

PHOTOFRIN®

Sterile Porfimer Sodium for Injection

For Intravenous Use

Antineoplastic Photosensitizing Agent

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CONTROL # 097598

DATE OF PREPARATION:

June 7, 2000

DATE OF REVISION:

May 16, 2005

PRODUCT MONOGRAPH**PHOTOFRIN®****Sterile Porfimer Sodium for Injection****For Intravenous Use****ANTINEOPLASTIC PHOTSENSITIZING AGENT**

CAUTION: PHOTOFRIN® IS AN INJECTABLE PHOTSENSITIZING DRUG FOR USE IN PHOTODYNAMIC THERAPY (PDT) FOR TREATMENT OF CANCER AND PRE-MALIGNANT CONDITIONS (E.G., HIGH-GRADE DYSPLASIA IN BARRETT'S ESOPHAGUS). PHOTODYNAMIC THERAPY IS A PHOTOCHEMICAL PROCESS REQUIRING SPECIFIC LASERS AND FIBER OPTICS. PHOTODYNAMIC THERAPY WITH PHOTOFRIN® SHOULD ONLY BE APPLIED BY PHYSICIANS TRAINED IN THE ENDOSCOPIC USE OF PDT WITH PHOTOFRIN® AND ONLY IN THOSE FACILITIES PROPERLY EQUIPPED FOR THE PROCEDURE. PHOTOFRIN® MAY CAUSE RESIDUAL PHOTSENSITIVITY FOR 30 DAYS OR MORE RESULTING IN ERYTHEMA AND BLISTERING OF THE SKIN WHEN IT IS EXPOSED TO DIRECT SUNLIGHT OR BRIGHTLY FOCUSED INDOOR LIGHT (E.G., FROM EXAMINATION

LAMPS, OPERATING ROOM LAMPS, FLOODLIGHTS, HALOGEN LAMPS, ETC.).

ACTION & CLINICAL PHARMACOLOGY

Pharmacodynamics

The cytotoxic and antitumor actions of PHOTOFRIN[®] (porfimer sodium) are light and oxygen dependent. Photodynamic therapy (PDT) with PHOTOFRIN[®] is a 2-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 and final stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN[®] and selective delivery of light. Photodynamic therapy-induced cytotoxicity may be due to free radical (superoxide or hydroxyl) generation and the production of singlet oxygen via energy transfer from light to triplet oxygen. Tumor death also occurs through ischemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A₂ release. The laser treatment induces a photochemical, not a thermal effect. The necrotic reaction and associated inflammatory responses may evolve over several days.

Pharmacokinetics

A pharmacokinetic study was performed on 12 lung cancer patients given 2 mg/kg of PHOTOFRIN[®] via the intravenous route. Samples of plasma were obtained up to 56

days post injection. PHOTOFRIN® was slowly cleared from the body with a mean apparent elimination half-life of 21.5 days (range 11-28 days).

The pharmacokinetics of PHOTOFRIN® was also studied in 24 healthy subjects (12 men and 12 women) who received a single dose of 2 mg/kg PHOTOFRIN® given via the intravenous route. Serum samples were collected out to 36 days after injection. The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The elimination half-life was 415 hours (17 days). C_{max} was determined to be 40 mcg/mL, and $AUC_{(inf)}$ was 2400 mcg·hour/mL. Gender had no effect on pharmacokinetic parameters except for t_{max} , which was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of PHOTOFRIN® in men and women were very similar.

No special precautions in renally impaired patients are necessary because excretion is primarily via the fecal route. The influence of impaired hepatic function on porfimer sodium 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 mcg/mL.

INDICATIONS AND CLINICAL USE

Papillary Bladder Cancer

Photodynamic therapy with PHOTOFRIN® (porfimer sodium) is indicated following transurethral resection in patients with recurring superficial papillary bladder cancer as second-line treatment for those who have failed a standard intravesical therapy.

Esophageal Cancer

Photodynamic therapy with PHOTOFRIN® is indicated for the reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer.

Endobronchial Cancer

Photodynamic therapy with PHOTOFRIN® is indicated for:

- reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer, and
- treatment of superficial endobronchial nonsmall cell lung cancer (carcinoma *in situ* or micro-invasive tumors) in patients for whom surgery and radiotherapy are not indicated.

High-Grade Dysplasia associated with Barrett's Esophagus

Photodynamic therapy with PHOTOFRIN® is indicated for ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) in patients who refuse esophagectomy and are in overall good health. PDT with PHOTOFRIN® reduces the risk of progression to esophageal cancer. Rigorous endoscopic surveillance is recommended every three months (until four consecutive negative evaluations have been recorded; further follow-up may be scheduled every 6 to 12 months, as per judgment of physicians) to ensure the detection and biopsy of cancer at an early stage. Ablation of HGD in BE with PDT was better achieved in patients having a single focus HGD and in those taking omeprazole for at least three months prior to PDT treatment.

CONTRAINDICATIONS

Photodynamic therapy with PHOTOFRIN® (porfimer sodium) is contraindicated in patients with porphyria or in patients with known allergies to porphyrins.

Photodynamic therapy is contraindicated in patients with tumors eroding into a major blood vessel. Photodynamic therapy is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula.

Papillary Bladder Cancer

Patients with prior total bladder irradiation, or with a functional bladder capacity less than 200 mL, must not be treated with PDT to the bladder; there is the possibility of irreversible bladder contracture from increased fibrosis.

Patients with coexisting bladder tumors of stage greater than T1, who have invasive cancer, must not receive PDT.

Endobronchial Cancer

Photodynamic therapy is not suitable for emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection with PHOTOFRIN® and laser light treatment.

High-Grade Dysplasia associated with Barrett's Esophagus

Photodynamic therapy is not suitable for patients with esophageal or gastric varices or patients with esophageal ulcers >1 cm in diameter.

WARNINGS

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

Esophageal Cancer

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.

Patients with esophageal varices should be treated with extreme caution. Light should not be given directly to the variceal area because of the high risk of bleeding.

Endobronchial Cancer

Patients should be assessed for the possibility that a tumor may be eroding into a pulmonary blood vessel (see CONTRAINDICATIONS). Patients at high risk for fatal hemoptysis include those with large, centrally located tumors, those with cavitating tumors or those with extensive tumor extrinsic to the bronchus.

If the endobronchial tumor invades deeply into the bronchial wall, the possibility exists for fistula formation upon resolution of the tumor.

Photodynamic therapy should be used with extreme caution for endobronchial tumors in locations where treatment-induced inflammation could obstruct the main airway, e.g., long or circumferential tumors of the trachea, tumors of the main carina that involve both mainstem bronchi circumferentially, or circumferential tumors in the mainstem bronchus in patients with prior pneumonectomy.

High-Grade Dysplasia associated with Barrett's Esophagus

The long-term effect with therapy of this nature is unknown. There is always a possibility of leaving cancer behind or leaving residual abnormal epithelium beneath the new squamous epithelium, facts that emphasize the risk of overlooking cancer in such patients and the need for rigorous continuing surveillance despite the endoscopic appearance of complete squamous reepithelialization. The follow-up of the pivotal study at the time of approval was a minimum of two years (ranging from 2 to 3.6 years).

PRECAUTIONS

Photosensitivity

All patients who receive PHOTOFRIN® will be photosensitive for 30 days or more and must observe precautions to avoid exposure of eyes and skin to direct sunlight or brightly focused indoor light (from examination lamps, dental lamps, operating room lamps, floodlights, halogen lamps, etc.). Some patients may remain photosensitive for up to 90 days or more. **Conventional UV sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.** When outdoors, patients should wear protective clothing and dark sunglasses. 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, however, beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, patients should not stay 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 two 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.

Ocular Sensitivity

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%.

Respiratory Distress

Patients with endobronchial lesions must be closely monitored between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress. Inflammation and mucositis may result from exposure of normal tissue to too much light. Necrotic debris may also obstruct the airway. If respiratory distress occurs, the physician should be prepared to carry out immediate bronchoscopy to remove secretions and debris to open the airway.

Use Before or After Radiotherapy

If PDT is to be used before or after radiotherapy, sufficient time should be allotted between the two therapies to ensure that the inflammatory response produced by the first treatment has subsided before commencing the second treatment. The inflammatory response from PDT will depend on tumor size and extent of surrounding normal tissue that receives light. It is recommended that two to four weeks be allowed after PDT before commencing radiotherapy. Similarly, if PDT is to be given after radiotherapy, the acute inflammatory reaction from radiotherapy usually subsides within four weeks after completing radiotherapy, after which PDT may be given.

Chest Pain

As a result of PDT treatment in esophageal or endobronchial cancer, or HGD in BE, 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.

