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers have been cleared for marketing and are commercially available as surgical lasers for use in a wide variety of surgical specialties. In these situations, the thermal energy of the lasers is used by surgeons to incise, excise, coagulate, vaporize, or ablate soft tissue.

3.6 Adverse Effects of the Device on Health

Please refer to the information in the PHOTOFRIN® NDA 20-451 for full and summarized reports of safety and effectiveness of this combination product.

Refer to the attachment for data on the Adverse Effects reported during the clinical trial for this combination product in treating esophageal cancer.

Adverse effects of the 630 and 630 XP Dye Modules and the Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers could be related to inappropriate laser power levels or improper use. Such situations would not occur if the conditions of use and instructions for use as fully described in the PHOTOFRIN® and the OPTIGUIDE™ Fiber Optic Diffuser Package Inserts are followed. If the laser power should drop such that the light dose delivered to tissue was below that necessary to activate PHOTOFRIN®, the treatment would fail. If the power should be greater than expected so that an excess light dose were delivered to tissue, then some areas of adjacent normal tissue, that should have been spared treatment, might be damaged by the PDT effect. At very high laser power levels there would be a risk of damaging the OPTIGUIDE™ Fiber Optic Diffuser if the laser power levels were greater than the OPTIGUIDE™ Fiber Optic Diffuser rated value. This might give rise to a nonuniform output, heating up of the diffusing tip and eventual tip destruction. The Dye Module, however, incorporates an optical feedback loop which informs the user if the output power level varies from the requested power level by more than 15%. This greatly reduces the chance of improper dosimetry due to the laser. The additional inclusion of the built-in wavelength meter and the integrating sphere power meter are intended to further reduce this possible event.

Please refer to the Summary of Safety and Effectiveness for the OPTIGUIDE™ Fiber Optic Diffuser for additional information and discussion of possible adverse effects of the combination product on health.

3.7 Summary of Studies

Use of the OPTIGUIDE™ Fiber Optic Diffuser in conjunction with specified lasers to investigate the clinical benefit of PHOTOFRIN® comprises a combination product as defined in the Safe Medical Devices Act of 1990.

The results of the clinical studies of PHOTOFRIN® in the photodynamic therapy of esophageal cancer are presented in the PHOTOFRIN® New Drug Application NDA 20-451. See the attachment for a summary of the clinical data obtained during this trial.

3.8 Conclusions Drawn from the Studies

The in vivo and in vitro nonclinical laboratory studies together with the clinical investigation reported in NDA 20-451 provide valid scientific evidence and reasonable assurance that the Laserscope 600 Series Dye Modules and the Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers are safe and effective when used in accordance with their labeling.

The PHOTOFRIN® Package Insert contains a summary of the clinical trial with the appropriate warnings, contraindications, and precautions.

3.9 Panel Recommendations

The Oncology Drug Advisory Committee, which included as voting members representatives from the Center for Devices and Radiological Health's General and Plastic Surgery Panel, reviewed this application at a public meeting on September 12, 1994 and recommended approval for the Laserscope 600 Series Dye Modules and the Series 700 and 800 KTP/532 and KTP/YAG Surgical Lasers as part of the combination device drug system which includes the drug PHOTOFRIN®. The recommendation of approval was for the indication of the combination product for use in the palliation of completely obstructing esophageal cancer and partially obstructing esophageal cancer where appropriate. As part of this recommendation, a Phase IV study is to be conducted to determine efficacy and safety in the partially obstructing esophageal cancer patients who are appropriate for this therapy.

3.10 FDA Decision

FDA completed an inspection of the Laser Surgical Systems manufacturing facility in San Jose, California on August 19, 1994. This inspection determined that the manufacturer was in compliance with the Medical Device Good Manufacturing Practice regulation as defined in 21 CFR 820.

FDA concurred with the above recommendation of the Oncology Drugs Advisory Committee regarding the combination drug device product which includes the drug PHOTOFRIN® submitted as NDA 20-451.

