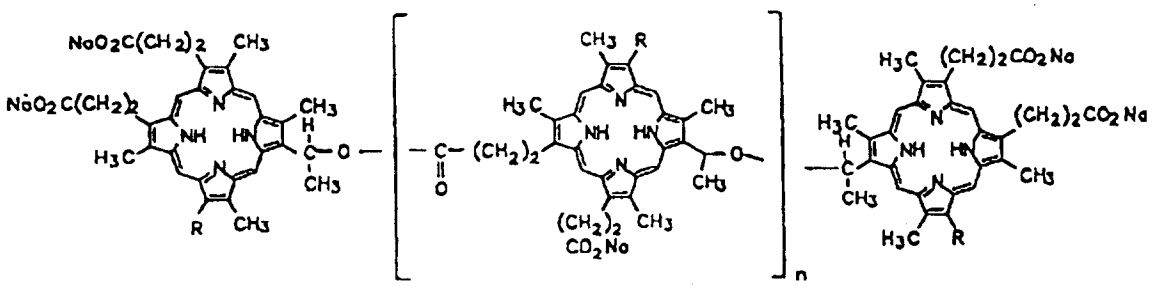
PHOTOFRIN® (sterile porfimer sodium)

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 = $HO\underset{\underset{CH_3}{|}}{CH}$ 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	Number (%) of Patients PDT with PHOTOFRIN® n=88	
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	Number (%) of Patients: PDT with PHOTOFRIN® n=88	
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	Number (%) of Patients 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, congestiveheartfailure, 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.