Esophageal strictures

Esophageal stenosis as a result of PDT in HGD in BE is a common side event. Esophageal stenosis includes esophageal narrowing and esophageal strictures. An esophageal narrowing was defined as a lumen narrowing without solid food dysphagia and not requiring dilation. An esophageal stricture was defined as a fixed lumen narrowing with solid food dysphagia and requiring dilation. In the pivotal study, 128 events of esophageal stenosis were reported in the PHOTOFRIN PDT + OM group

(55% mild, 37% moderate, 8% severe). Esophageal strictures occurred in 36% of the patients within six months following PDT and were manageable through dilations. (See CLINICAL STUDIES). Multiple dilations of esophageal strictures may be required.

Special care should be taken during dilation to avoid perforation of the esophagus.

A high proportion of patients who developed an esophageal stricture received a nodule pre-treatment prior to developing the event (49%) was compared to patients who did not develop esophageal strictures during the study (37%). A high proportion of patients who developed an esophageal stricture had a mucosal segment treated twice (82%) as compared to patients who did not develop esophageal stricture (52%). Therefore, nodule pre-treatment and re-treating the same mucosal segment more than once may influence the risk of developing an esophageal stricture.

PDT with PHOTOFRIN® should be applied by physicians trained in the endoscopic use of PDT with PHOTOFRIN® and only in those facilities properly equipped for the procedure.

Others

PDT has not been studied in patients with significant cardio-pulmonary symptoms. The effect on such patients is not known.

Drug Interactions

There is no clinical information concerning drug-drug interactions involving PHOTOFRIN®. However, it is possible that concomitant use of other agents known to produce photosensitivity reactions (e.g., tetracyclines, sulfonamides, phenothiazines,

sulfonylurea hypoglycemic agents, thiazide diuretics, griseofulvin and fluoroquinolones) would have the potential to increase the photosensitivity reaction.

Since the basic effects of PDT are thought to involve vasoconstriction and platelet activation and aggregation at the site of treatment, as well as the generation of active oxygen species, treatments which alter blood flow or availability of oxygen would be expected to affect the effectiveness of PDT. Data from animal models and *in vitro* tissue culture studies suggest the following: Thromboxane A₂ receptor antagonists, thromboxane synthetase inhibitors, drugs which quench active oxygen species, and compounds which react with hydroxyl radicals, including dimethyl sulfoxide (DMSO), ethanol, formate, and mannitol, have been shown to decrease the effectiveness of PDT. Steroids administered 24-48 hours following PDT enhanced antitumor effects, whereas steroids administered concomitantly inhibited the PDT effect. Animal or *in vitro* studies involving combination therapy with PDT and standard antineoplastic agents (including doxorubicin, mitomycin C, and BCG for bladder cancer, and mitomycin C in a colon cancer cell line) resulted in an increase in effectiveness compared with single therapies. Similarly, combinations of PDT with PHOTOFRIN® and different photosensitizers with different biodistribution properties (including tetraphenylporphine sulfonate) resulted in enhanced tumor eradication in a murine mammary tumor model.

Use in Pregnancy

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. Women of childbearing potential should practice an effective method of contraception during therapy, and have a pre-treatment pregnancy test performed.

Nursing Mothers

It is unknown whether the drug is excreted in human milk. Therefore, women receiving PHOTOFRIN® must not breast feed.

Use in Children

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Approximately 70% 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.

Information for the Patient

Photodynamic therapy is indicated for ablation of cancerous and pre-cancerous cells that uses a photosensitive drug called PHOTOFRIN®, in combination with a laser light delivery system. When injected intravenously, PHOTOFRIN® tends to be retained for a longer period of time by cancer cells than by most other tissues, thus minimizing any effect to normal tissue. Exposing the drug to light causes a chemical reaction, which results in the destruction of cancer cells containing the drug.

In addition to retention by cancer cells, PHOTOFRIN® is retained by the skin for a period of time, normally four to six weeks. Due to this retention by the skin, the major side effect of PHOTOFRIN® is skin photosensitivity. Exposure of unprotected skin to

sunlight or focused indoor lighting may result in erythema or blistering. Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has also been reported in patients who received PHOTOFRIN®. Therefore, following the injection of PHOTOFRIN®, patients must be advised to take precautions to protect the eyes and skin from exposure to direct or indirect sunlight or bright focused indoor light for a period of 30 days. The duration of photosensitivity may vary from patient to patient. It is important that each patient determine their individual photosensitivity reaction to the drug through a careful test program which should be explained by their physician: after 30 days, patients should expose a small area of skin to the sun for ten minutes to test it for residual photosensitivity. If significant erythema, edema, or blistering occurs within 24 hours, the patient should continue precautions against sun and bright light exposure for another two weeks before retesting the effects of limited sun exposure. UV sunscreens are of no value, because photoactivation is caused by visible light. While photosensitivity precautions must be considered, patients should also be advised to avoid total darkness. Exposure to normal ambient lighting is important to aid in the clearance of PHOTOFRIN® from the skin through the process of photobleaching. Patients should be instructed to raise any additional questions regarding this treatment with their physician.

THE FOLLOWING INFORMATION SHOULD BE DISCUSSED WITH THE PATIENTS WHO ARE CANDIDATES FOR PHOTODYNAMIC THERAPY.

Patients offered PDT with PHOTOFRIN® for ablation of HGD in BE should be made aware that PDT decreases cancer risk but does not eliminate it. Following treatment, the patient should undergo endoscopic surveillance with biopsies every three months (until four consecutive negative evaluations have been recorded; further follow-up may

be scheduled every 6 to 12 months, as per judgment of physicians) to detect the occurrence of cancer at an early stage. Patients should be informed on the procedure of treatment, and the possibility of the need for a re-treatment (up to three courses). Short- and long-term adverse events directly related to therapy (such as esophageal stricture formation and, as a result, the need for dilations) should be discussed.

ADVERSE REACTIONS

The skin of all patients who receive PHOTOFRIN® (porfimer sodium), will be photosensitive for 30 days or more (see PRECAUTIONS). Photosensitivity reactions are avoidable through proper patient education. In clinical studies in cancer, the incidence of photosensitivity was 20%; this incidence was 68% in patients with HGD in BE.

Typically these reactions were mostly mild to moderate erythema but they also included swelling, itching, burning sensations, feeling hot, or blisters. In a single study of 24 healthy subjects, some evidence of photosensitivity reactions occurred in all subjects (incidence of 100%). Other less common skin manifestations, in areas where photosensitivity reactions had occurred, were also reported such as increased hair growth, skin discoloration, skin nodules, increased wrinkles and increased skin fragility. These manifestations may be attributed to a pseudoporphyria state (temporary drug-induced cutaneous porphyria). Ocular discomfort (sensitivity to sun, bright lights or car headlights) has also been reported. The only other known systemic reaction is constipation.

The toxicities associated with PDT across all indications are primarily local, in the immediate area that received laser light, and sometimes extending into adjacent

tissues. The local/regional reactions are consistent with an inflammatory reaction induced by the photodynamic effect (see below for specific reactions by indication).

A few cases of fluid imbalance have been reported following the use of PDT with PHOTOFRIN® in patients with overtly disseminated intraperitoneal malignancies. Fluid imbalance is an expected PDT treatment related event.

Accelerated development of early bilateral cataracts following therapy has been reported in one patient with a positive family history of cataracts.

Papillary Bladder Cancer

Patients with papillary bladder cancer may develop transient (up to several weeks) irritative bladder symptoms after PDT with PHOTOFRIN®. This post-PDT response, thought to be due to inflammation, includes increased micturition frequency (60% of patients), hematuria (56%), dysuria (36%), urgency (32%) and suprapubic pain (20%). Additional common urinary symptoms observed were strangury (32%), genital edema (24%), urinary incontinence (20%) and nocturia (12%) and urinary tract infection (12%). Transient reduction in bladder capacity may occur; irreversible bladder contracture occurred in 20% of patients, a median of 99 days post-PDT.

Additional adverse reactions, which occurred in $\geq 10\%$ of patients with papillary bladder cancer, were anxiety (12%), insomnia (20%), peripheral edema (16%), non-specific pain (12%), nausea (12%) and constipation (12%).

Esophageal Cancer

In a clinical trial involving patients with partially-obstructing esophageal cancer PDT with PHOTOFRIN® was compared to thermal ablation with the Nd:YAG laser. Adverse events that occurred significantly more often in PDT-treated than in Nd:YAG-treated patients (besides photosensitivity) were fever (33% versus 10%, respectively), pleural effusion (28% versus 6%), respiratory insufficiency (10% versus 1%), anemia (26% versus 12%), and constipation (23% versus 9%). With the exception of anemia and respiratory insufficiency, these reactions were generally mild or moderate in severity and easily managed. Anemia was manageable by transfusion and was more common in patients with large tumors (>10 cm) and in tumors in the lower area of the esophagus. The etiology of respiratory insufficiency is unclear. Fever and pleural effusion, as well as pain (22% versus 20%), esophageal edema (6% versus 2%) and atrial fibrillation (8% versus 4%) are thought to be manifestations of a local/regional inflammatory reaction. Esophageal edema occurred more frequently when the tumor was located in the upper third of the esophagus; atrial fibrillation was more likely to occur when the tumor was in the middle third of the esophagus.

