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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-525

NDA 20-451/S-012

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY REVIEW OF NDA 21-525

Sponsor and/or agent: Axcan Scandipharm Inc., Birmingham, AL.

Review number/Date of submission: 000/May 24, 2002

Information to sponsor: Yes () No (X)

Reviewer name: Yash M. Chopra, M.D., Ph.D.

Division name: Division of Gastrointestinal & Coagulation Drug Products, HFD-180

Date of Submission: May 24, 2002

Date of HFD180 Receipt: June 4, 2002

Review completion date: November 15, 2002

Drug:

Trade name: Photofrin[®] Injection

Each vial contains 75 mg Porfimer sodium

Generic name (list alphabetically): Porfimer sodium

Code name: CL184,116

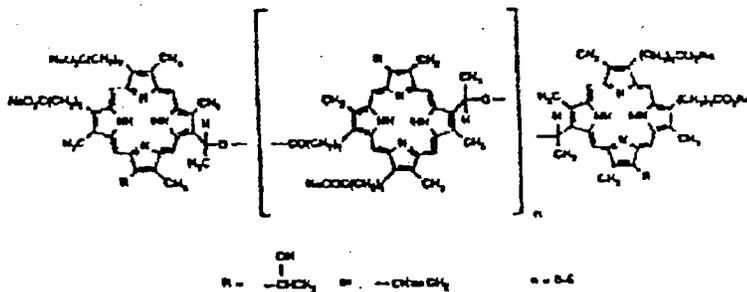
Chemical name: Porfimer sodium is a Complex mixture (aggregates) of porphyrin oligomers (PHE), porphyrin monomers, hematoporphyrin (HP), hydroxethylinyl-deuteroporphyrin (HVD) and protoporphyrins. In the oligomers, porphyrin units are linked by ether and/or ester groups.

CAS registry number: NA

Mole files number: NA

Molecular formula/molecular weight: C₆₈H₇₄N₈O₄/1066

Structure:



Relevant INDs/NDAs/DMFs:

NDA 20-451 (Photofrin Injection)

Drug class: Photosensitising Agent

Indication: Ablation of high grade dysplasia in Barrett's Esophagus

Clinical formulation: Each vial of Photofrin Injection contains 75 mg porfimer sodium as a sterile freeze-dried cake or powder. It is reconstituted in 5% dextrose or 0.9% sodium chloride

Route of administration: Intravenous

Proposed Clinical Use: For the ablation of high grade dysplasia in Barrett's esophagus among patients who are not considered to be the candidates for esophagectomy. Photodynamic therapy (PDT) with Photofrin is 2-stage procedure. In the first stage, an intravenous dose of 2 mg/kg Photofrin is administered, which is, followed by illumination with laser light 40 to 50 hr for 40 to 50 hr following the injection. A second laser light may be given 96 to 120 hr after injection.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

None

Appears This Way
On Original

Executive Summary

I. Recommendations

A. Recommendation on Approvability: From preclinical standpoint, approval of the application is recommended.

B. Recommendation for Nonclinical Studies: None

C. Recommendations on Labeling: Photofrin was not mutagenic in Chinese hamster ovarian cells gene mutation assay (CHO/HGPRT).

II. Summary of Nonclinical Findings

A. Pharmacological Activity:

Intravenously administered Photofrin is selectively retained for a prolonged period in tumor cells than in normal cells. The intracellular compound when irradiated at 630 nm wavelength produces singlet oxygen. The singlet oxygen initiates the process of cell membrane damage, DNA fragmentation and apoptosis and, destroys tumor cells. Photofrin-PDT exerts direct action on the tumor cells.

