Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Photofrin powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15 mg or 75 mg of porfimer sodium.

After reconstitution, the final concentration of porfimer sodium is 2.5 mg/mL (see section 6.6).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Solution for Injection
Dark red to reddish brown lyophilized powder/cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Photodynamic therapy (PDT) with PHOTOFRIN® is indicated for:

- Palliative treatment of obstructing endobronchial nonsmall cell lung cancer.
- Palliative treatment of obstructing oesophageal cancer.

4.2 Posology and method of administration

Photodynamic therapy (PDT) with Photofrin is a two−stage process requiring administration of both medicinal product and light. The first stage of PDT is the slow intravenous injection of Photofrin at a dose of 2 mg/kg. The second stage of therapy is illumination with laser light 40−50 hours following injection with Photofrin. Patients may receive a second laser light application 96−120 hours after medicinal product administration. Therefore, one course of PDT consists of one injection plus one or two light applications. Up to 2 more courses of PDT may be given, with each injection separated by a minimum of 30 days.

Photofrin **Administration**

Photofrin should be reconstituted according to the directions given in section 6.6, and administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight.

$$\text{Photofrin (mL)} = \frac{\text{Patient's weight (kg)} \times 2 \text{ mg/kg}}{2.5 \text{ mg/mL}} = 0.8 \times \text{Patient's weight}$$

As with all intravenous injections, care should be taken to prevent extravasation at the injection site. If extravasation does occur, the area should be protected from light for at least 30 days and up to 90 days or more. There is no known benefit from injecting the extravasation site with another substance.

Photoactivation of Photofrin

Uniform and complete light delivery to the tumour mass is essential for activation of porfimer sodium. Photofrin is activated by light in the spectral region of 630 nm. Approximately 40−50 hours after Photofrin administration, laser light should be delivered to the tumour by a cylindrical fibre optic diffuser or a microlens fibre optic passed through the operating channel of an endoscope/bronchoscope. The choice of the fibre optic diffuser length will depend on the tumour size.

Cylindrical diffusers are available in several lengths and the diffuser tip length should be chosen to match the length of the tumour. Tumours with lengths 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 non-malignant tissue to light and to prevent overlapping of previously treated malignant tissue. Diffusers or combinations of diffusers should be selected to minimise patient treatment time.

Light Doses: Photoactivation of Photofrin is controlled by the total light energy (light dose) delivered to the tumour site and depends on the indication and the means of light delivery, as follows:

- For endobronchial tumours, the cylindrical diffuser will be suitable for most tumours. The light dose for endobronchial tumours using the cylindrical diffuser is 200 joules/cm of diffuser length. Alternatively, the microlens fibre optic may be appropriate for small, flat, non-circumferential tumours. The light dose using the microlens fibre optic is 100 j/cm^2.
- For oesophageal tumours, a light dose of 300 j/cm of diffuser length should be delivered using a cylindrical diffuser.

Cylindrical Diffuser (Endobronchial or Oesophageal Lesions): The cylindrical diffuser uniformly distributes laser light radially in a cylindrical pattern over the entire length of the fibre optic tip. The following light dosimetry equation applies.

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

Hence, the total power output from the diffuser, as measured by a suitable integrating sphere power meter, should be set to [400 mW/cm x length of diffuser in cm] to deliver the appropriate dose using exposure times of either 8 minutes, 20 seconds (endobronchial tumours, 200 J/cm) or 12 minutes, 30 seconds (oesophageal tumours, 300 J/cm).

The cylindrical diffusers may be used either interstitially or intraluminally. For non-circumferential endobronchial tumours that are soft enough to penetrate, interstitial fibre 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 tumour mass.

Microlens (Endobronchial lesions only): The microlens fibre optic delivers a diverging, forward-directed beam of light similar to that produced by a torch. It is used to treat small lesions by positioning the microlens tip so that the lesion is uniformly illuminated by a circular spot. The diameter of the spot can be increased or decreased by moving the microlens tip further from or nearer to the lesion. The following light dosimetry equation applies:

$$\text{Light dose (J/cm}^2\text{)} = \frac{\text{Total power output at fibre tip (W) x Treatment time (seconds)}}{\text{Treatment area (cm2)}}$$

Hence, the power output at the microlens fibre tip, as measured by a power meter, should be set to [200 mW/cm^2 x tumour area in cm^2]. This will deliver the dose of 100 J/cm^2 of tumour using an exposure time of 8 minutes, 20 seconds per area treated.