Other adverse reactions which occurred commonly (>10% of either group of patients) in both the PDT group and the Nd:YAG laser group were insomnia (14% versus 9%), abdominal pain (19% versus 11%), hematemesis (11% versus 7%), nausea (21% versus 15%), vomiting (16% versus 8%), dyspnea (18% versus 15%), pneumonia (16% versus 13%) and chest pain (23% versus 19%). Some of these adverse events reflect symptoms of esophageal cancer or concurrent conditions such as respiratory disease, although they may have been exacerbated by either treatment.

Endobronchial Cancer

Adverse events reported in 5% or more of patients (n=99) with obstructing endobronchial nonsmall cell lung cancer were most commonly associated with the respiratory system; their relationship to therapy is unclear: dyspnea (32%), coughing (17%), pneumonia (13%), nonfatal hemoptysis (12%), bronchitis (11%), fatal massive hemoptysis (10%), increased sputum (9%) and respiratory insufficiency (7%). Other frequent events were photosensitivity reaction (20%), fever (15%), chest pain (9%), insomnia (7%), anxiety (5%) and constipation (5%).

Transient inflammatory reactions occur in about 10% of patients and manifest as fever, bronchitis, chest pain and dyspnea. Most cases of bronchitis occurred within one week of treatment and all but one were mild or moderate in intensity. The events usually resolved within 10 days with antibiotic therapy. Treatment-related worsening of dyspnea is generally transient and self-limiting. Debridement of the treated area is mandatory to remove exudate and necrotic tissue. Life-threatening respiratory insufficiency likely due to therapy occurred in 3% of PDT-treated patients and in 2% of patients treated with the comparator, Nd:YAG thermal ablation (see WARNINGS AND PRECAUTIONS).

There was a trend toward a higher rate of fatal hemoptysis (FMH) occurring on the PDT arm (10%) versus Nd:YAG (5%), however, the rate of FMH occurring within 30 days of treatment was the same for PDT and Nd:YAG (4% total events, 3% treatment-associated events) and median survival was similar in the two groups (PDT 174 days, Nd:YAG 161 days). Patients who have received radiation therapy have a higher incidence of FMH after treatment with PDT and after other forms of local therapy than patients who have not received radiation therapy, but analyses suggest that this

increased risk may be due to associated prognostic factors such as having a recurrent, centrally located tumor. The incidence of FMH in patients previously treated with radiotherapy was 21% (6/29) in the PDT group and 10% (3/29) in the Nd:YAG group. Characteristics of patients at high risk for FMH are described in WARNINGS.

Serious and other notable adverse events observed in less than 5% of PDT-treated patients with obstructing endobronchial cancer included pleural effusion, pulmonary thrombosis, pulmonary embolism and lung abscess. Cardiac failure, sepsis, and possible cerebrovascular accident have also been reported in one patient each. Their relationship to therapy is uncertain.

In patients with superficial endobronchial tumors, adverse events were similar in nature to those reported in patients with late-stage disease, but much less frequent and milder in intensity. Fifty-one of 102 patients (50%) experienced an adverse event, two-thirds of which were related to the respiratory system. A mucositis reaction occurred more frequently in patients with superficial tumors; one-fifth of the patients experienced manifestations of mucositis, such as edema, exudate, and obstruction. The obstruction (mucous plug) is easily removed with suction or forceps. Mucositis can be minimized by avoiding exposure of normal tissue to excessive light (see PRECAUTIONS). Three patients experienced life-threatening dyspnea: one was given a double dose of light, one was treated concurrently in both mainstem bronchi and the other had had prior pneumonectomy and was treated in the sole remaining main airway (see WARNINGS). In addition, fatal massive hemoptysis occurred within thirty days of treatment in one patient who had received prior endobronchial brachytherapy. Stent placement was required in 3% of the patients due to endobronchial stricture.

High-Grade Dysplasia associated with Barrett's Esophagus

In a clinical trial, PDT with PHOTOFRIN[®] plus omeprazole (PDT+OM) was compared to a control group of patients receiving omeprazole alone (OM Only) in producing complete ablation of High-Grade Dysplasia (HGD) in patients with Barrett's esophagus (BE).

The majority (99%) of patients in the PHOTOFRIN[®] PDT + OM group reported treatment emergent adverse events (regardless of association with treatment) compared to 74% of patients in the OM Only group. Adverse events that occurred significantly more often in PHOTOFRIN[®] PDT + OM group than in the OM Only group (>10% in either group of patients) were photosensitivity reaction (68% versus 0%), esophageal narrowing/strictures (40% versus 1%), vomiting (38% versus 6%), constipation (27% versus 7%), chest pain (25% versus 12%), fever (24% versus 4%), upper or lower abdominal pain (20% versus 6%), dysphagia (19% versus 1%), nausea (14% versus 7%), dehydration (12% versus 3%), hiccups (11% versus 0%), and dyspnea (10% versus 4%). Other adverse reactions, which occurred commonly (>10% of either group of patients) in both groups, were diarrhea (16% versus 10%) and headache (11% versus 9%). Other adverse events reported included pleural effusion (6% versus 0%) and atrial fibrillation (3% versus 1%).

Esophageal stenosis as a result of PDT in HGD in BE is a common side event.

Esophageal stenosis includes esophageal narrowing, defined as a lumen narrowing without solid food dysphagia and not requiring dilation, and esophageal strictures, defined as a fixed lumen narrowing with solid food dysphagia and requiring dilation. The

majority of esophageal stenosis reported in the PHOTOFRIN® PDT + OM group were of mild or moderate intensity (55% mild, 37% moderate). Approximately 8% of events were of severe intensity. The majority of esophageal strictures reported in the PHOTOFRIN® PDT + OM group were reported during Course 2 of treatment. All esophageal strictures were considered to be associated with treatment. Most esophageal strictures were manageable through dilations.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose of PHOTOFRIN®

There is no information on overdose situations involving PHOTOFRIN®. Higher than recommended drug doses of two 2 mg/kg doses given two days apart (10 patients), and three 2 mg/kg doses given within two weeks (one patient), were tolerated without notable adverse reactions. Effects of overdose 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

Papillary Bladder Cancer

Whole bladder photoradiation at light levels exceeding the recommended dose may significantly increase adverse urinary symptoms seen after PDT treatment, and may create irreversible bladder contracture in some patients.

Esophageal Cancer

There is no information on overdose of laser light following PHOTOFRIN® injection in patients with esophageal carcinoma.

Endobronchial Cancer

Light doses of two to three times the recommended dose have been administered to a few patients with superficial endobronchial tumors. One patient experienced life-threatening dyspnea and the others had no notable complications. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

High-Grade Dysplasia associated with Barrett's Esophagus

There is no information on overdose of laser light following PHOTOFRIN® injection in patients with Barrett's esophagus.

DOSAGE AND ADMINISTRATION

Photodynamic therapy (PDT) with PHOTOFRIN® is a two-stage process requiring administration of both drug and light. Physicians should be trained in the safe and efficacious treatment of papillary bladder, esophageal, endobronchial cancer, or HGD in BE 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. The second stage of therapy is illumination with laser light 40-50 hours following injection with PHOTOFRIN®. In patients with bladder cancer, no further doses of drug or light should be administered due to increased risk of bladder contracture; patients with esophageal cancer, endobronchial cancer, or HGD in BE may receive a second laser light application 96-120 hours after drug administration. If needed, up to one or two more courses of drug and light may be given, with each injection separated by a

minimum of 30 days, except for HGD in BE where each injection should be separated by a minimum of 90 days.

PHOTOFRIN® Administration

PHOTOFRIN® should be reconstituted according to the directions given under Reconstitution and administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. As with all intravenous injections, care should be taken to prevent extravasation at the injection site. If extravasation occurs, the area should be protected from light for a minimum of 30 days. There is no known benefit from injecting the extravasation site with another substance.

Photoactivation of PHOTOFRIN®

Uniform and complete light delivery to the tumor mass or Barrett's segment is essential for activation of PHOTOFRIN®. Light from a laser is delivered to the tumor or Barrett's segment via OPTIGUIDE™ Fiber Optic Diffusers, designed specifically for use in photodynamic therapy. While there are numerous lasers available for medical applications, the use of the OPTIGUIDE™ Fiber Optics for photoactivation of PHOTOFRIN® requires a continuous output laser operating at a wavelength of 630 ± 3 nm, and producing a stable power output. The choice of the type and size of the fiber optic diffuser tip will depend on the indication, tumor or Barrett's segment location and size.