B. Brief Overview of Toxicology

In 90-day intravenous (i.v.) toxicity study in rats, the target organs of toxicity were lymphatic system, liver and bone marrow. In 90-day intravenous dog study, the target organs of toxicity were liver, adrenal glands and lymphatic system. Intravenous segment I. Fertility and general reproductive performance study in rats showed no impairment of fertility and reproductive toxicity in male and female rats. In i.v. segment II. Teratology studies in rats and rabbits, it was not teratogenic. Photofrin-PDT was not mutagenic in Ames test and chromosomal aberrations test in Chinese hamster ovarian cell, Chinese hamster ovarian cell (CHO/HGPRT) mutation test. A significant but less than 2- fold increase in sister chromatid exchanges were seen in CHO irradiated cells (with near UV visible light). In Chinese hamster irradiated lung (CHL) fibroblasts, 3-fold increase in sister chromatid exchanges were seen. 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 produced an increase in DNA-strand breaks in malignant human cervical carcinoma cells and the effects were dependent on the intensity of light intensity. In a vivo mouse micronucleus test, Photofrin was not mutagenic. Photofrin was negative in a Chinese hamster ovarian cell (CHO/HGPRT) mutation test.

C. Non-Clinical Safety Issues Relevant to Clinical Use:

None

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____

(See memo attached)

C. C.:

Original NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Chopra

HFD-180/Dr. Choudary

HFD-345/Dr. Viswanathan

TABLE OF CONTENTS

Photofrin, a mixture of photosensitizers' species of monomer, dimer and tetramer oligomers of porphyrins, has previously been approved in the treatment of oesophageal cancer (NDA 20-451). In the present application, sponsor referred to this application and submitted summaries of the studies. The pharmacology review of this application was available and considered for the evaluation of present submission. The studies reviewed under Pharmacology review dated September 16, 1994 of the NDA were the pharmacology, absorption, distribution, metabolism and excretion (ADME) studies in rats, dogs and rabbits, acute toxicity studies in mice (i.v.), rats (p.o./i.v.) and rabbits (intradermal), 6- and 13- week i.v. toxicity studies in rats, 90-day i.v. toxicity study in dogs, i.v. Segment I. Fertility and reproductive performance study in rats, Segment II. Teratology studies in rats and rabbits, Ames test, induction of gene mutation at HGPRT locus in Chinese hamster ovary cells, chromosomal aberration test in CHO cells and human hamatopoietic cells, sister chromatid exchange induction test, mutagenicity at the tk-locus in mouse L51784Y cells, in vivo micronucleus test in male mice, transformational and mutagenic potential in mammalian cells, and special toxicity studies on the primary ocular and dermal irritation in the rabbits, active anaphylaxis in guinea pigs and in vitro human blood compatibility study.

The following new preclinical studies are submitted in the present application:

1. Three studies in dogs for the assessment of efficacy and safety of the use of catheters (devices) were submitted. The animals included in the studies were not treated with Photofrin.
2. A genotoxicity study on the induction of gene mutation at HGPRT locus in Chinese hamster ovary cells (HGPRT/CHO) with Photofrin (non-irradiated) and,
3. A test on the delayed dermal contact sensitization of the extract of coated PET balloon material in guinea pigs. Photofrin was not administered to the animals during the study.

The studies on #1 and 3 were on the evaluation of the safety of the devices used for the light exposure on the site of dysplasia.

GENETIC TOXICOLOGY:

The Agency in their approval letter of NDA 20-451 (dated July 13, 1995) asked the sponsor to consider repeating mutagenicity study with the drug alone in the absence of light activation. Sponsor submitted a test for the induction of gene mutation potential of Photofrin in cultured Chinese hamster ovary cells at the HGPRT locus (CHO/HGPRT).

1. In Vitro Mammalian Cell Gene Mutation Test (CHO/HGPRT) in Cultured Chinese Hamster Ovarian Cells (CHO/HGPRT): (Study # TX-98007/ C J 0526-2510)

CONDUCTING LABORATORY: C

J

DATES OF INITIATION AND January 12, 1999 and July 22, 1999

COMPLETION:

GLP COMPLIANCE: A statement of compliance was attached

MATERIALS AND METHODS:

Indicator Cells: CHO cultured cells

Solvent Control: Saline

Positive Controls: Ethyl methanesulfonate (EMS) 0.5 ug/ml without metabolic activation
7,12-Dimethylbenz(α)anthracene (DMBA) with metabolic activation

Photofrin Concentrations Used:

- a. Initial Assay: 10, 25, 50, 100 and 250 ug/ml (without metabolic activation) and, 50, 100, 250, 500 and 1000 ug/ml (with metabolic activation)
- b. Confirmatory Assay: 25, 50, 100, 250 and 500 ug/ml (without metabolic activation) and, 50, 100, 250, 500 and 1250 ug/ml (with metabolic activation). The concentrations were increased because the highest concentrations was in solution and showed no toxicity.

