

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

**NDA 21-525
NDA 20-451/S-012**

Administrative/Correspondence

EXCLUSIVITY SUMMARY for NDA # 21-525 SUPPL # N/A
Trade Name PHOTOFRIN® for Injection
Generic Name porfimer sodium
Applicant Name Axcan Scandipharm, Inc. HFD- 180
Approval Date July 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X/ NO / /

b) Is it an effectiveness supplement? YES / / NO / X/

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X/ NO / /

d) Did the applicant request exclusivity?

YES / / NO / X/

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /x/ NO /___/

IF THE ANSWER TO QUESTION 1 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # NDA 20-451 PHOTOFRIN (porfimer sodium) for Injection

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two

products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / X /

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ / NO / X /

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PHO BAR 01

Investigation #2, Study # TCSC 93-07

Investigation #3, Study # TCSC 96-01

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO / <u>X</u> /
Investigation #2	YES /___/	NO / <u>X</u> /
Investigation #3	YES /___/	NO / <u>X</u> /

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO / <u>X</u> /
Investigation #2	YES /___/	NO / <u>X</u> /
Investigation #3	YES /___/	NO / <u>X</u> /

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # PHO BAR 01

Investigation # 2 , Study # TCSC 93-07

Investigation # 3 , Study # TCSC 96-01

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 61,011 YES / X / NO / / Explain:

Investigation #2

IND # 42,313 YES / / NO / X / Explain: This was a sponsor-investigator study sponsored by Bergein Overholt, M.D.

Investigation #3

IND # 42,313 YES / / NO / X / Explain: This was a sponsor-investigator study sponsored by Bergein Overholt, M.D.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or

conducted by its predecessor in interest.)

YES / /

NO / /

{See appended electronic signature page}

Signature of Preparer

Date

Title: Brian Strongin, R.Ph., M.B.A.

Regulatory Health Project Manager

Division of Gastrointestinal

and Coagulation Drug Products

{See appended electronic signature page}

Signature of Office or Division Director

Date

Title: Robert Justice, M.D., M.S.

Director, Division of Gastrointestinal

and Coagulation Drug Products

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Brian Strongin
7/29/03 01:56:55 PM

Robert Justice
7/29/03 02:34:09 PM

DIVISION'S PROPOSED LABELING:

The sponsor will proposed new labeling in response to the approvable letter for this cycle (November 29, 2002). The Division will mark-up this labeling for the next action.

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On Original

Strongin, Brian K

From: Debbie Co, PhD, RAC [dco@canreg.ca]
Sent: Wednesday, July 30, 2003 6:21 PM
To: justicer@cder.fda.gov; korvickj@cder.fda.gov; gallotorresh@cder.fda.gov; kaminskag@cder.fda.gov; fanm@cder.fda.gov; stronginb@cder.fda.gov
Cc: François Martin MD (E-mail); Patrick Colin PhD (E-mail); Michelle Depot PhD (E-mail); jspenard@axcan.com; Becky Prokipcak, PhD; Irma Monaco, BSc.; Patricia Anderson BSc, RAC (EU); Anne Tomalin, BA,BSc, RAC
Subject: NDA 21-525 Response to Photofrin PI received July 30, 2003



PHOTOFRIN
21-525 PI 30JL

Axcan Scandipharm has reviewed the Package Insert for Photofrin (received July 30, 2003 from the Division). We have accepted the additional paragraph added to the CLINICAL PHARMACOLOGY section, Pharmacokinetic subsection. We have also agreed to the sentence that was added to the Carcinogenesis subsection.