3.11 Approval Specification

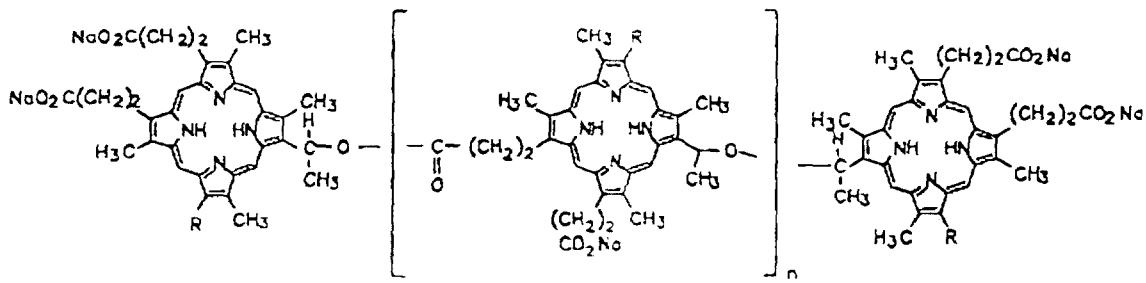
Information on the use of the 630 and 630 XP Dye Modules pumped by either a Series 700 or 800 KTP/532 or KTP/YAG Surgical Laser is found in the Dye Module and Laser Operating Manuals. Instructions for use of these activation systems as photoactivation sources for PHOTOFRIN® using the OPTIGUIDE™ Fiber Optic Diffuser can be found in the drug and fiber optic Package Inserts.

Refer to the PHOTOFRIN® and OPTIGUIDE™ Fiber Optic Diffuser labeling and package inserts for full information and instructions concerning their respective uses.

PHOTOFRIN® (sterile porfimer sodium)

DESCRIPTION

PHOTOFRIN® porfimer sodium is a photosensitizing agent used in the photodynamic therapy (PDT) of tumors. Following reconstitution of the freeze-dried product with 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), it is injected intravenously. This is followed 40–50 hours later by illumination of the tumor with laser light (630 nm wavelength). PHOTOFRIN® is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. It is a dark red to reddish brown cake or powder. Each vial of PHOTOFRIN® contains 75 mg of porfimer sodium as a sterile freeze-dried cake or powder. Hydrochloric Acid and/or Sodium Hydroxide may be added during manufacture to adjust pH. There are no preservatives or other additives. The structural formula below is representative of the components present in PHOTOFRIN®.



n = 0–6

R = $-CH(OH)CH_3$ or $-CH=CH_2$

CLINICAL PHARMACOLOGY

Pharmacology

The cytotoxic and antitumor actions of PHOTOFRIN® are light and oxygen dependent. Photodynamic therapy (PDT) with PHOTOFRIN® is a two-stage process. The first stage is the intravenous injection of PHOTOFRIN®. Clearance from a variety of tissues occurs over 40–72 hours, but tumor, skin, and organs of the reticuloendothelial system (including liver and spleen) retain PHOTOFRIN® for a longer period. Illumination with 630 nm wavelength laser light constitutes the second stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN® and selective delivery of light. Cellular damage caused by PHOTOFRIN® PDT is a consequence of the propagation of radical reactions. Radical initiation may occur after PHOTOFRIN® absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN® to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals. Tumor death also occurs through ischemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A_2 release. The laser treatment induces a photochemical, not a thermal, effect.

Pharmacokinetics

Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was 15 ± 3 μg/mL, the elimination half-life was 250 ± 285 hour, the steady-state volume of distribution was 0.49 ± 0.28 L/kg, and the total plasma clearance was 0.051 ± 0.035 mL/min/kg. The mean plasma concentration at 48 hours was 2.6 ± 0.4 μg/mL. The influence of impaired hepatic function on PHOTOFRIN® disposition has not been evaluated.

PHOTOFRIN® was approximately 90% protein bound in human serum, studied in vitro. The binding was independent of concentration over the concentration range of 20–100 μg/mL.