Photofrin concentrations were selected on the basis of 2 range finding studies conducted in the presence and absence of S-9 mix.

Activation System: S-9 rat liver fraction

The test was conducted in duplicate including solvent controls. After 8 days of expression period, the cultured colonies were counted and relative colony efficacy (RCE=average # colonies in test plates/average # colonies in solvent platesX100) was estimated. These experiments were done under subdued light conditions.

Criteria of Positive Test:

The article was considered as positive if there was a dose response or at least 2 consecutive doses showed positive response or significant increase in the # of mutants by at least two-folds per 10^6 cells over that of the concurrent and historical controls. If no dose group showed average mutant frequency greater than 15 mutants/ 10^6 cells, the test article was considered as negative.

RESULTS:

- a. Initial Test:

(i). Without Metabolic Activation: The average number of colonies were 6, 11, 11, 16, 9 and 8.5 in the culture containing 0 (solvent control), 25, 50, 100 and 250 ug/ml Photofrin, respectively. The number of mutant colonies was not increased in a dose-related manner. (ii) With Metabolic Activation: The average mutant counts/ 10^6 cells were 4, 6.5, 7.5, 2.5, 4 and 7 in cultures containing 0 (solvent control), 50, 100, 250, 500 and 1000 ug/ml Photofrin. None of the cultures showed 2 fold increase in the average mutant counts/ 10^6 cells in the cultures. The mean number of mutants/ 10^6 cells in positive control, DMBA (5.0 ug/ml) with metabolic activation was 105.5. In cultures without metabolic activation, the mean number of mutants/ 10^6 cells in positive control (EMS 0.5 mg/ml) was 494.0. Photofrin was non-mutagenic in the initial test.

b. Confirmatory Test:

(i). Without Metabolic Activation The average number of mutants/ 10^6 cells were from 6, 8.5, 8.5, 16, 0.5 and 0 in cultures containing 0 (solvent control), 25, 50, 100, 250 and 500 ug/ml Photofrin. (ii). With Metabolic Activation The mean number of mutants/ 10^6 cells with metabolic activation was 3.5, 2.5, 0.5, 3, 2.5 and 8.5 at the 0 (solvent control), 50, 100, 250, 500 and 1250 ug/ml Photofrin, respectively. There was neither a dose related nor a 2 times increase in any of the cultures of the study. The mean number of mutants/ 10^6 cells without metabolic activation in positive control, EMS (0.5 ul/ml) were 212.5 and in positive control DMBA (5 ug/ml) culture, with metabolic activation was 233.5. In the present HGPRT study, Photofrin alone (non-irradiated) was not mutagenic in the presence and absence of metabolic activation.

LABELING:

The submitted label generally conforms to 21 CFR, 201 .50, Subpart B (April 1, 1991). The finding of the above gene mutation induction test with non-irradiated Photofrin at HGPRT locus in Chinese hamster ovarian cell should be inserted in the proposed version of the label. This is described here first as the "Sponsor Version" followed by "Recommended Version":

Proposed Sponsor's Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN[®]. In vitro, PHOTOFRIN[®] 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. 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. ☐

☑ 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/m² 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.

Evaluation: Sponsor in the present application submitted a new in vitro Chinese hamster ovarian cell (CHO/HGPRT) gene mutation test with non-irradiated Photofrin. Photofrin was negative in the test. This finding should be inserted in the proposed text of the label under subsection of Carcinogenesis, Mutagenesis, Impairment of Fertility as shown below under 'Recommended Version'.

Recommended Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN®. In vitro, PHOTOFRIN® 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. 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. PHOTOFRIN was negative in a Chinese hamster ovarian cells (CHO/HGPRT) mutation test." 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/m² 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.