<<PHOTOFRIN NDA 21-525 PI 30July03 Strikeout.doc>>

Please find attached a clean copy of the Photofrin PI that contains the last minor revisions, which are mainly editorial in nature. These changes appear as underlined/strikeout text in the attached document:

- 1) Line 7 and 10 (Page 1): high-grade dysplasia (HGD) in Barrett's esophagus (BE)
- 2) Line 75: tumor diffuser length
- 3) Line 248: There were five secondary efficacy endpoints
- 4) Table 5: This is the corrected table that was submitted to the Division on July 28, and approved at the July 25 teleconference
Table 6: This is the corrected table that was submitted to the Division on July 28, and approved at the July 25 teleconference
- 6) Paragraph after Table 6: The phrase "had a mucosal segment treated twice (82%)" was inadvertently left out in the version we received from the Division today.
- 7) Table 10 footnote NOTE: Adverse events classified using MedDRA 5.0 dictionary, except esophageal strictures/narrowing.
Rationale: In MedDRA, narrowing and strictures are lumped together under esophageal stenosis acquired.
- 8) Paragraph after Table 12: "retreatment" changed to "treatment" of skip areas

With regard to the PHO BAR 02 study, the Sponsor expects to have the final study report available by July 2005.

If you require more information, please feel free to contact me at (905) 689-3980 Ext, 305.

Thank you.

Debbie O. Co
CanReg Inc., Regulatory consultant for Axcan Scandipharm

74 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Annual Report Review: Postmarketing Study Commitment Summary

(This form must be filled out for all open postmarketing commitments whether or not they are subject to posting on the publicly available database.)

Reviewer: _____

Discipline: _____

SECTION A: Application Information

NDA/ANDA/BLA	
Drug	
Applicant	
Annual Report Number	
Annual Report Received	

SECTION B: Status of Open Commitments

Origin of Commitment (i.e., Original, Supplement #, or date of post-approval letter)	Commitment # (as numbered in the letter)	Do you agree with the reported status? (Yes / No / Not Reported) If no, explain in Section C.	Do you agree with the firm's explanation of the status? (Yes / No / Not Reported) If no, explain in Section C.

SECTION C: Explanation of Disagreements

For each commitment where we do not agree with the applicant's reported status and/or the explanation, please address the following in the comments section below:

- Explain the disagreement.
- State the correct status/explanation as it should be reflected in the database.

Supplement (if appropriate)

Commitment #

Comments:

Was an agreement reached with the firm? Yes / No

Supplement # (if appropriate)

Commitment #

Comments:

Was an agreement reached with the firm? Yes / No

Supplement # (if appropriate)

Commitment #

Comments:

Was an agreement reached with the firm? Yes / No

Division Director Summary Review of a New Drug Application

NDA: 21-525

Drug: PHOTOFRIN® (porfimer sodium) for Injection

Applicant: Axcan Scandipharm, Inc.

Date: July 29, 2003

PHOTOFRIN® is currently approved for (1) 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, (2) for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC), and (3) for treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated.

This type 6 new drug application was received on May 31, 2002. The applicant sought approval of a new indication for the use of PHOTOFRIN® injection in combination with a laser light delivery system as photodynamic therapy (PDT) of high-grade dysplasia (HGD) in patients with Barrett's esophagus (BE) who are not candidates for esophagectomy. An approvable letter was sent on November 29, 2002. The preliminary efficacy data suggested that PDT is effective in the treatment of high-grade dysplasia associated with Barrett's esophagus. However, the minimum follow-up in the original submission (6 months) was too short to determine whether the duration of response is clinically meaningful (see Division Director Memorandum dated November 29, 2003). A final study report with a minimum follow-up of 24 months was submitted on September 26, 2002 and a complete response to the action letter was submitted on January 28, 2003.

The following summary of the safety and effectiveness data is from the negotiated labeling text. One controlled study and two supportive studies were submitted in support of the application. In all three studies a course of therapy consisted of one injection of PHOTOFRIN® (2 mg/kg administered as a slow intravenous injection over 3–5 minutes) followed by up to two non-thermal applications of 630 nm laser light. The light dose administered was 130 J/cm of diffuser length using a centering balloon. The first application of light occurred 40–50 hours after PHOTOFRIN® injection. A second laser light application of 50 J/cm of diffuser length without a centering balloon could be given 96–120 hours after the PHOTOFRIN® injection for skip areas. Additional courses of PDT with PHOTOFRIN® were allowed after 3 months, up to a maximum of three courses.