Photoactivation of PHOTOFRIN® is controlled by the total energy delivered to the tumor or Barrett's segment site. This is determined by the power delivered from the OPTIGUIDE™ Fiber Optic to the treatment site and the total treatment time.

The OPTIGUIDE™ Package Insert provides details relating to the assembly, function and operation of the fiber optic light delivery system, including accepted laser light sources, and should be used in conjunction with the information presented for each indication below.

Superficial Papillary Bladder Cancer

Whole bladder treatment will require a total light delivery of 15 joules/cm², using the spherical cavity diffuser. Approximately 40-50 hours after injection with PHOTOFRIN®, the patient should be anesthetized and the bladder distended with a volume of saline or water sufficient to smooth mucosal folds, without compromising circulation. This 'treatment volume' should be within 50-75% of the bladder's functional capacity, as measured by cystometrography.

Referring to the OPTIGUIDE™ Package Insert, attach the OPTIGUIDE™ Model DSPH spherical cavity diffuser to an acceptable laser light source. To minimize the treatment time and thus the period of bladder distention, the total power output at the fiber optic tip should be at least 1.25 watts but less than the maximum power specification for the fiber optic.

The cystoscope should be positioned securely at the bladder neck using clamps and metal rods, a gooseneck or similar stationary apparatus, and should not be moved once it is secured. The patient is placed in Trendelenberg position, which relaxes the abdominal wall to facilitate centering the treatment tip. By adjusting the position of the patient, the cystoscope is aimed at the point where the posterior wall meets the dome, which is the maximum distance from the bladder neck. The trigone should not be visible. Correct placement of the fiber tip in the center of the bladder is essential to

ensure uniform irradiation of the bladder, as areas, which receive excessive amounts of light, may result in pain or sensitivity post-treatment. Correct placement can be achieved by one of two methods:

a. Ultrasound Imaging

Ultrasound imaging is recommended to verify the mid-bladder placement of the fiber tip, as well as to monitor the bladder volume during treatment:

- (1) After the bladder is filled, an initial examination of the bladder is made in cross-sectional and longitudinal planes using an ultrasound apparatus.
- (2) The probe is then placed in the longitudinal position in the midline of the abdomen just above the symphysis pubis. Once the bladder filling has begun, the fluid can be easily detected as a black or clear space in the ultrasound image. The probe may have to be moved side to side (right to left or left to right) to locate the optimum long axis of the bladder once the bladder is filled.
- (3) Once the bladder has been filled, the cystoscope can easily be imaged by ultrasound.
- (4) Centering of the cystoscope and laser fiber should be done using the linear distance calipers on the ultrasound equipment.

b. Sounding

To determine the midpoint of the bladder by sounding, a urethral catheter with one end plugged to prevent leakage is directed to the dome. The maximum distance is measured from the bladder neck to the point where the posterior bladder wall meets the dome. The spherical diffuser tip is passed through the port of the cystoscope to the midpoint of the neck-dome measurement. Once the

spherical diffuser tip is situated at the midpoint of the bladder, the catheter should be withdrawn.

Calculation of Treatment Time

The surface area of the bladder wall and the subsequent treatment time required to deliver a total light dose of 15 joules/cm² should be calculated knowing the bladder treatment volume (i.e., the volume instilled to distend the bladder) and the laser power output from the fiber optic tip, using the following equation:

$$\text{Light dose (J/cm}^2\text{)} = \frac{\text{Power output from diffuser (W) x Treatment time (seconds)}}{\text{Bladder surface area (cm}^2\text{)}}$$

where:

$$\text{Light dose} = 15 \text{ joules/cm}^2$$

$$\text{Bladder surface area} = 4.83 \times (\text{bladder treatment volume})^{2/3}$$

Urine production or irrigant leakage during treatment can change the bladder surface area and therefore the power density and the delivered light dose. The bladder volume, power output at the fiber tip and positioning of the fiber tip should be checked at the beginning, middle (particularly if the total treatment time is to exceed 45 minutes) and end, and at any time that bleeding is observed or significant changes in bladder volume, fiber power output or fiber tip position are suspected. Whenever treatment is interrupted, 'pause' the laser output, ensuring that the original laser settings and elapsed treatment time are retained. If the bladder appears to be filling during the procedure, sufficient

urine should be evacuated to restore the original volume. By the end of the procedure, the cumulative laser light dose should total 15 ± 1 joules/cm².

The patient should remain under observation for 24 hours post-cystoscopy or until the physician determines that he or she may be safely discharged.

No further courses of treatment with PHOTOFRIN® or light should be used to treat superficial papillary bladder cancer, due to increased risk of bladder contracture.

Esophageal or Endobronchial Cancers

Approximately 40-50 hours after PHOTOFRIN® administration, light should be delivered to the tumor by OPTIGUIDE™ Fiber Optic Diffusers passed through the operating channel of the endoscope/bronchoscope.

Light Doses: Photoactivation of PHOTOFRIN® is controlled by the total light energy (light dose) delivered to the tumor site and depends on the indication, as follows:

- For endobronchial (obstructing or superficial) tumors: 200 joules/cm of tumor length.
- For esophageal tumors: 300 joules/cm of tumor length.

The **cylindrical diffuser** uniformly distributes laser light radially in a cylindrical pattern over the entire length of the fiber optic tip. The following light dosimetry equation applies.

$$\text{Light dose (J/cm)} = \frac{\text{Total power output from diffuser (W)} \times \text{Treatment time (sec)}}{\text{Diffuser length (cm)}}$$

It is recommended that the total power output from the diffuser, as measured by a suitable integrating sphere power meter, be set to [400 mW/cm x cm diffuser length]

which will deliver the appropriate dose using exposure times of either 8 minutes, 20 seconds (endobronchial tumors, 200 J/cm) or 12 minutes, 30 seconds (esophageal tumors, 300 J/cm).

OPTIGUIDE™ cylindrical diffusers are available in several lengths (refer to OPTIGUIDE™ Package Insert) and the diffuser tip length should be chosen to match the length of the tumor. Tumors that differ from available diffuser lengths may require multiple use of a single diffuser or the use of two or more diffusers of differing lengths. Diffuser length should be sized to avoid exposure of nonmalignant tissue to light and to prevent overlapping of previously treated malignant tissue. Diffusers or combinations of diffusers should be selected to minimize patient treatment time.

Examples of diffuser lengths/tumor sizes follow:

TABLE 1. Examples of Use of OPTIGUIDE™ Cylindrical Diffusers

Tumor Length	OPTIGUIDE		Fiber Optic Power Output (mW)	Esophageal Cancer (300 J/cm)		Endobronchial Cancer (200 J/cm) ^a	
	Diffuser Length	Segment Number		Min: Sec Per Segment	Total Time (min:sec)	Min:Sec Per Segment	Total Time (min:sec)
1.0 cm	1.0 cm	1	400	12:30	12:30	8:20	8:20
2.0 cm	2.0 cm	1	800	12:30	12:30	8:20	8:20
3.0 cm	1.5 cm	1	600	12:30	25:00	8:20	16:40
	1.5 cm	2	600	12:30		8:20	
5.0 cm	5.0 cm	1	2000	12:30	12:30	8:20	8:20
7.0 cm	5.0 cm	1	2000	12:30	25:00	8:20	16:40
	2.0 cm	2	800	12:30		8:20	

^a for superficial or obstructing tumors

The cylindrical diffusers may be used either interstitially or intraluminally. For non-circumferential endobronchial tumors that are soft enough to penetrate, interstitial fiber placement is preferred to intraluminal activation, since this method produces better efficacy and results in less exposure of normal bronchial mucosa to the light. When the interstitial technique is used, up to 90% of the length of the diffuser should be inserted into the tumor mass.

Debridement and Retreatment

In patients with endobronchial tumors, gentle debridement is mandatory to remove necrotic tumor debris and clear secretions or mucous plugs, thereby preventing dyspnea, obstruction, atelectasis and infection. For esophageal cancer, debridement is optional since the residua will be removed naturally by peristaltic action. Debridement of residua should be performed two days after light treatment. Vigorous debridement may cause tumor bleeding. Debridement should be discontinued if the volume of bleeding increases, as this may indicate that debridement has gone beyond the zone of PDT treatment effect. Patients with residual tumor may be retreated with laser light at the time of debridement at the same dose as used in the initial treatment. The second light dose is administered 96 to 120 hours after the PHOTOFRIN® injection.

Patients may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each injection 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 or the possibility that the tumor may be eroding into a major blood vessel (see CONTRAINDICATIONS).

High-Grade Dysplasia in Barrett's Esophagus

Approximately 40-50 hours after PHOTOFRIN® administration, light should be delivered by a fiber optic diffuser passed through the central channel of a centering balloon. The choice of fiber optic/balloon diffuser combination will depend on the length of esophagus to be treated (Table 2).