Clinical Studies

PDT with PHOTOFRIN® was utilized in a multicenter, single-arm study in 17 patients with completely obstructing esophageal carcinoma. Each course of PDT with PHOTOFRIN® consisted of one injection of the drug (2 mg/kg administered as a slow intravenous injection over 3–5 minutes) followed by up to two nonthermal laser light applications (630 nm administered at a dose of 300 J/cm of tumor), the first application of light occurring 40–50 hours after injection. Debridement of residua was performed via endoscopy 96–120 hours after injection, after which any residual tumor could be retreated with a second laser light application at the same dose used for the initial treatment. Additional courses of PDT with PHOTOFRIN® were allowed after 1 month, up to a total of 3. Assessments were made at 1 week and 1 month after the last treatment procedure. As shown in Table 1, after a single course of therapy, 94% of patients obtained an objective tumor response and 76% of patients experienced some palliation of their dysphagia. On average, before treatment these patients had difficulty swallowing liquids, even saliva. After one course of therapy, there was a statistically significant improvement in mean dysphagia grade (1.5 units, $p < 0.05$) and 13 of 17 patients could swallow liquids without difficulty 1 week and/or 1 month after treatment. Based on all courses, three patients achieved a complete tumor response (CR). In two of these patients, the CR was documented only at Week 1 as they had no further assessments. The third patient achieved a CR after a second course of therapy, which was supported by negative histopathology and maintained for the entire follow-up of 6 months.

Of the 17 treated patients, 11 (65%) received clinically important benefit from PDT. Clinically important benefit was defined hierarchically by obtaining a complete tumor response (3 patients), achieving normal swallowing (2 patients went from Grade 5 dysphagia to Grade 1), or achieving a dramatic improvement of two or more grades of dysphagia with minimal adverse reactions (6 patients). The median duration of benefit in these patients was 69+ days. Duration of benefit was calculated only for the period with documented evidence of improvement. All of these patients were still in response at their last assessment and, therefore, the estimate of 69 days is conservative. The median survival for these 11 patients was 115 days.

TABLE 1. Course 1 Efficacy Results in Patients with Completely Obstructing Esophageal Cancer

	PDT n=17
IMPROVEMENT[a] IN DYSPHAGIA (% of Patients)	
Week 1	71%
Month 1	47%
Any assessment[b]	76%
MEAN DYSPHAGIA GRADE[c] AT BASELINE	4.6
MEAN IMPROVEMENT[c] IN DYSPHAGIA GRADE (units)	
Week 1	1.4
Month 1	1.5
OBJECTIVE TUMOR RESPONSE[d] (% of Patients)	
Week 1	82%
Month 1	35%[e]
Any assessment[b]	94%
MEAN NUMBER OF LASER APPLICATIONS PER PATIENT	1.4

[a] Patients with at least a one-grade improvement in dysphagia grade
[b] Week 1 or Month 1
[c] Dysphagia Scale: Grade 1 = normal swallowing, Grade 2 = difficulty swallowing some hard solids; can swallow semisolids, Grade 3 = unable to swallow any solids; can swallow liquids, Grade 4 = difficulty swallowing liquids, Grade 5 = unable to swallow saliva.
[d] CR+PR, CR = complete response (absence of endoscopically visible tumor), PR = partial response (appearance of a visible lumen)
[e] Eight of the 17 treated patients did not have assessments at Month 1.

INDICATIONS AND USAGE

Photodynamic therapy with PHOTOFRIN® is indicated for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

CONTRAINDICATIONS

PHOTOFRIN® is contraindicated in patients with porphyria or in patients with known allergies to porphyrins.

PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula.

PDT is contraindicated in patients with tumors eroding into a major blood vessel.

WARNINGS

If the esophageal tumor is eroding into the trachea or bronchial tree, the likelihood of tracheoesophageal or bronchoesophageal fistula resulting from treatment is sufficiently high that PDT is not recommended.

Following injection with PHOTOFRIN® precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light (see PRECAUTIONS).

PRECAUTIONS

Information for Patients

All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for 30 days. The photosensitivity is due to residual drug which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, patients should not be kept in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue precautions for another 2 weeks before retesting. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received PHOTOFRIN®. For 30 days, when outdoors, patients should wear dark sunglasses which have an average white light transmittance of $< 4\%$.

As a result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may

be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Women of childbearing potential should practice an effective method of contraception during therapy (see Pregnancy).

Drug Interactions

There have been no formal interaction studies of PHOTOFRIN® and any other drugs. However, it is possible that concomitant use of other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics, and griseofulvin) would have the potential to increase the photosensitivity reaction.

PHOTOFRIN® PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many drugs could influence the effects of PDT, possible examples of which are described below. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN® PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN®. In vitro, PHOTOFRIN® PDT, with or without S9 activation, did not cause mutations in the Ames test, nor did it cause chromosome aberrations or

mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN® caused < 2-fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3-fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN® PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN® PDT caused a light-dose dependant increase in DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN® without light has not been adequately determined. In vivo, PHOTOFRIN® did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN® given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through Day 7 of pregnancy caused no impairment of fertility. In this study, long-term dosing with PHOTOFRIN® caused discoloration of testes and ovaries and hypertrophy of the testes. PHOTOFRIN® also caused decreased body weight in the parent rats.