A multicenter, 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 compared to control patients receiving omeprazole alone (OM Only). All histologic assessments were performed at a central pathology laboratory and read by pathologists blinded to the treatment administered. A total of 485 patients with the diagnosis of HGD

were screened for the study; 208 (43%) were randomized to treatment, 237 (49%) were excluded because the diagnosis of HGD was not confirmed, and 40 (8%) did not meet other screening criteria or declined to participate. Patients were randomized 2:1 to receive PHOTOFRIN® PDT + OM (138 patients) or OM Only (70 patients).

Of the 208 patients who had biopsy-proven HGD in BE and no invasive esophageal cancer or history of cancer, 130 of 138 (94%) patients randomized to the PHOTOFRIN® PDT + OM group and 69 of 70 (99%) patients randomized to the OM Only group received at least one PHOTOFRIN® PDT course or one week of OM treatment, respectively. The mean age of patients in both treatment groups was 66-67 years. Patients were predominantly male (85%), Caucasian (99%), and former smokers (64%).

All patients underwent surveillance consisting of systematic quarterly endoscopic biopsies. Four-quadrant jumbo biopsies at every 2 cm of the entire Barrett's mucosa were obtained at each follow-up visit (every three months or six months if four consecutive quarterly follow-up endoscopic biopsy results were negative for HGD). The primary efficacy endpoint was the Complete Response rate (CR3, CR2, or CR1) defined as the complete ablation of HGD at any one of the endoscopic assessment time points. CR1 was defined as complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium, CR2 was defined as squamous epithelium with some areas of metaplasia, and CR3 was defined as replacement with normal squamous epithelium but containing areas of low-grade dysplasia, indefinite dysplasia, and metaplasia.

The table below presents the overall clinical response for both treatment groups in the intent-to-treat (ITT) population whose response was CR3 or better at any one of the evaluation time points. Overall, PHOTOFRIN® PDT + OM was effective in eliminating HGD in patients with BE. The proportion of responders was significantly higher in the PHOTOFRIN® PDT + OM group than in the OM Only group (77% versus 39%, respectively; $p < 0.0001$).

Complete Response Rates After a Minimum Follow-Up of 24 Months in the ITT population

Responders		Treatment Groups		p-value ^A
		PHOTOFRIN® PDT + OM	OM Only	
Numbers of patients	N	138	70	
CR3 or better ^B	n	106	27	
	Proportion (%)	0.768 (76.8)	0.386 (38.6)	< 0.0001
	95% CI	(0.698, 0.839)	(0.272, 0.500)	

^A Fisher's Exact test.