TABLE 2. Fiber Optic Diffuser/Balloon Combination^a

Treated Barrett's Mucosa Length (cm)	Fiber Optic Diffuser Size (cm)	Balloon Window Size (cm)
6-7	9	7
4-5	7	5
1-3	5	3

^a Whenever possible, the BE segment selected for treatment should include normal tissue margins of a few millimeters at the proximal and distal ends

Light Doses: Photoactivation is controlled by the total light dose delivered. The objective is to expose and treat all areas of HGD and the entire length of BE. The light dose administered will be 130 J/cm of diffuser length using a centering balloon. Based on preclinical studies, acceptable light intensity for the balloon/diffuser combinations range from 175-270 mW/cm of diffuser.

To calculate the light dose, the following specific light dosimetry equation applies for all fiber optic diffusers:

$$\text{Light Dose (J/cm)} = \frac{\text{Power Output From Diffuser (W)} \times \text{Treatment Time (sec)}}{\text{Diffuser Length (cm)}}$$

Table 3 provides the settings that will be used to deliver the dose within the shortest time (light intensity of 270 mW/cm). A second option (light intensity of 200 mW/cm) has

also been included where necessary to accommodate lasers with a total capacity that dose not exceed 2.5 W.

TABLE 3. Fiber Optic Power Outputs and Treatment Times Required to Deliver 130 J/cm of Diffuser Length Using Balloon for Areas with HGD

Balloon Window Length (cm)	Diffuser Length (cm)	Light Intensity (mW/cm)	Required Power Output from Diffuser ^a (W)	Treatment Time (sec)	Treatment Time (min:sec)
3	5	270	1.35	480	8:00
5	7	270	1.90	480	8:00
		200	1.40	650	10:50
7	9	270	2.44	480	8:00
		200	1.80	650	10:50

^a As measured by immersing the diffuser into the cuvet in the power meter and slowly increasing the laser power. Note: No more than 1.5 times the required diffuser power output should be needed from the laser. If more than this is required, the system should be checked.

Omeprazole administration: As an adjunctive treatment in BE with HGD, omeprazole should be administered at a minimum of 20 mg twice daily or higher if judged necessary by the attending physician, beginning at least two days before the PHOTOFRIN[®] injection. For additional information, please refer to the Product Monograph for omeprazole.

Pretreatment of Nodules and Post-treatment of Skip Areas

Short fiber optic diffusers (≤ 2.5 cm) are to be used to pretreat nodules with 50 J/cm diffuser length prior to regular balloon treatment in the first laser light session or for the retreatment of "skip" areas after the first light session. For this treatment, the fiber optic diffuser is used without a balloon, and a light intensity of 400 mW/cm should be used.

Table 4 lists appropriate fiber optic power outputs and treatment times using a light intensity of 400 mW/cm.

TABLE 4. Short Fiber Optic Diffusers to be Used Without A Centering Balloon to Deliver 50 J/cm of Diffuser Length at a Light Intensity of 400 mW/cm for Nodules and Skipped Areas

Diffuser Length (cm)	Required Power Output From Diffuser ^a (W)	Treatment Time (sec)	Treatment Time (min: sec)
1.0	0.4	125	2:05
1.5	0.6	125	2:05
2.0	0.8	125	2:05
2.5	1.0	125	2:05

^a As measured by immersing the diffuser into the cuvet in the power meter and slowly increasing the laser power. Note: No more than 1.5 times the required diffuser power output should be needed from the laser. If more than this is required, the system should be checked.

Nodules are to be pretreated at a light dose of 50 J/cm of diffuser length with a short (≤ 2.5 cm) fiber optic diffuser placed directly against the nodule followed by standard balloon application as described above.

First Treatment Course

A maximum of 7 cm of Barrett's mucosa is treated at the first light session using an appropriate size of centering balloon and fiber optic diffuser (Table 2). Whenever possible, the segment selected for the first light application should contain all the areas of HGD. Also, whenever possible, the BE segment selected for the first light application should include normal tissue margin of a few millimeters at the proximal and distal ends.

Repeat Light Application (Treatment of Skip Areas)

A second laser light application may be given to a previously treated segment that shows a 'skip' area, (i.e., an area that does not show sufficient mucosal response) using a short, ≤ 2.5 cm fiber optic diffuser at the light dose of 50 J/cm of the diffuser length (see Table 4).

The treatment regimen is summarized in Table 5. Patients with BE >7 cm, should have the remaining untreated length of Barrett's epithelium treated with a second PDT course at least 90 days later.

TABLE 5. High-Grade Dysplasia in Barrett's Esophagus of ≤ 7 cm

Procedure	Study Day	Light Delivery Devices	Treatment Intent
PHOTOFRIN® Injection	Day 1	NA	Uptake of photosensitizer
Laser Light Application	Day 3 ^a	3,5, or 7 cm balloon (130 J/cm)	Photoactivation
Laser Light Application (Optional)	Day 5	short (≤ 2.5 cm) fiber optic diffuser (50 J/cm)	Treatment of "skip" areas only

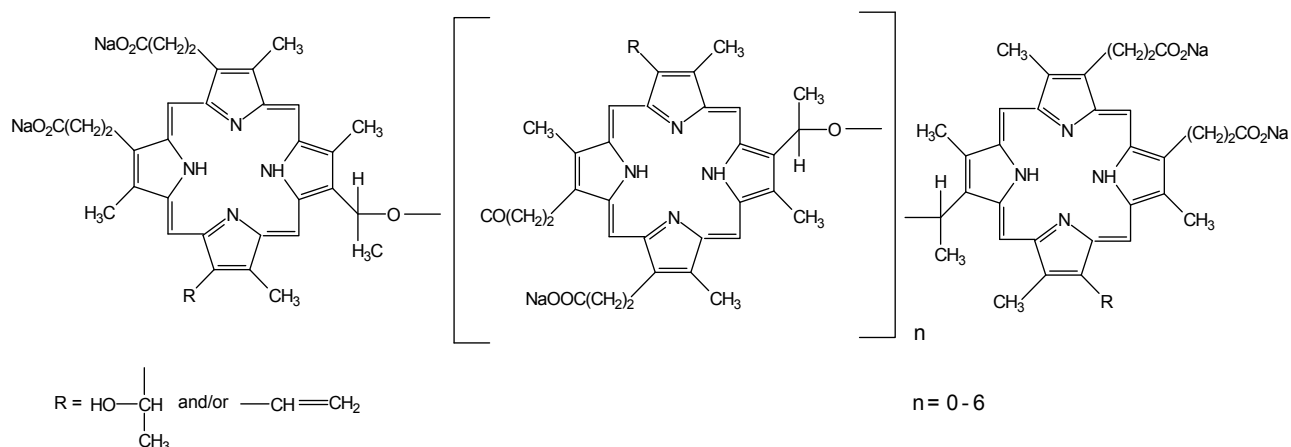
^a Discrete nodules will receive an initial light application of 50 J/cm (using a short diffuser) before the balloon light application

Additional Treatment Courses

Patients may receive a second course of PDT a minimum of 90 days after the initial therapy; up to three courses of PDT (each injection separated by a minimum of 90 days) can be given to a previously treated segment which still shows HGD, low-grade dysplasia (LGD) or Barrett's metaplasia, or to a new segment if the initial Barrett's segment was >7 cm in length. Both residual and additional segments may be treated in the same light session(s) provided that the total length of the segments treated with the

balloon/diffuser combination is not greater than 7 cm. In the case of a previously treated esophageal segment, if it has not sufficiently healed and/or histological assessment of biopsies is not clear, the subsequent course of PDT may be delayed for an additional 1-2 months.

Surveillance: PDT therapy is an adjunct to rigorous surveillance with biopsies (four quadrant jumbo biopsies every 1-2 cm) every three months (until four consecutive negative evaluations have been recorded; further follow-up may be scheduled every 6 to 12 months, as per judgment of physicians).

PHARMACEUTICAL INFORMATION**Drug Substance****Proper Name:** porfimer sodium**Chemical Name:** porfimer sodium is a mixture of oligomers formed by ether and ester linkages of up to 8 porphyrin units.**Structural Formula:****Description:**

Freeze-dried porfimer sodium is a dark red to reddish-brown cake or crystalline powder, which is hygroscopic. The aqueous solubility of porfimer sodium is at least 25 mg/mL in the pH range of 7-8. Porfimer sodium will precipitate out of solution at a pH below 5; Also soluble in methanol and insoluble in methylene chloride. Porfimer sodium has no melting point and decomposes above 250°C.

Composition:

Each vial of PHOTOFRIN[®] (porfimer sodium) contains 15 mg or 75 mg of porfimer sodium as a sterile freeze-dried cake or powder. Sodium hydroxide

and/or hydrochloric acid are used in the manufacturing process to adjust pH.

There are no antimicrobial preservatives or formulation excipients.

Storage:

Unreconstituted PHOTOFRIN® for Injection is stored at 15° to 25°C.