SUMMARY AND EVALUATION:

Photofrin, an anionic lipophilic mixture of monomers, dimers and tetramer oligomers of porphyrins, is retained selectively in tumor cells. The intracellular compound when irradiated (at 630 nm wavelength) showed cytotoxic/anti-tumor effects. Photodynamic therapy with Photofrin (PDT-Photofrin) form singlet oxygen radicals which on interaction with the cell membrane initiates cell membrane damage, DNA fragmentation, mitochondrial vacuolization and swelling and apoptosis. The action was due to superoxide ion formation, increased purine degradation, tissue destruction and hypoxia. Photofrin was accumulated in higher amounts inside the implanted tumor than the normal tissues. The tumorocidal effects of PDT-Photofrin had been demonstrated in vitro and in vivo experimental models and the therapy had been used in esophageal cancer (NDA 20-451). Sponsor in the present application intends to use photodynamic therapy of Photofrin (irradiated with laser light) for the ablation of high-grade dysplasia in Barrett's esophagus among patients who are not considered for esophagectomy.

In support of the present application, sponsor submitted the summaries of pre-clinical pharmacology and toxicology studies of Photofrin submitted with NDA 20-451. The

pharmacology reviews of these studies were available and utilized for the evaluation of the present application.

The new pre-clinical studies submitted in support of the present application were on the evaluation of the safety of device used for the delivery of radiation to the esophagus. During the studies, Photofrin was not administered. A new gene mutation study using cultured Chinese hamster ovarian cells (HGPRT/CHO) with non-irradiated Photofrin (initial and confirmatory tests) and, iso-sensitization of coated PET balloon in Guinea-pigs were also submitted.

In absorption, distribution, metabolism and excretion (ADME) studies, Photofrin at an intravenous dose of (caudal vein) 2 or 20 mg/kg attained a dose proportional plasma concentration of 208 and 2040 ug.hr/ml, respectively. It had biexponential half-lives of 1.25 ($t_{1/2} \alpha$) and 12 ($t_{1/2} \beta$) hr. Photofrin was distributed throughout the body tissues, tumor site and normal brain within six hours of its administration and the highest concentration of about 28% of the total dose radioactivity was found in the liver. Photofrin was localized in rat cecum, transverse, descending or sigmoid colon or the rectum. According to sponsor, the retention of higher concentration of porphyrins in cecum was due to retention of compound in the compacting and dehydrating fecal material. The intravenously administered compound was seen to cross blood brain barrier and was detected in brain and other areas of central nervous system. Photofrin was initially localized in the cytosol of normal rat liver cells (Kupffer cells). It was excreted in rat feces (42%) and urine (8%). It was secreted in rat milk after 6 hr of its administration in insignificant amounts and transferred in to rat fetus. Photofrin was metabolized in three major polar components, i.e., unreacted hematoporphyrin (HP, component 2) and isomers of 2(4)-hydroxyethyl-4(2)-vinyl-deuteroporphyrin (HVD, component 4). A less polar component 7 was not significantly fluorescent. In dogs, after 2 and 10 mg/kg doses, plasma concentrations at steady state (AUCs) were 1670 and 6152 ug.hr/ml with a half-life of 40 hr (about 3 times of rat). In human, C_{max} after the dose of 2 mg/kg Photofrin was 15 to 80 mg/ml and 90% of the injected compound was bound to serum protein (albumin) with dimer/oligomer fraction associated with lipoproteins. In human, an intravenous dose of 2 mg/kg attained a C_{max} ranged from 14.2 to 79.6 ug/ml.

Single dose acute toxicity of the compound was determined in mice, rats, dogs and rabbits. The minimum intravenous lethal doses of Photofrin (non-irradiated) were 125, 75 and 50 mg/kg in mice rats and dogs. The common clinical signs of toxicity with Photofrin were reduced activity, reduced body weights, intravascular hemolysis, necrosis of liver and enlargement of spleen among rats and mice. The minimal lethal doses of activated Photofrin (irradiated at 630 nm) in mice and rats were 25 and 80 mg/kg, respectively. The common signs in animals exposed to irradiated Photofrin were dose-related edema, erythema in rats and mice. In rats, alopecia at ear, head and dorsum was the additional toxicity. The increased toxicity of the irradiated Photofrin was attributed to the phototoxicity.