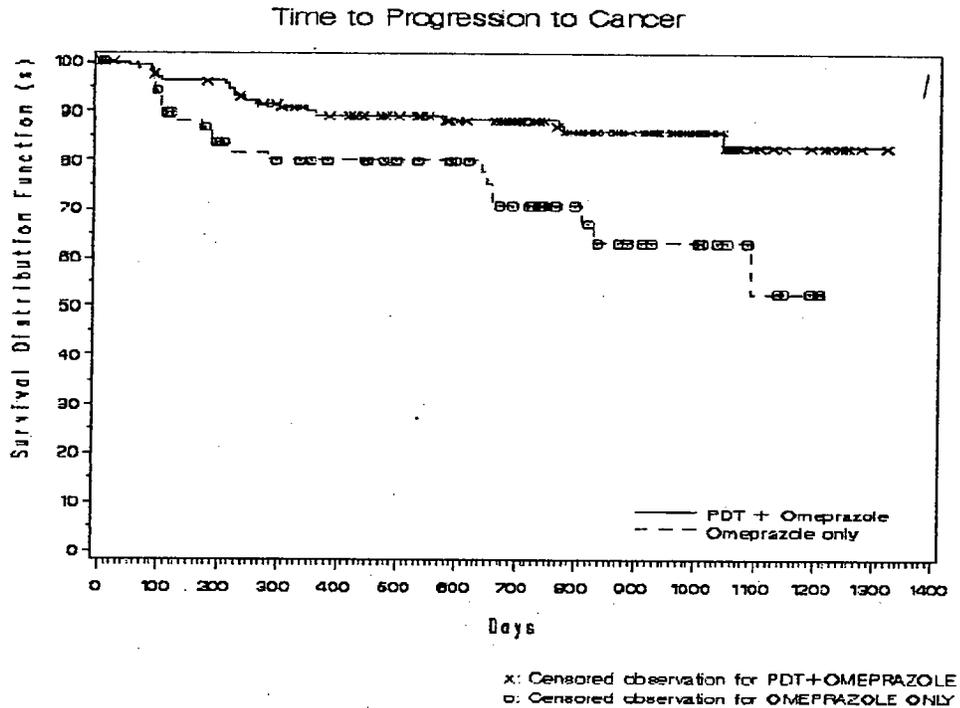
^B CR3 or better: Ablation of all areas of HGD.

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

Seventy-two (52%) patients in the PHOTOFRIN® PDT + OM group achieved a CR1 response as compared to five (7%) patients in the OM Only group. Eighty-one (59%) patients in the PHOTOFRIN® PDT + OM group achieved a CR2 or better response as compared to ten (14%) patients in the OM Only group. The probability of maintaining a complete response (CR3 or better) by the end of the follow-up period was 53% in PHOTOFRIN® PDT + OM group and 13% in OM Only group.

The time to progression to cancer was significantly longer in the PHOTOFRIN® PDT + OM group than in OM Only group (p=0.0014, see Kaplan-Meier plot below).

Comparison by Treatment Group of the Time to Progression to Cancer Over Time (ITT population)



At the end of 24 months of follow-up, patients in the PHOTOFRIN® PDT + OM group had an 83% chance of being cancer-free compared to 53% chance among patients in the OM Only group. Durability of cancer risk reduction beyond two years has not been demonstrated.

At a minimum follow-up of 24 months, the proportion of patients with progression to cancer was statistically lower in the PHOTOFRIN® PDT + OM group than in the OM Only group: 13% versus 28% (p=0.0060). Progression to cancer was related to complete response status. Patients who did not have a complete response had a greater risk of progression to cancer than patients who achieved a CR3 or better response, both in the

PHOTOFRIN® PDT + OM group (38% vs. 6%) and in the OM Only group (44% vs. 4%). Patients who progressed to cancer after a complete response had mostly a CR3 response. No CR1 patients progressed to cancer during the follow-up period.

Eighteen (13%) patients in the PHOTOFRIN® PDT + OM group and 22 (31%) patients in the OM Only group had another therapeutic intervention for HGD. Patients who experienced a progression of HGD to cancer, or who underwent therapy for HGD other than specified in the treatment arm were discontinued from the study. A disproportionate percentage of patients were discontinued from the OM Only group during the course of the study. By the end of the minimum 24-month follow-up period, 81 (59%) patients in the PHOTOFRIN® PDT + OM group and 28 (40%) patients in the OM Only group remained in their respective treatment arms.

Median survival time could not be estimated for either group, because very few (3) patients died during the follow-up period.

Two uncontrolled, supportive studies were conducted that were physician-sponsored, single center Phase II trials. Both studies included patients that had low-grade dysplasia (LGD), HGD and early adenocarcinoma. The first study enrolled 99 patients (44 with HGD). The second study enrolled 86 patients (42 with HGD), who were randomized to receive either PHOTOFRIN® PDT with prednisone or PHOTOFRIN® PDT without prednisone to determine whether steroid treatment would reduce the incidence and/severity of esophageal strictures.