Reconstitution:

PHOTOFRIN® in the 75 mg or 15 mg vial should be reconstituted as follows with 5% Dextrose Injection, USP resulting in a final concentration of 2.5 mg porfimer sodium per mL.

Vial Size*	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration
75 mg	31.8 mL	30.0 mL	2.5 mg/mL
15 mg	6.6 mL	6.0 mL	2.5 mg/mL

* Some excess added to allow complete recovery of vial contents.

Store reconstituted solutions at 2 to 8°C protected from light. Discard unused portion after 24 hours.

Incompatibilities

PHOTOFRIN® should only be reconstituted with dextrose 5% in water. PHOTOFRIN® should not be mixed with other drugs in the same solution.

Special Instructions**Spills and Disposal**

Spills of PHOTOFRIN® should be wiped up with a damp cloth, at which time the wearing of rubber gloves and eye protection are recommended. Skin and eye contact should be avoided. 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. 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 overdose, any accidentally exposed person must be protected from bright light.

AVAILABILITY OF DOSAGE FORMS

PHOTOFRIN® (porfimer sodium) is available in the following sizes:

75 mg vial

15 mg vial

CLINICAL STUDIES

Papillary Bladder Cancer

A Phase III, multicenter, randomized, open-label study was performed in patients with superficial papillary transitional cell carcinoma of the urinary bladder, stage TaG1 with frequently recurring disease or stages TaG2, T1G1-3. Following transurethral resection, patients were randomized to either single doses of PHOTOFRIN® plus light or an observation control arm and the time to tumor recurrence was compared between

groups. Efficacy analysis was performed on 30 patients. The median follow-up time for all randomized patients was 456 days. In the PHOTOFRIN® group, 9 of 17 patients (53%) recurred compared with 10 of 13 patients (77%) in the observation group. The median time to tumor recurrence for patients who received PHOTOFRIN® was 379 days versus 93 days for the observed group.

Esophageal Cancer

A Phase III, multicenter, randomized, open-label clinical trial was conducted comparing PDT with PHOTOFRIN® and controlled uniform laser light versus thermal ablation therapy using the Nd:YAG laser for the removal of tumor mass and subsequent local palliation of dysphagia in 236 patients with partially obstructing esophageal carcinoma. Each course of PDT with PHOTOFRIN® consisted of one injection of the drug followed by up to two laser light applications. A maximum of three courses of PDT with PHOTOFRIN® was allowed. Repeat Nd:YAG laser sessions were given until maximal anticipated tumor debulking and palliation of dysphagia were achieved. Thus, a course of Nd:YAG laser therapy consisted of multiple laser application sessions. An unlimited number of Nd:YAG courses was permitted. Efficacy results after one course of therapy, based on all 236 randomized patients, are provided in Table 6. Based on all courses, nine PDT-treated patients and two Nd:YAG-treated patients had no visible evidence of tumor and were considered to be in complete response (CR). In six PDT-treated patients and two Nd:YAG-treated patients, CR was verified by pathology.

TABLE 6. Course 1 Efficacy Results in Patients with Partially Obstructing Esophageal Cancer

	Month 1 Improvement in Dysplasia (% of Pts)	Month 1 Objective Tumor Response Rate (% of Pts)	Median TPF ^a (Days)	Mean No. of Treatment Endoscopies Per Patient ^b
PHOTFRIN® PDT (n=118)	35%	32%* (CR 2%, PR ^c 30%)	34	2.1
Nd: YAG (n=118)	29%	20% (CR 0%, PR 20%)	42	2.8

* Statistically significant difference between PDT and Nd:YAG (p<0.05)

^a Time to Palliation Failure

^b Treatments not compared statistically

^c Partial response, based on change in smallest esophageal luminal diameter

In addition, PDT with PHOTOFRIN® was utilized in a Phase III, multicenter, single-arm study in 19 patients with completely obstructing esophageal carcinoma using the same schedule as above. Based on Month 1 assessments for Course 1 for all 19 patients enrolled, 42% of patients showed improvement in dysphagia grade, 32% of patients achieved partial objective tumor responses (PR), and median time to palliation failure was 30 days. Based on all courses, three patients achieved a complete tumor response; one of these was verified by pathology.

Endobronchial Cancer

Two randomized multicenter Phase III studies were conducted to compare the safety and efficacy of PHOTOFRIN® PDT versus Nd:YAG laser therapy for reduction of obstruction and palliation of symptomatic patients with partially or completely obstructing endobronchial nonsmall cell lung cancer. Assessments were made at one week and at monthly intervals after treatment. Table 7 shows the results from all randomized patients in the two studies combined. Objective tumor response rates (CR +

PR), which demonstrate reduction of obstruction, were 59% for PDT and 58% for Nd:YAG at Week 1. The response rates at one month were 55% for PDT and 29% for Nd: YAG. These reductions in endobronchial obstruction resulted in improvements in atelectasis and pulmonary symptoms in many patients (Tables 7 and 8).

TABLE 7. Efficacy Results from Studies in Late-stage Obstructing

Endobronchial Cancer – All Randomized Patients^a

EFFICACY PARAMETER (% of Patients)	PDT N=102	Nd:YAG N=109
OBJECTIVE TUMOR RESPONSE^b		
Week 1	59%	58%
Month 1	55%	29%
SYMPTOM IMPROVEMENT^c		
Week 1	58%	51%
Month 1	54%	35%
ATELECTASIS IMPROVEMENT^d		
Any Time in Course 1	n=60 50%	n=71 34%

^a Statistical comparisons were precluded by the amount of missing data at Month 1 (e.g., for tumor response PDT 32%, Nd:YAG 46%).

^b CR+PR, CR = complete response (absence of bronchoscopically visible tumor), PR = partial response (increase of =50% in the smallest luminal diameter); for completely obstructing tumors, any appearance of a lumen).

^c Individual symptoms were evaluated using 5- or 6-grade severity scales. A change of at least 1 grade on at least one symptom was counted as improvement. Clinically significant improvements for specific symptoms are summarized in Table 4.

^d In patients with atelectasis at baseline.

Patient symptoms were evaluated using a 5- or 6-grade pulmonary symptom severity rating scale for dyspnea, cough, and hemoptysis. Patients with moderate to severe symptoms are those most in need of palliation. Improvements of two or more grades are considered to be clinically significant. Table 8 shows the percentages of patients with moderate to severe symptoms at baseline who demonstrated at least a 2-grade improvement at any time during the interval evaluated.

TABLE 8. Efficacy Results from Studies in Late-stage Obstructing Endobronchial Cancer – Clinically Significant Improvements in Patients with Moderate to Severe Symptoms at Baseline^a

CLINICALLY SIGNIFICANT SYMPTOM IMPROVEMENT ^b (% of Patients)	PDT	Nd:YAG
ANY SYMPTOM	n=89	n=89
Week 1	25%	29%
Month 1	35%	17%
DYSPNEA	n=60	n=68
Week 1	15%	18%
Month 1	20%	7%
COUGH	n=63	n=65
Week 1	6%	9%
Month 1	13%	5%
HEMOPTYSIS	n=24	n=31
Week 1	58%	29%
Month 1	71%	32%

^a Statistical comparisons were precluded by the amount of missing data at Month 1.

^b Dyspnea was graded on a 6-point severity scale; cough and hemoptysis on 5-point scales. Clinically significant improvement was defined as a change of at least two grades from baseline.

In a separate retrospective analysis, patients were individually evaluated to identify those patients whose benefit to risk ratio was most favorable, i.e., those who obtained clinically important benefit with minimal adverse reactions. Clinically important benefit was defined as one of the following:

1. a substantial improvement in pulmonary symptoms at Month 1 or later (dyspnea ≥ 2 grades, hemoptysis ≥ 3 grades, cough ≥ 3 grades or increase in FEV₁ $\geq 40\%$);
2. a moderate improvement in symptoms at Month 2 or later (dyspnea 1 grade, cough 2 grades, hemoptysis 2 grades or increase in FEV₁ $\geq 20\%$); or
3. a durable objective tumor response (CR or PR maintained to Month 2 or longer).

Thirty-six (36) of the 99 PDT-treated patients (36%) and 23 of the 99 Nd:YAG-treated patients (23%) received clinically important benefit with only minimal or moderate toxicities of short duration. Thirty-four (34) of 99 PDT-treated patients demonstrated improvements in 2 or more efficacy endpoints (dyspnea, cough, hemoptysis, sputum,

atelectasis, pulmonary function tests of FEV₁ or FVC, Karnofsky Performance Score or tumor response) and 29 patients had improvements in 3 or more. The median duration of documented benefit in the 36 patients was 63 days.