Pregnancy: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PHOTOFRIN® given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2 basis) for 10 days caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight. PHOTOFRIN® caused no major malformations when given to rabbits intravenously during organogenesis at 4 mg/kg/d (0.65 times the clinical dose on a mg/m^2 basis) for 13 days. This dose caused maternal toxicity resulting in increased resorptions, decreased litter size, and reduced fetal body weight.

PHOTOFRIN® given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) for at least 42 days caused a reversible decrease in growth of offspring. Parturition was unaffected.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PHOTOFRIN®, women receiving PHOTOFRIN® must not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Almost 80% of the patients treated with PDT using PHOTOFRIN® in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

ADVERSE REACTIONS

Systemically induced effects associated with PDT with PHOTOFRIN® consist of photosensitivity and mild constipation. All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see PRECAUTIONS). Photosensitivity reactions (mostly mild erythema on the face and hands) occurred in approximately 20% of patients treated with PHOTOFRIN®.

Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. The local adverse reactions are characteristic of an inflammatory response induced by the photodynamic effect.

Esophageal Carcinoma

The following adverse events were reported in at least 5% of patients treated with PHOTOFRIN® PDT, who had completely or partially obstructing esophageal cancer. Table 2 presents data from 88 patients who received the currently marketed formulation. The relationship of many of these adverse events to PDT with PHOTOFRIN® is uncertain.

TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	PDT with PHOTOFRIN® n=88 Number (%) of Patients	
Patients with at Least One Adverse Event	84	(95)
AUTONOMIC NERVOUS SYSTEM		
Hypertension	5	(6)
Hypotension	6	(7)
BODY AS A WHOLE		
Asthenia	5	(6)
Back pain	10	(11)
Chest pain	19	(22)
Chest pain (substernal)	4	(5)
Edema generalized	4	(5)
Edema peripheral	6	(7)
Fever	27	(31)
Pain	19	(22)
Surgical complication	4	(5)
CARDIOVASCULAR		
Cardiac failure	6	(7)
GASTROINTESTINAL		
Abdominal pain	18	(20)
Constipation	21	(24)
Diarrhea	4	(5)
Dyspepsia	5	(6)
Dysphagia	9	(10)
Eructation	4	(5)
Esophageal edema	7	(8)

TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	PDT with PHOTOFRIN® n=88 Number (%) of Patients	
GASTROINTESTINAL (continued)		
Esophageal tumor bleeding	7	(8)
Esophageal stricture	5	(6)
Esophagitis	4	(5)
Hematemesis	7	(8)
Melena	4	(5)
Nausea	21	(24)
Vomiting	15	(17)
HEART RATE/RHYTHM		
Atrial fibrillation	9	(10)
Tachycardia	5	(6)
METABOLIC & NUTRITIONAL		
Dehydration	6	(7)
Weight decrease	8	(9)
PSYCHIATRIC		
Anorexia	7	(8)
Anxiety	6	(7)
Confusion	7	(8)
Insomnia	12	(14)
RED BLOOD CELL		
Anemia	28	(32)
RESISTANCE MECHANISM		
Moniliasis	8	(9)

TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	PDT with PHOTOFRIN® n=88	
RESPIRATORY		
Coughing	6	(7)
Dyspnea	18	(20)
Pharyngitis	10	(11)
Pleural effusion	28	(32)
Pneumonia	16	(18)
Respiratory insufficiency	9	(10)
Tracheoesophageal fistula	5	(6)
SKIN & APPENDAGES		
Photosensitivity reaction	17	(19)
URINARY		
Urinary tract infection	6	(7)

Location of the tumor was a prognostic factor for three adverse events: upper-third of the esophagus (esophageal edema), middle-third (atrial fibrillation), and lower-third, the most vascular region (anemia). Also, patients with large tumors (>10 cm) were more likely to experience anemia. Two of 17 patients with complete esophageal obstruction from tumor experienced esophageal perforations which were considered to be possibly treatment associated; these perforations occurred during subsequent endoscopies.