A CR3 or better response was demonstrated in 93% of 44 patients with HGD in the first study and in 95% of 42 patients with HGD in the second study after a minimum follow-up of 12 months. A CR2 or better response was achieved in 82% of patients in the first study and in 91% of patients in the second study. A CR1 response occurred in 57% of patients in the first study and in 60% of the second study. Progression to cancer during the above follow-up period occurred in 18% of patients in the first study and in 7% of patients in the second study. No reduction in the incidence or severity of esophageal strictures was found in the prednisone group in the second study.

Esophageal strictures as a result of PDT of HGD in BE were common adverse events. An esophageal stricture was defined as a fixed lumen narrowing with solid food dysphagia and requiring dilation. Regardless of the indication, esophageal strictures were reported in 122 of the 318 (38%) patients enrolled in the three clinical studies. Overall, esophageal strictures occurred within six months following PDT and were manageable through dilations. Multiple dilations of esophageal strictures may be required, as shown in the table on the next page.

Esophageal Dilations in Patients with Treatment-related Strictures

Number of Dilations	Number of Patients with Strictures, N=122	Percentage of Patients with Strictures
1 – 2 Dilations	38	31%
3 – 5 Dilations	33	27%
6 – 10 Dilations	26	21%
> 10 Dilations	25	20%

A high proportion of patients who developed an esophageal stricture received a nodule pre-treatment prior to developing the event (49%) and/or had a mucosal segment treated twice (82%). The tables on the next two pages present adverse events that were reported, regardless of the relationship to treatment, in at least 5% of patients in either controlled or uncontrolled clinical trials.

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**Treatment Emergent Adverse Events Reported in $\geq 5\%$ of Patients Treated with
PHOTOFRIN® PDT in the Clinical Trials on High-Grade Dysplasia in Barrett's
Esophagus^a**

(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Treatment Groups			
	HGD ^A PHOTOFRIN ® PDT + OM N=219 n (%)	HGD ^B OM Only N=69 n (%)	Other ^C PHOTOFRIN ® PDT N=99 n (%)	Total PHOTOFRIN® PDT N=318 n (%)
Patients with at Least One Adverse Event	217 (99)	51 (74)	99 (100)	316 (99)
GASTROINTESTINAL	180 (82)	25 (36)	87 (88)	267 (84)
Nausea	61 (28)	5 (7)	63 (64)	124 (39)
Esophageal Stricture ^d	85 (39)	0	37 (37)	122 (38)
Vomiting	72 (33)	4 (6)	35 (35)	107 (34)
Dysphagia	50 (23)	1 (1)	27 (27)	77 (24)
Esophageal Narrowing ^e	60 (27)	4 (6)	16 (16)	76 (24)
Constipation	45 (21)	5 (7)	9 (9)	54 (17)
Abdominal Pain (Upper, lower, NOS)	32 (15)	4 (6)	8 (8)	40 (12)
Diarrhea	22 (10)	7 (10)	6 (6)	28 (9)
Esophageal Pain	15 (7)	0	9 (9)	24 (8)
Hiccup	18 (8)	0	1 (1)	19 (6)
Dyspepsia	12 (5)	3 (4)	6 (6)	18 (6)
Odynophagia	13 (6)	0	4 (4)	17 (5)
Eructation	11 (5)	0	4 (4)	15 (5)
GENERAL and ADMINISTRATION SITE CONDITIONS	135 (62)	17 (25)	66 (67)	201 (63)
Chest Pain	71 (32)	8 (12)	40 (40)	111 (35)
Pyrexia	47 (21)	3 (4)	13 (13)	60 (19)
Chest Discomfort	14 (6)	1 (1)	21 (21)	35 (11)
Pain	17 (8)	2 (3)	7 (7)	24 (8)
Fatigue	13 (6)	2 (3)	0	13 (4)
SKIN and SUBCUTANEOUS TISSUE	120 (55)	8 (12)	29 (29)	149 (47)
Photosensitivity Reaction	101 (46%)	0	16 (16)	117 (37)
Rash	14 (6)	3 (4)	7 (7)	21 (7)
Pruritis	13 (6)	1 (1)	1 (1)	14 (4)
RESPIRATORY, THORACIC and MEDIASTINAL	67 (31)	21 (30)	22 (22)	89 (28)
Pleural Effusion	25 (11)	0	15 (15)	40 (13)
Dyspnea	16 (7)	3 (4)	4 (4)	20 (6)