Debridement and Retreatment

In patients with endobronchial tumours, debridement is mandatory to remove necrotic tumour debris and clear secretions or mucous plugs, thereby preventing possible dyspnoea, obstruction, atelectasis and infection which may cause life-threatening respiratory failure.

For oesophageal cancer, debridement is optional since the residua will be removed naturally by peristaltic action. Debridement of residua should be performed 2 days after light treatment. Patients with residual tumour may be retreated with laser light at the time of debridement at the same light dose as used for the initial treatment. The second light dose should be 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 tracheo-oesophageal or broncho-oesophageal fistula or for the possibility that the tumour may be eroding into a major blood vessel (see section 4.3).

Use in Children

Safety and effectiveness in children have not been established. Photofrin should not be used in children until further data are available.

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 the effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

Use in Patients with Impaired Hepatic or Renal Function

The influence of renal and hepatic impairment on exposure to Photofrin has not been evaluated.

4.3 Contraindications

Photodynamic Therapy (PDT) with porfimer sodium is contraindicated in patients with:

- Porphyria or known allergies to porphyrins or to any ingredient in the formulation or component of the container.
- Tracheo-oesophageal or broncho-oesophageal fistula.
- Suspected erosion of major blood vessels due to risk of massive potentially fatal haemorrhage.
- Severe hepatic and/or renal impairment.
- 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 porfimer sodium and laser light treatment.

4.4 Special warnings and precautions for use

PDT with porfimer sodium for treatment of oesophageal or endobronchial cancers should be applied by physicians trained in the endoscopic use of PDT with porfimer sodium and only in those facilities properly equipped for the procedure.

All patients who receive Photofrin will be photosensitive for 30 days or more 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.). Some patients may remain photosensitive for up to 90 days or more. Patients with mild to moderate hepatic impairment should be clearly informed that the period requiring the precautionary measures described above may be longer than 90 days. Photosensitivity is due to residual medicinal product which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is, however, beneficial because the remaining medicinal product 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. Patients should wear protective clothing and dark sunglasses when outdoors.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 the skin for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, oedema, 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 the patient travels to a different geographical area with greater sunshine, their level of photosensitivity should be retested. **Conventional ultraviolet (UV) sunscreens will only protect against UV light-related photosensitivity and will be of no value in protecting against porfimer sodium-induced photosensitivity reactions caused by visible light.**

As the 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.

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 tumour 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, at least four weeks should be allowed to pass between the two treatments in order for the acute inflammatory reaction from radiotherapy to subside.
The risk of acute hypersensitivity reactions including anaphylaxis cannot be ruled out. Although no cases of anaphylaxis have been reported, rashes have been observed. In case of an allergic reaction, appropriate measures (standard of care) should be taken and the PDT treatment should not be repeated.

Photofrin is not dialysable.

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received porfimer sodium. For at least 30 days and up to 90 days, when outdoors, patients should wear dark sunglasses, which have an average white light transmittance of <4%. Patients should be advised to consult their ophthalmologist if they notice any vision changes after treatment with porfimer sodium and PDT.

Oesophageal Cancer

PDT is not recommended when the oesophageal tumour erodes into the trachea or bronchial tree and the likelihood of tracheo-oesophageal or broncho-oesophageal fistula formation is sufficiently high.

Patients with oesophageal varices should be treated with extreme caution because of the high risk of bleeding.

Endobronchial Cancer

Patients should be assessed for tumours that may be eroding into a pulmonary blood vessel (see section 4.3). Patients at high risk for fatal massive haemoptysis include those with large, centrally located tumours, those with cavitating tumours or those with extensive tumour extrinsic to the bronchus.

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

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

Patients with endobronchial lesions must be closely monitored between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress (see Section 4.2). 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.