Serious and other notable adverse events observed in less than 5% of PDT-treated patients in the clinical studies include the following; their relationship to therapy is uncertain. In the gastrointestinal system, esophageal perforation, gastric ulcer, gastrointestinal hemorrhage, ileus, jaundice, and peritonitis have occurred. Sepsis has been reported occasionally. Cardiovascular events have included angina

pectoris, bradycardia, cerebrovasculardisorder, congestiveheart failure, myocardial infarction, sick sinus syndrome, and supraventricular tachycardia. Respiratory events of bronchitis, bronchospasm, laryngotracheal edema, pneumonitis, pulmonary hemorrhage, pulmonary edema, respiratory failure, and stridor have occurred. The temporal relationship of some gastrointestinal, cardiovascular and respiratory events to the administration of light was suggestive of mediastinal inflammation in some patients. Vision-related events of abnormal vision, diplopia, eye pain and photophobia have been reported.

Laboratory Abnormalities

PDT with PHOTOFRIN® may result in anemia due to tumor bleeding. No consistent effects were observed for other parameters.

OVERDOSAGE

PHOTOFRIN® Overdose

There is no information on overdosage situations involving PHOTOFRIN®. Effects of overdosage on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of PHOTOFRIN® is administered. In the event of an overdose, patients should protect their eyes and skin from direct sunlight or bright indoor lights for 30 days. At this time, patients should test for residual photosensitivity (see PRECAUTIONS). PHOTOFRIN® is not dialyzable.

Overdose of Laser Light Following PHOTOFRIN® Injection

There is no information on overdose of laser light following PHOTOFRIN® injection in patients with esophageal carcinoma. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

DOSAGE AND ADMINISTRATION

Photodynamic therapy with PHOTOFRIN® is a two-stage process requiring administration of both drug and light. Practitioners should be trained in the safe and efficacious treatment of esophageal cancer using photodynamic therapy with PHOTOFRIN® and associated light delivery devices. The first stage of PDT is the intravenous injection of PHOTOFRIN® at 2 mg/kg. Illumination with laser light 40–50 hours following injection with PHOTOFRIN® constitutes the second stage of therapy. A second laser light application may be given 96–120 hours after injection, preceded by gentle debridement of residual tumor (see Administration of Laser Light). In clinical studies, debridement via endoscopy was required 2 days after the initial light application. However, experience has indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus and may, in fact, needlessly traumatize the area.

Patients may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each separated by a minimum of 30 days) can be given. Before each course of treatment, patients should be evaluated for the presence of a tracheoesophageal or bronchoesophageal fistula (see CONTRAINDICATIONS).

PHOTOFRIN® Administration

PHOTOFRIN® should be administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. Reconstitute each vial of PHOTOFRIN® with 31.8 mL of either 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), resulting in a final concentration of 2.5 mg/mL. Shake well until dissolved. Do not mix PHOTOFRIN® with other drugs in the same solution. PHOTOFRIN®, reconstituted with 5% Dextrose Injection (USP) or with 0.9% Sodium Chloride Injection (USP), has a pH in the range of 7 to 8. PHOTOFRIN® has been formulated with an overage to deliver the 75 mg labeled quantity. The reconstituted product should be protected from bright light and used immediately. Reconstituted PHOTOFRIN® is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted PHOTOFRIN®, however, like all parenteral drug products, should be inspected visually for

particulate matter and discoloration prior to administration whenever solution and container permit.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, care must be taken to protect the area from light. There is no known benefit from injecting the extravasation site with another substance.

Administration of Laser Light

Initiate 630 nm wavelength laser light delivery to the patient 40–50 hours following injection with PHOTOFRIN®. A second laser light treatment may be given as early as 96 hours or as late as 120 hours after the initial injection with PHOTOFRIN®. No further injection of PHOTOFRIN® should be given for such retreatment with laser light. Before providing a second laser light treatment, the residual tumor should be debrided. Vigorous debridement may cause tumor bleeding.