^A Includes all HGD patients in the Safety population from PHO BAR 01 (N=133), TCSC 93-07 (N=44), and TCSC 96-01 (N=42)

^B Includes all HGD patients in the Safety population from PHO BAR 01 (N=69)

^C Includes patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma at baseline in the Safety population from TCSC 93-07 (N=55) and TCSC 96-01 (N=44)

^d In the controlled clinical trial, an esophageal stricture was defined as a fixed lumen narrowing with solid food dysphagia which required dilations; In the uncontrolled clinical trials, an esophageal stricture was defined as any dilated esophageal narrowing.

^e An esophageal narrowing was defined as an undilated esophageal stenosis.

NOTE: Adverse events classified using MedDRA 5.0 dictionary.

**Treatment Emergent Adverse Events Reported in ≥5% of Patients Treated with
PHOTOFRIN® PDT in the Clinical Trials on High-Grade Dysplasia in Barrett's
Esophagus^a**

(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Treatment Groups			
	HGD ^A PHOTOFRIN ® PDT + OM N=219 n (%)	HGD ^B OM Only N=69 n (%)	Other ^C PHOTOFRIN ® PDT N=99 n (%)	Total PHOTOFRIN® PDT N=318 n (%)
INFECTIONS and INFESTATIONS				
Sinusitis	58 (26)	22 (32)	8 (8)	66 (21)
Bronchitis	11 (5)	3 (4)	2 (2)	13 (4)
	10 (5)	3 (4)	2 (2)	12 (4)
METABOLISM and NUTRITION				
Dehydration	53 (24)	9 (13)	16 (16)	69 (22)
Anorexia	24 (11)	2 (3)	8 (8)	32 (10)
	6 (3)	2 (3)	8 (8)	14 (4)
NERVOUS SYSTEM				
Headache	51 (23)	14 (20)	11 (11)	62 (19)
	17 (8)	6 (9)	2 (2)	19 (6)
INJURY, POISONING and PROCEDURAL				
Post Procedural Pain	42 (19)	10 (14)	19 (19)	61 (19)
Sunburn	16 (7)	1 (1)	14 (14)	30 (9)
	8 (4)	0	6 (6)	14 (4)
MUSCULOSKELETAL and CONNECTIVE TISSUE				
Back Pain	46 (21)	18 (26)	9 (9)	55 (17)
Arthralgia	15 (7)	4 (6)	1 (1)	16 (5)
	10 (5)	6 (9)	1 (1)	11 (3)
INVESTIGATIONS				
Weight Decreased	41 (19)	5 (7)	14 (14)	55 (17)
Body Temperature Increased	17 (8)	2 (3)	3 (3)	20 (6)
	8 (4)	0	8 (8)	16 (5)
PSYCHIATRIC				
Insomnia	37 (17)	8 (12)	4 (4)	41 (13)
Depression	11 (5)	3 (4)	1 (1)	12 (4)
Anxiety	10 (5)	3 (4)	0	10 (3)
	10 (5)	1 (1)	0	10 (3)
VASCULAR				
Hypertension	25 (11)	6 (9)	4 (4)	29 (9)
	10 (5)	1 (1)	0	10 (3)

^A Includes all HGD patients in the Safety population from PHO BAR 01 (N=133), TCSC 93-07 (N=44), and TCSC 96-01 N=42)

^B Includes all HGD patients in the Safety population from PHO BAR 01 (N=69)

^C Includes patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma at baseline in the Safety population from TCSC 93-07 (N=55) and TCSC 96-01 (N=44)

NOTE: Adverse events classified using MedDRA 5.0 dictionary.