4.5 Interaction with other medicinal products and other forms of interaction

There is no clinical information concerning interactions with other medicinal products involving porfimer sodium. However, it is possible that concomitant use of other agents known to produce photosensitivity reactions (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin and fluoroquinolones) 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 ischaemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many medicinal products 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 sulphoxide, beta−carotene, ethanol, formate and mannitol would be expected to decrease PDT activity.

Preclinical data also suggest that tissue ischaemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with Photofrin PDT. Medicinal products 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.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women Animal studies showed no teratogenicity although some foetotoxic effects were observed (see section 5.3). Porfimer sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Women of childbearing potential should practice an effective method of contraception during and for at least 90 days after the PDT period and have a pre-treatment pregnancy test performed.

It is unknown whether porfimer sodium is excreted in to human milk. Women receiving Photofrin should not breast feed.

4.7 Effects on ability to drive and use machines

Photofrin has no or negligible influence on ability to drive and use machines.

For the PDT procedure, sedation may be required and consequently caution should be taken. Patients should not drive or use machines after the light treatment if they have been sedated for the procedure.

4.8 Undesirable effects

The skin of all patients who receive porfimer sodium will be photosensitive for 30 days or more (see section 5). Photosensitivity reactions are avoidable through proper patient education.

Photosensitivity reactions occurred in approximately 20% of patients treated with PHOTOFRIN® in clinical studies. 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. Other less common skin manifestations were also reported in areas where photosensitivity reactions had occurred, such as increased hair growth, skin disorders, skin nodules, increase wrinkles and increased skin fragility.

These manifestations may be attributable to a pseudoporphyria state (temporary drug-induced cutaneous porphyria). The only other known systemic reaction is constipation.

The toxicities associated with PDT across all indications are primarily local, in the immediate area of the laser light application, and sometimes extending into adjacent tissues. The local and 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 porfimer sodium in patients with overtly disseminated intraperitoneal malignancies.

One case of possible precipitation of cataracts has been reported. A 51 year-old obese man was treated with porfimer sodium for HGD in Barrett's Oesophagus (BO), off label. Four months later he noted vision changes along with a mild skin photosensitivity reaction. A visit to his ophthalmologist revealed a refractive error change that later progressed to cataracts in both eyes. Both of his parents had a history of cataracts in their 70s. Whether porfimer sodium directly caused, or accelerated a familial underlying weakness is unknown.
MedDRA conversion Version 10.1 at a Preferred Term level has been used for adverse event terms in this document.

Oesophageal Cancer
Very common (≥10/100) and common (≥5/100 to <10/100) adverse events reported in patients (n=127) who had completely or partially obstructing oesophageal cancer treated with porfimer sodium PDT are presented below. Serious and other notable adverse events observed in less than 5% of patients included: abnormal vision, angina pectoris, bradycardia, bronchitis, bronchospasm, diplopia, eye pain, gastric ulcer, ileus, jaundice, laryngotracheal oedema, myocardial infarction, oesophageal perforation, oesophagitis, peritonitis, photophobia, pneumonitis, pulmonary haemorrhage, pulmonary oedema, respiratory failure, sick sinus syndrome, stridor, supraventricular tachycardia.

Very Common (≥10/100)

SYSTEM ORGAN CLASS	**Adverse Event**
BLOOD and LYMPHATIC SYSTEM DISORDERS	Anaemia
GASTROINTESTINAL DISORDERS	Abdominal pain (Upper, lower), constipation, nausea, vomiting
GENERAL and ADMINISTRATION SITE CONDITIONS	Chest pain, pain, pyrexia
PSYCHIATRIC DISORDERS	Insomnia
RESPIRATORY, THORACIC and MEDIASTINAL DISORDERS	Dyspnoea, pharyngitis, pleural effusion, pneumonia, respiratory distress
SKIN and SUBCUTANEOUS TISSUE DISORDERS	Photosensitivity reaction

Common (>5/100 to <10/100)