In 13-week toxicity study with 8 weeks of recovery period, 4 groups of rats were administered intravenous doses of 0, 5, 10 and 20 mg/kg/week Photofrin. Reversible anorexia and weight loss in animals included in 10 mg/kg treatment group. Treatment produced a dose-related decrease in red blood cells counts, hematocrit values and hemoglobin concentration. It also produced dose-related increases in WBC and reticulocytes counts. The changes in white cell counts were not completely reversed after 8 weeks of recovery. The brown colored pigment deposits in macrophages of the spleen, lymph nodes, and bone marrow and in Kupffer cells were seen in

treatment related manner. Hyperplasia of the bile ducts and lymphoid tissues of spleen was seen in animals of 20 mg/kg treatment group sacrificed at the termination of treatment period. It was resolved slowly and partially during recovery period. The target organs of toxicity were lymphatic system, liver and bone marrow. Dose of 20 mg/week was the 'highest tolerable dose'.

In 90-day IV toxicity studies in dogs, 5 groups of animals were treated with 0, 2.5, 5.0, 7.5 or 10.0 mg/kg/week. A dose related 10 to 30% decrease in red blood cell, hematocrit and hemoglobin was seen in animals of 10 mg/kg/day treatment group. A dose related 30 to 50% increase in WBC counts was seen in high dose treatment group males and females. A dose of 5 mg/kg/week was considered as a 'highest tolerable dose' in the study. The target organs of toxicity were liver, adrenal glands and lymphatic system.

In Segment I. Reproductive performance and fertility toxicity study in rats, Photofrin was administered at the doses of 0, 0.5, 1.0, 2.0 and 4.0 mg/kg/day Photofrin. The male and female rats were treated during the study. Photofrin did not produce any adverse effect on reproductive performance and fertility of the study animals.

In Segment II. Teratology study in rats, Photofrin was administered at 0, 2, 4 and 8 mg/kg/day from gestation day 7 to 17. Photofrin was not teratogenic in rats.

In Segment II Teratology study in rabbits, 4 groups of animals were administered 0, 1, 2 and 4 mg/kg/day Photofrin IV on gestation day 6 to 18. It produced increased number of fetal resorptions and small sized fetuses in females of 4 mg/kg/day treatment group. Photofrin did not produce developmental/teratology abnormalities in rabbits.

Photofrin plus light was not mutagenic in Ames test, in the gene mutation at HGPRT locus test in Chinese hamster ovary (CHO) cells. Photofrin with and without light irradiation was not clastogenic in chromosomal aberrations test in CHO cells. Irradiated to 630 J/m² Photofrin caused less than two-folds increases in sister chromatid exchange in CHO cells. Photofrin was not mutagenic in mouse micronucleus test. In a vitro mammalian cell gene mutation test in cultured Chinese hamster ovarian cells (CHO/HGPRT), non-irradiated Photofrin was not mutagenic.

The published reports on special toxicity of Photofrin were reviewed in the Pharmacology review of NDA 20-451. Photofrin at a single i.v. or intra arterial dose produced a reversible erythema/edema in rabbits. It was not immunogenic in mice and no anaphylactic reactions were seen in guinea pigs sensitized with Photofrin and FCA.

In conclusion, Photofrin has been adequately tested in preclinical pharmacology and toxicology studies. From preclinical standpoint, the approval of the application is recommended. Sponsor should insert the proposed changes as described in Label section of the present review.

RECOMMENDATIONS:

From a preclinical standpoint, the approval of Photofrin for the ablation of high-grade dysplasia in patients with Barrett's esophagus is recommended.

Yash M. Chopra, M.D., Ph.D.
Pharmacologist

Date

COMMENTS:

Jasti Choudary, B.V.Sc, Ph.D.,
Supervisory Pharamcologist, HFD-180

Date

cc:

Original NDA
HFD-180
HFD-181/CSO
HFD-180/Dr.Chopra
HFD-180/Dr.Choudary
HFD-345/Dr. Viswanathan

R/D Init. J. Choudary 11/1/02

YMC/7/27/02;11/8/02;11/15/02
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/s/

Yash Chopra
11/15/02 04:31:50 PM
PHARMACOLOGIST

Jasti Choudary
11/15/02 04:40:23 PM
PHARMACOLOGIST