More adverse events were associated with treatment among patients in the PHOTOFRIN® PDT + OM group (53%) than in the OM group (5%). The majority of treatment-associated adverse events in the PHOTOFRIN® PDT + OM group were of mild (53%) or moderate (28%) intensity. These included photosensitivity reaction (68%), esophageal strictures (36%), vomiting (32%), chest pain of non-cardiac origin (20%), and pyrexia (20%). The most commonly reported serious adverse event associated with treatment was dehydration (4%). In the PHOTOFRIN® PDT + OM group, severe treatment-associated adverse events included chest pain of non-cardiac origin, dysphagia, nausea, vomiting, regurgitation, and

heartburn. The severity of these symptoms decreased within 4 to 6 weeks following treatment.

The majority of the photosensitivity reactions occurred within 90 days following PHOTOFRIN® injection and was of mild (69%) or moderate (24%) intensity. Almost all (98%) of the photosensitivity reactions were considered to be associated with treatment. Fourteen (10%) patients reported severe reactions, all of which resolved. The typical reaction was described as skin disorder, sunburn or rash, and affected mostly the face, hands, and neck. Associated symptoms and signs were swelling, pruritis, erythema, blisters, itching, burning sensation, and feeling of heat.

The most frequently reported adverse events in the first supportive study were chest pain (69%), nausea (56%), esophageal stricture defined as any dilated esophageal narrowing (42%), dysphagia (35%), esophageal narrowing defined as any undilated esophageal stenosis (28%), vomiting (28%), photosensitivity reaction (27%), fever (23%), and pleural effusion (20%). More than 90% of these most commonly reported adverse events were considered associated with treatment. Of the adverse events that were considered associated with PHOTOFRIN® PDT, the majority were of mild (52%) or moderate (40%) intensity. The serious adverse events reported by more than one patient were atrial fibrillation (three patients), pleural effusion (two patients), and cardiac failure (two patients).

The most commonly reported adverse events in the second supportive study were nausea (60%), chest pain (55%), esophageal stricture defined as any dilated esophageal narrowing (36%), vomiting (33%), photosensitivity reaction (28%), pain (21%), fever (20%), odynophagia (20%), dysphagia (17%), pleural effusion (14%), and esophageal narrowing defined as any undilated esophageal stenosis (12%). Almost all of the most commonly reported adverse events were considered to be associated with treatment. Of the adverse events that were considered associated with PHOTOFRIN® PDT, the majority was of mild (57%) or moderate (37%) in intensity.

Clinical Review

The Medical Officer Review by Dr. Edvardas Kaminskas was completed on July 18, 2003 and recommended that Photodynamic therapy with PHOTOFRIN® should be approved for the indication of "...ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy." The review included recommended changes to the labeling text. The Medical Team Leader Review by Dr. Hugo Gallo-Torres was completed on July 28, 2003 and also recommended that the application should be approved.

Clinical Inspection

The Division of Scientific Investigations inspected Dr. Bergein Overholt's site since it enrolled approximately 25% of subjects enrolled in PHO BAR 01. The overall assessment was that "Dr. Overholt did not adhere to the applicable regulations and good clinical practices governing the conduct of clinical investigations. There were issues related to

protocol deviation, inadequate and inaccurate recordkeeping, inadequate reporting of adverse events and inadequate informed consent.” However, “the inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, endoscopies were performed and copies of biopsy reports from the central reference laboratory were maintained at the site.” The recommendation was that “the data submitted in support of this NDA appear to be acceptable.”

Statistical Review

The statistical review by Dr. Milton Fan was completed on June 23, 2003 and noted that “the results of the 24-month data from the PHO BAR 01 study confirmed those reported in the 6-month study report.”