SYSTEM ORGAN CLASS	**Adverse Event**
CARDIAC DISORDERS	Atrial fibrillation, cardiac failure, tachycardia
GASTROINTESTINAL DISORDERS	Diarrhoea, dyspepsia, dysphagia,, haematemesis, oesophageal oedema, oesophageal stenosis, oesophageal tumour bleeding
GENERAL and ADMINISTRATION SITE CONDITIONS	Asthenia, generalised oedema, oedema peripheral
INFECTIONS and INFESTATIONS	Candidiasis, sepsis, urinary tract infection

investigations	Weight decreased
METABOLISM and NUTRITION DISORDERS	Anorexia, dehydration
MUSCULOSKELETAL and CONNECTIVE TISSUE DISORDERS	Back pain
PSYCHIATRIC DISORDERS	Confusional state
RESPIRATORY, THORACIC and MEDIASTINAL DISORDERS	Tracheo-oesophageal fistula
VASCULAR DISORDERS	Hypertension, hypotension

Obstructing Endobronchial Cancer

Very common (≥10/100) and common (≥5/100 to <10/100) adverse events reported in patients (n=99) with obstructing endobronchial cancers treated with porfimer sodium with PDT are listed below.

Debridement of the treated area is mandatory to remove exudate and necrotic tissue. Life-threatening respiratory failure may occur. Fatal massive haemoptysis, with or without prior radiotherapy, has been observed with greater frequency in the PDT-treated group. In half of the patients with fatal haemoptysis, the event occurred more than 30 days after the last treatment procedure and was judged by the investigator to be unrelated to PDT. Fatal massive haemoptysis may be due to disease progression or due to resolution of tumour eroding into a major blood vessel (see Section 4 Contraindications). Cough, dyspnoea, haemoptysis and increased sputum, while reported as adverse events, are also symptoms of the disease.

Serious and other notable adverse events observed in less than 5% of PDT-treated patients with endobronchial cancer included: lung abscess, pleural effusion, pulmonary embolism and pulmonary thrombosis.

Very Common (≥10/100)

SYSTEM ORGAN CLASS	**Adverse Event**
GENERAL and ADMINISTRATION SITE CONDITIONS	Pyrexia
RESPIRATORY, THORACIC and MEDIASTINAL DISORDERS	Bronchitis, cough, dyspnoea, haemoptysis, pneumonia
SKIN and SUBCUTANEOUS TISSUE DISORDERS	Photosensitivity reaction

Common (>5/100 to <10/100)

SYSTEM ORGAN CLASS	**Adverse Event**
GASTROINTESTINAL DISORDERS	Constipation, dyspepsia
GENERAL and ADMINISTRATION SITE CONDITIONS	Chest pain, oedema peripheral, pain
MUSCULOSKELETAL and CONNECTIVE TISSUE DISORDERS	Back pain
PSYCHIATRIC DISORDERS	Anxiety, insomnia
RESPIRATORY, THORACIC and MEDIASTINAL DISORDERS	Respiratory distress, sputum abnormal

4.9 Overdose

Overdose of Photofrin

There is no information on overdose situations involving Photofrin. Higher than the recommended medicinal product 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 at least 30 days and up to 90 days or more. At this time, patients should test for residual photosensitivity (see section 4.4). Photofrin is not dialysable.

Overdose of Laser Light Following Photofrin

Oesophageal Cancer
There is no information on overdose of laser light following porfimer sodium injection in patients with oesophageal carcinoma.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensitizers Used in Photodynamic/Radiation Therapy, ATC Code: L01X D01

The cytotoxic actions of Photofrin 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 tumours, skin, and organs of the reticuloendothelial system (including liver and spleen) retain Photofrin for a longer period. Illumination of the target area with 630 nm wavelength laser light constitutes the second stage of therapy. Tumour and dysplastic tissue selectivity in treatment may occur through a combination of selective retention of Photofrin but mainly through a selective delivery of light. Cellular damage caused by Photofrin PDT is a consequence of the propagation of free 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 free radical reactions can form superoxide and hydroxyl radicals.

Tumour death also occurs through ischaemic 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. The necrotic reaction and associated inflammatory response evolve over several days.

5.2 Pharmacokinetic properties

General Characteristics

A pharmacokinetic study was conducted in 12 endobronchial cancer patients given 2 mg/kg of PHOTOFRIN® intravenously. Samples of plasma were obtained out to 56 days (1,344 hours) post injection and total porphyrin units determined. The mean peak plasma concentration (C_{max}) immediately following injection was 79.6 µg/mL (C.V. 61%, range 39−222); the mean elimination half-life ($T_{1/2}$) was 515 hours, i.e. 21.5 days (C.V. 26%, range 264−672). Thus, porfimer sodium is cleared slowly from the body, with a mean total body clearance CL_T of 0.859 mL/h/kg (C.V. 53%).