The laser system must be approved for delivery of a stable power output at a wavelength of 630 ±3 nm. Light is delivered to the tumor by cylindrical OPTIGUIDE™ fiber optic diffusers passed through the operating channel of an endoscope. Instructions for use of the fiber optic and the selected laser system should be read carefully before use. Photoactivation of PHOTOFRIN® is controlled by the total light dose delivered. In the treatment of esophageal cancer, a light dose of 300 joules/cm of tumor length should be delivered. OPTIGUIDE™ cylindrical diffusers are available in several lengths. The choice of diffuser tip length depends on the length of the tumor. Diffuser length should be sized to avoid exposure of nonmalignant tissue to light and to prevent overlapping of previously treated malignant tissue. The total power output at the fiber tip is set to deliver the appropriate light dose using exposure times of 12 minutes and 30 seconds. Refer to the OPTIGUIDE™ instructions for use for complete instructions concerning the fiber optic diffuser.

HOW SUPPLIED

PHOTOFRIN® (sterile porfimer sodium) is supplied as a freeze-dried cake or powder as follows:

NDC XXXX-XXXX-XX – 75 mg vial

PHOTOFRIN® freeze-dried cake or powder should be stored at Controlled Room Temperature 15–30°C (59–86°F).

Distributed by

DIST. LOGO
[Name and address to be inserted when finalized]

Manufactured by

LEDERLE PARENTERALS, INC.
Carolina, Puerto Rico 00987

for

QLT LOGO

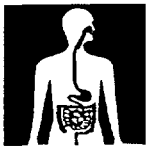
QLT PHOTOTHERAPEUTICS INC.
Seattle, WA 98101

Spills and Disposal

Spills of PHOTOFRIN® should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended. All contaminated materials should be disposed of in a polyethylene bag in a manner consistent with local regulations.

Accidental Exposure

PHOTOFRIN® is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, PHOTOFRIN® might be an eye and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic overdosage, any overexposed person must be protected from bright light.



KTP/532 Applications
Gastroenterology

Indications:

- Tissue ablation and hemostasis in the gastrointestinal tract
- Esophageal neoplastic obstructions including:
  - Squamous cell carcinoma
  - Adenocarcinoma
- Gastrointestinal hemostasis including:
  - Varices
  - Esophagitis
  - Esophageal ulcer
  - Mallory-Weiss tear
  - Gastric ulcer
  - Angiodysplasia
  - Stomal ulcers
  - Non-bleeding ulcers
  - Gastric erosions
- Gastrointestinal tissue ablation including:
  - Benign and malignant neoplasm
  - Angiodysplasia
  - Polyps
  - Ulcer
  - Colitis
  - Hemorrhoids

KTP/532 Applications
Gastroenterology

- Pump laser source including:
  - For use as a pump source for the Laserscope Model 630 and Model 630 XP Dye Module for the photoactivation of PHOTOFRIN® under conditions described in the Package Inserts for PHOTOFRIN and OPTIGUIDE™ Fiber Optic Diffuser for the palliation of patients with competely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy. Refer to the Laserscope Model 630 or the Model 630 XP Dye Module Operator's Manual for complete instructions con cerning the Dye Modules.

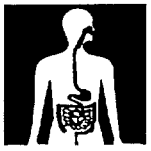
Specific Warnings and Precautions:

- **It is essential that the surgeon and attending staff be trained in all aspects of this procedure. No surgeon should use these laser products for Gastroenterological surgical applications without first obtaining detailed instructions in laser use.**
- Refer to *General Warnings and Precautions for the Surgical Laser System*, for additional information.

Section 9: ..... *Warranty Policy and Product Returns*

Section 10: ..... *Professional Use*

Appendix: ..... *Laser Safety and Standards References*



DYE/630 Applications
Gastroenterology

Indications:

- The Laserscope Model 630 and Model 630 XP Dye Modules are intended for use in Photodynamic Therapy (PDT) as sources of photoactivation of PHOTOFRIN® for the palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be treated satisfactorily with Nd:YAG laser therapy. Refer to the PHOTOFRIN Package Insert for information and instructions for use of the drug. Refer to the OPTIGUIDE™ Package insert for information and instructions for use of the fiber optic, and information on laser power, duration and light dose.

OPTIGUIDE™ Cylindrical Diffusers

OPTIGUIDE™ Fiber Optic Diffusers are cylindrical diffusers that provide a uniform, cylindrical pattern of light radially along the tip length, keeping forward illumination to a minimum. These diffusers are designed for use on lesions of varying size and location requiring intraluminal illumination. Figure 4.1 shows a Cylindrical Diffuser.

Figures 4.1 Cylindrical Diffuser