PHOTOFRIN® PDT was also evaluated in the treatment of superficial endobronchial tumors in 100 inoperable patients in three noncomparative studies. These patients had either carcinoma *in situ* or microinvasive tumors. Microinvasive lung cancer is defined histologically as disease, which invades beyond the basement membrane but not through or into the cartilage. For 24 of the 100 patients, it was clearly documented that surgery and radiotherapy were not indicated. These 24 patients were all inoperable for medical or technical reasons. Radiotherapy was not indicated due to prior high-dose radiotherapy (nine patients), poor pulmonary function (seven patients), multifocal multilobar disease (eight patients), and poor medical condition (one patient). As shown in Table 9, the tumor response rate (biopsy proven at any time after treatment) was 92%, median time to tumor recurrence was more than 2.7 years, median survival was 3.4 years and disease-specific survival was >3.5 years. The results from the whole population were comparable to those in the subset and in the remaining patients.

TABLE 9. Overall Efficacy Results in Patients with Superficial Endobronchial Tumors

EFFICACY PARAMETER	PHOTOFRIN [®] PDT	
	N=24	N=100
COMPLETE TUMOR RESPONSE, BIOPSY-PROVEN Number of Patients (%)	22 (92%)	79 (79%)
TIME TO TUMOR RECURRENCE IN PATIENTS WITH COMPLETE RESPONSE		
Number of Patients (%) with Recurrences	10 (46%)	33 (42%)
Median Time to Tumor Recurrence	2.7 years	2.8 years
[95% Confidence Interval]	[1.0, -- ^a]	[1.5, -- ^a]
SURVIVAL		
Number of Patients (%) who Died of Any Cause	9 (38%)	44 (44%)
Median Survival	3.4 years	3.5 years
[95% Confidence Interval]	[2.9, -- ^a]	[2.9, 6.1]
DISEASE SPECIFIC SURVIVAL		
Number of Patients (%) who Died of Lung Cancer	7 (29%)	31 (31%)
Median Disease-Specific Survival	>3.5 years	5.7 years
[95% Confidence Interval]	[3.2, -- ^a]	[3.5, -- ^a]

^a The upper limit of the confidence interval could not be estimated due to an insufficient number of patients whose tumors recurred (Time to Tumor recurrence) or who died (Survival).

High-Grade Dysplasia associated with Barrett's Esophagus

A multicentre, partially blinded, randomized, controlled study was conducted in North America and Europe to assess the efficacy of PDT with PHOTOFRIN[®] for injection plus omeprazole (PHOTOFRIN[®] PDT + OM) in producing complete ablation of HGD in patients with BE as compared to patients receiving omeprazole alone (OM Only).

Omeprazole was administered as 20 mg twice daily. Patients were centrally randomized in a 2:1 design to receive PHOTOFRIN[®] PDT plus omeprazole or omeprazole alone. All patients underwent rigorous systematic quarterly endoscopic biopsy surveillance. Four-quadrant jumbo biopsies at every 2 cm of the entire Barrett's mucosa were obtained at each follow-up visit. All histological assessments were carried out at a central pathology

laboratory and read by pathologists blinded to the treatment administered. The main efficacy endpoint was the complete response rate (CR3 responders) defined as the complete ablation of HGD at any one of the endoscopic assessment time points. The secondary efficacy endpoints were the quality of the complete response defined as CR2 responders (complete ablation of all grades of dysplasia) and CR1 responders (complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium), Duration of Response (CR), Time to Progression to Cancer (TTP), Time to Treatment Failure (TTF), and Survival time.

A total of 208 patients who had biopsy-proven HGD in BE and no esophageal invasive cancer or history of cancer participated in the study. The mean age was 66.13 years (38.4 to 88.5 years) in the PHOTOFRIN® PDT + OM group, and 67.27 (36.1 to 87.6) in the OM Only group. The patients in both treatment groups were predominantly male (85%), Caucasian (99%), and former smokers (64%).

Table 10 presents the overall clinical response for both treatment groups in the ITT population whose response was at CR3 or better at any one of the evaluation time points.

TABLE 10. Complete Response Rates (ITT Population)

Responders		Treatment Groups				p-value ^a
		PHOTOFRIN® PDT + OM		OM Only		
Follow-up period		6-month	24-month	6-month	24-month	
Numbers of Patients	N	138	138	70	70	
CR3 or better^b	n	99	106	22	27	<0.0001
	Proportion	0.717	0.768	0.314	0.386	
	95% CI	(0.642, 0.739)	(0.698, 0.839)	(0.206, 0.423)	(0.272, 0.500)	

^a Fisher's Exact test.

^b CR3 or better: Ablation of all areas of HGD.

Note: Six patients in the PHOTOFRIN® PDT + OM group and three patients in the OM Only group without post-baseline biopsy are considered as non-responders

Table 11. Proportion of patients responding to treatment, progressing to cancer, and developing esophageal stricture per response category after a minimum of 6 and 24 months of follow-up (ITT population)

Response Category	Outcome Parameters	Statistics	Treatment Groups			
			PHOTOFRIN [®] PDT + OM N=138		OM Only N=70	
			6-month follow-up	24-month follow-up	6-month follow-up	24-month follow-up
Overall	CR3 or better responders ^A	n (%)	99 (72)	106 (77)	22 (31)	27 (39)
	Cancer rate	n (%)	14 (10)	18 (13)	13 (19)	20 (28)
	Esophageal strictures ^B	n (%)	48 (35)	49 (37)	0	0
CR3 or better responders	CR3 or better responders ^A	n (%)	99 (72)	106 (77)	22 (31)	27 (39)
	Cancer rate	n (%)	4 (4)	6 (6)	0	1 (4)
	Esophageal strictures ^B	n (%)	28 (28)	39 (37)	0	0
Non-responders	CR3 or better responders ^A	n (%)	39 (28)	32 (23)	48 (69)	43 (61)
	Cancer rate	n (%)	10 (26)	12 (38)	13 (27)	19 (44)
	Esophageal strictures ^B	n (%)	20 (51)	10 (31)	0	0

^a Complete ablation of high-grade dysplasia

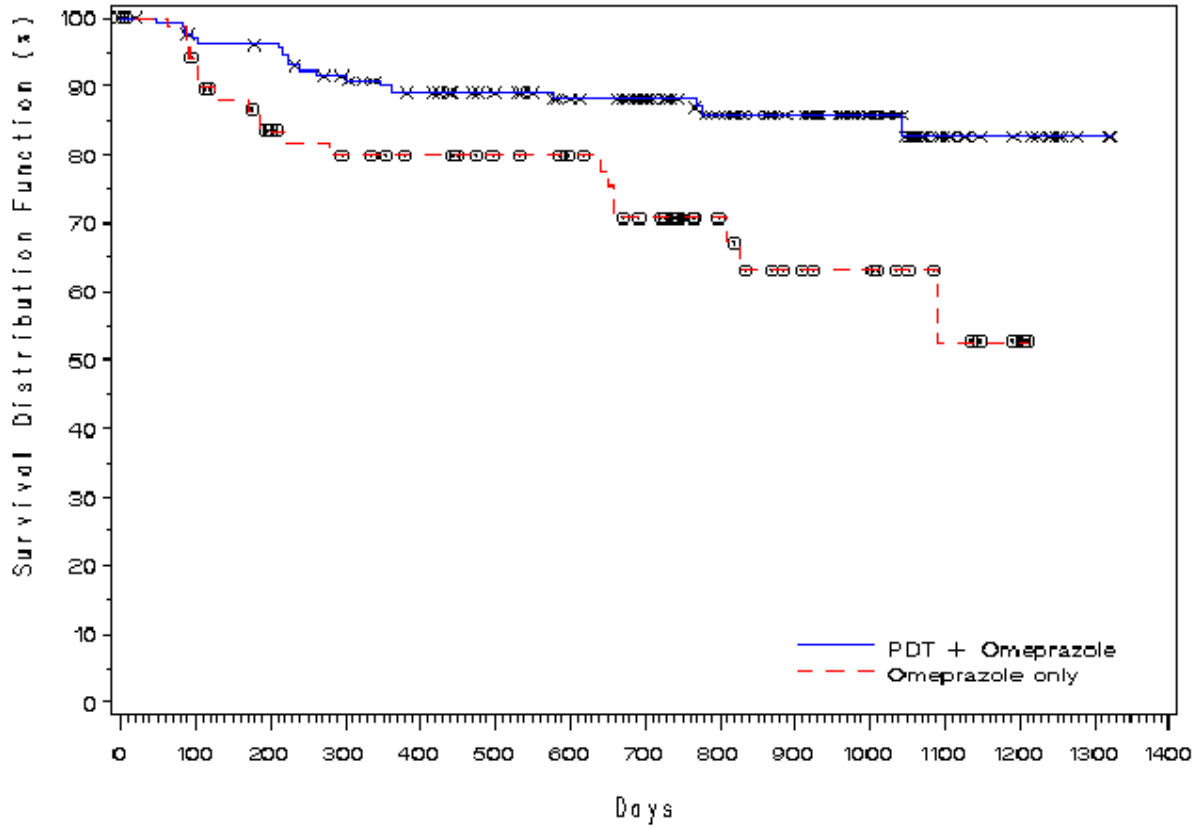
^b Defined as dilated esophageal narrowing

The proportion of responders was significantly higher in the PHOTOFRIN[®] PDT + OM group as compared to the proportion of responders observed in the OM Only group (77% versus 39%, respectively; $p < 0.0001$).