The pharmacokinetics of Photofrin was also studied in 24 healthy subjects who received a single dose of 2mg/kg Photofrin given via the intravenous route. Blood samples were obtained and pharmacokinetic parameters were calculated for 23 subjects (11 men and 12 women). 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 $t_{1/2}$was 415 hours (17 days), C_{max} was determined to be 40 µg/mL, and area under the curve ($AUC_{(inf)}$) was 2400 µg.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. This difference may have been due to the sensitivity of the assay used.

At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of Photofrin in men and women were very similar.

In vitro binding of Photofrin to human serum protein is around 90% and independent of concentration between 20 and 100 µg/mL. Preclinical studies indicate that the excretion of Photofrin components occurs primarily via the faecal route.

Characteristics in Specific Populations

Pharmacokinetics of porfimer sodium has not been established in children and adolescents.

No special precautions in renally impaired patients are necessary because excretion is primarily via the faecal route.

The influence of renal and hepatic impairment on exposure to Photofrin has not been evaluated.

5.3 Preclinical safety data

No long-term studies have been conducted to evaluate the carcinogenic potential of porfimer sodium. In vitro, porfimer sodium with PDT did not cause mutations in the Ames test, nor did it cause chromosome aberrations or mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. Porfimer sodium 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. Porfimer sodium with PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. Porfimer sodium with PDT caused a light-dose dependant increase in DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Porfimer sodium was negative in a Chinese hamster ovarian cells (CHO/HGPRT) mutation test. *In vivo*, porfimer sodium did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN® was not mutagenic in standard genotoxicity tests in the absence of light. With light activation, PHOTOFRIN® was mutagenic in some tests *in-vitro.* Foetotoxicity, but not teratogenicity, occurred in rats and rabbits only at elevated intravenous doses (greater than or equal to 4 mg/kg) and at greater dose frequency (daily) compared to the clinical dose regimen.

Porfimer sodium 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 porfimer sodium caused discoloration of testes and ovaries and hypertrophy of the testes. Porfimer sodium also caused decreased body weight in the parent rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following may be added to adjust pH:

Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Contents of the vial before opening: 3 Years

After reconstitution: use immediately (within 3 hours).

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 3°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The reconstituted solution should be protected from light.

6.4 Special precautions for storage

Store below 25°C.
Keep the vial in the outer carton in order to protect from light

For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Vial: Flint, type I glass, treated, 7 mL or 40 mL capacity.
Closure: Grey butyl stopper.
Pack size: 1 vial in a carton box

6.6 Special precautions for disposal and other handling

The 15mg vial and the 75mg vial of Photofrin contain an overage to allow withdrawal and administration of the label claim amount.

Photofrin 15 mg should be reconstituted with 6.6 mL of 5% glucose injection, resulting in a final concentration of 2.5 mg/mL. Photofrin 75 mg should be reconstituted with 31.8 mL of 5% glucose injection, resulting in a final concentration of 2.5 mg/mL. Do not use other diluents. Do not mix Photofrin with other medicinal products in the same solution. Sufficient vials of Photofrin should be reconstituted to provide the patient with a dose of 2 mg/kg. For most patients (up to 75 kg) two vials of Photofrin 75 mg will suffice. Each Photofrin 15 mg vial will treat an additional 7.5 kg of body weight.

Reconstituted Photofrin gives a dark red to reddish brown opaque solution. Do not use any solution containing particles or showing evidence of degradation.

Spills and Disposal

Spills of porfimer sodium 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. Any unused product or waste material should be disposed of in accordance with local requirements.

Accidental Exposure

Porfimer sodium is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, porfimer sodium 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 accidentally overexposed person must be protected from bright light (see section 4.9).

7 MARKETING AUTHORISATION HOLDER

Axcan Pharma International B.V.
Engelenkampstraat 72
6131JJ Sittard
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 960/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2000

Date of last renewal: 29 September 2010

10 DATE OF REVISION OF THE TEXT

December 2011