The quality of response in the PHOTOFRIN[®] PDT + OM group was significantly better than that measured in the OM Only group at all response levels. Seventy-two (52.2%) patients in the PHOTOFRIN[®] PDT + OM group achieved a CR1 response as compared to five (7.1%) patients in the OM Only group. Eighty-one (58.7%) patients in the PHOTOFRIN[®] PDT + OM group achieved a CR2 or better response as compared to

ten (14.3%) patients in the OM Only group. The rate of patients who progressed to cancer in the PHOTOFRIN PDT + OM group was statistically lower than that in the OM only group ($p=0.0060$). By the end of the minimum 2-year follow-up, 18 (13%) of patients in the PHOTOFRIN® PDT + OM group had progressed to cancer in contrast with 20 patients (28%) in the OM Only group. By the end of the 24-month follow-up period, patients in the PHOTOFRIN® PDT + OM group experienced a significant delay in the TTP compared to those in the OM Only group ($p=0.0014$). The following graph shows a comparison of TTP between the two treatment groups. The TTP for the OM Only group started to differ significantly from that for the PHOTOFRIN® PDT + OM group at the 90-day time point. A further, more pronounced disparity in TTP occurred at the 650-day time point.

Time to Progression to Cancer



x: Censored observation for PDT+OMEPPRAZOLE
o: Censored observation for OMEPPRAZOLE ONLY

PHARMACOLOGY

Pharmacokinetics

Animal Studies

Protein binding of porfimer sodium to rat, dog and human sera was similar (80-90%). Binding was to both albumin and lipoproteins.

Tissue distribution of radiolabelled PHOTOFRIN® was studied in mice and rats. The highest concentrations of radioactivity were observed in the liver followed by spleen, adrenal gland, bladder and kidney, whereas relatively low concentrations were observed in the skin. PHOTOFRIN® related porphyrins were cleared slowly from tissues (half-lives >100 hours). The clearance from tumor was slower than from normal tissue with maximum tumor/normal tissue and tumor/skin ratios observed at 48 to 72 hours after dosing. Porphyrins related to PHOTOFRIN® did not cross the placental barrier.

The major route of elimination for porphyrins related to PHOTOFRIN® in mice and rats was via feces (40-60%) with a small percentage of the dose excreted in urine (4-6%).

TOXICOLOGY

Acute Toxicity

The acute toxicity of PHOTOFRIN® was evaluated in mice and rats with and without light irradiation, and in dogs without light irradiation. In the absence of photoirradiation, no mortality occurred with intravenous doses of PHOTOFRIN® up to 100 mg/kg in the mouse, 75 mg/kg in the rat and 25 mg/kg in the dog. As expected with this type of agent, the acute intravenous toxicity in mice and rats was highly dependent on light

activation. With light irradiation, the maximum non-lethal dose of PHOTOFRIN® was 12.5 mg/kg in the mouse and 40 mg/kg in the rat. Dogs were not tested with light activation of PHOTOFRIN®.

Deaths were attributed to hypoxemia and/or the rapid transfer of intravascular fluids to the interstitial fluid compartment in mice and to hemolysis/hypoxemia in rats.

Multiple Dose Toxicity

The toxicity of PHOTOFRIN® was evaluated in multiple-dose studies without light activation in rats and dogs. PHOTOFRIN® was given intravenously to rats (at doses of 5, 10, 15 or 20 mg/kg) and dogs (at doses of 2.5, 5, 7.5, or 10 mg/kg) once weekly for 13 weeks.

The multidose effects were relatively minor, being limited to transient clinical signs, decreases in red blood cell parameters consistent with hemolysis, increases in neutrophils and total leukocytes, and some sporadic serum biochemical changes, the magnitude of which was not considered to be biologically meaningful. Pigment, associated with direct deposition of PHOTOFRIN®, was observed in spleen, liver, lymph nodes, and bone marrow. The pigment was slowly cleared by the reticuloendothelial system (macrophages). There was no morphologic evidence to suggest any adverse effect. Biliary duct hyperplasia seen in rats was minimal to mild and not associated with overt hepatotoxicity. Mild to moderate atrophy and/or vacuolation of the adrenal zona fasciculata was observed in dogs but was considered minor and was not accompanied by organ weight changes. When animals were allowed to recover for 8 weeks after

treatment (rats only) reversal of these effects was noted, further indicating no long-term or irreversible toxicity.

Special Toxicity Studies

Phototoxicity

In rats, susceptibility to skin phototoxicity induced by fluorescent light persisted between 12 and 16 weeks after a single high intravenous dose (60 mg/kg) of PHOTOFRIN® .

This is consistent with results in clinical trials, where skin photosensitivity persists up to 6 weeks after photodynamic therapy with PHOTOFRIN® .

***In Vitro* Human Blood Compatibility**

In the absence of light, PHOTOFRIN® causes hemolysis at concentrations approximately four to five times the mean blood concentration (C_{max}) achieved in humans with the recommended dose.

Immunotoxicity

PHOTOFRIN® has no antigenicity as determined by passive cutaneous anaphylaxis and active systemic anaphylaxis in guinea pigs and antibody production in mice.

Irritation Potential

PHOTOFRIN® is not an ocular, dermal, or intravascular irritant in the absence of light.

PHOTOFRIN® is an irritant when injected intramuscularly into rabbits (1.5 mL at 2.5 mg/mL) in the absence of light.

Reproduction and Teratology in Rats and Rabbits

A reproduction study performed in rats revealed no evidence of impaired fertility due to PHOTOFRIN® up to a dose which is two times the maximum recommended human dose based on body weight and one-half the human dose based on body-surface area.

Teratology studies in rats and rabbits revealed no evidence of teratogenicity due to PHOTOFRIN® at doses which are up to four (rats) and two (rabbits) times the maximum recommended human dose based on body weight and which are similar to the human dose based on body surface area.

PHOTOFRIN®, when given to rats during the perinatal/postnatal period, had no effects on parturition or lactation of the dams and no effects on the development of offspring, with the exception of transient, small body weight at the highest maternally toxic dose tested. This dose is 2 times the maximum recommended human dose based on body weight and one half the human dose based on body surface area.

Mutagenicity

PHOTOFRIN® was evaluated in a validated, standard battery of mutagenicity assays. PHOTOFRIN® was nonmutagenic in microbial mutagenicity assays conducted at concentrations up to 5000 mcg/plate without and with light irradiation (200 footcandles). PHOTOFRIN® was also nonmutagenic in a mammalian point mutation assay using Chinese hamster ovary cells (CHO/HPRT) without and with light irradiation (up to 630 J/m²) at a PHOTOFRIN® concentration of 10 mcg/mL without metabolic activation and a concentration of 50 mcg/mL with metabolic activation. In an *in vitro* cytogenetics assay, PHOTOFRIN® did not induce chromosome aberrations in Chinese hamster ovary cells (CHO) without and with light irradiation (up to 630 J/m²) at a concentration of 3 mcg/mL without metabolic activation and 25 mcg/mL with metabolic activation. In a sister chromatid exchange assay in CHO cells, PHOTOFRIN® at a concentration of 2 mcg/mL without metabolic activation and 15 mcg/mL with metabolic activation induced a marginally positive response only after irradiation by light (210 to 630 J/m²). *In vivo*, PHOTOFRIN® without light irradiation did not induce chromosomal aberrations in mice at IV doses up to 75 mg/kg. This dose is 38 times the maximum recommended human dose based on body weight and four times the human dose based on body surface area.

PHOTOFRIN® was also studied in mutagenicity assays reported in the published literature, some of which were nonvalidated, nonstandard assays. PHOTOFRIN® with and without light irradiation was nonmutagenic in a mammalian point mutation assay in Chinese hamster lung fibroblast V79 cells, and it did not increase cell transformation activity in mouse embryo C3H 10T ½ cells. PHOTOFRIN® with light irradiation produced multilocus mutations in two of three substrains of mouse lymphoma L5178Y cells and

induced a positive response in a sister chromatid exchange assay in Chinese hamster lung fibroblast V79 cells. PHOTOFRIN® with light irradiation also produced DNA strand breaks in NHIK 3025 human cervical carcinoma cells and increases in the number of DNA-protein crosslinks in mouse lymphoma L5178Y cells. Based on all of these data, the overall mutagenic risk of PHOTOFRIN® is considered minimal.

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