Clinical Pharmacology and Biopharmaceutics Review

The review was completed by Dr. Tien-Mien Chen on August 8, 2002. The review noted that “the new indication is acceptable from OCPB/DPE II viewpoint provided that previous labeling changes (under NDA 20-451) as proposed by the Agency dated 12/11/01 regarding PK section (including the results of gender analysis) are incorporated into the labeling.”

Chemistry Review

The chemistry review by Dr. Marie Kowblansky was completed on 10/3/02 and recommended approval of the application. There were no CMC changes and the applicant claimed categorical exclusion.

Pharmacology/Toxicology Review

This review by Dr. Yash Chopra was completed on November 15, 2002. The review recommended approval and that the following language be included in the labeling: “Photofrin was not mutagenic in Chinese hamster ovarian cells gene mutation assay (CHO/HGPRT).”

Gastrointestinal Drugs Advisory Committee

The application was discussed at the June 26, 2003 meeting of the Gastrointestinal Drugs Advisory Committee meeting. The committee was asked to discuss and vote on the following questions.

1. Appropriate patients for PHOTOFRIN PDT
 - a) The diagnosis of high-grade dysplasia was confirmed by the Central Reference Laboratory in about 50% of patients with that diagnosis. Discuss what impact the inability to confirm a high-grade dysplasia diagnosis has on the use of PHOTOFRIN. Provide recommendations to ensure use of this therapy in the appropriate population.

The committee expressed the need for review of pathology by experts in GI pathology.

- b) Should the diagnosis of high-grade dysplasia be confirmed by a reference laboratory of acknowledged experts before PHOTOFRIN PDT is undertaken?

Vote: Yes = 7 No = 3

2. Efficacy

- a) Do the applicant's data demonstrate efficacy of PHOTOFRIN PDT in complete ablation of high-grade dysplasia in Barrett's esophagus?

Vote: Yes = 9 No = 0 Abstain = 1

- b) Is a 2-year follow-up period adequate to demonstrate cancer risk reduction in high-grade dysplasia patients treated with PHOTOFRIN PDT?

Vote: Yes = 5 No = 5

The Committee expressed concern about the need to follow up over a longer time period.

- c) How frequently should patients who have undergone PHOTOFRIN PDT be monitored by esophagoscopy?

The Committee recommended every 3 months for 1 year followed by every 6 months for the 2nd year, and annually thereafter.

- d) This question was added by the Committee to rephrase the proposed indication to: "Photodynamic therapy with Photofrin® is indicated for the ablation of high-grade dysplasia in Barrett's esophagus among patients who do not undergo esophagectomy".

Vote: Yes = 9 No = 1

3. Safety:

Is the safety profile of PHOTOFRIN PDT acceptable?

Vote: Yes = 10 No = 0

4. Follow-up

The applicant is continuing to collect patient follow-up data in the PHO BAR 02 extension study for an additional 3 years. PHO BAR 01 and PHO BAR 02 taken together will provide a maximum of 5 years of follow-up for patients in the 2 arms of the study. Is this adequate to demonstrate cancer risk reduction in high-grade dysplasia patients?

Vote: Yes = 9 No = 1

The Committee also expressed a concern that practitioner training should be required and the need for a formal education program.

Recommended Regulatory Action

PHOTOFRIN® (porfimer sodium) for Injection should be approved for the indication of "Ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy." However, the approval should be contingent on the applicant's agreement to a Phase 4 commitment to submit the 5-year results of the PHO BAR 02 study.

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Justice
7/29/03 03:14:23 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

DATE: July 6, 2003

TO: Robert Justice, MD, MSc
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

SUBJECT NDA 21-525 [PHOTOFRIN[®] (porfimer sodium)]
Photodynamic Therapy for the Ablation of High-Grade
Dysplasia in Barrett's Esophagus
Sponsor: Axcan Scandipharm Inc.

RE: Recommendation for Approval

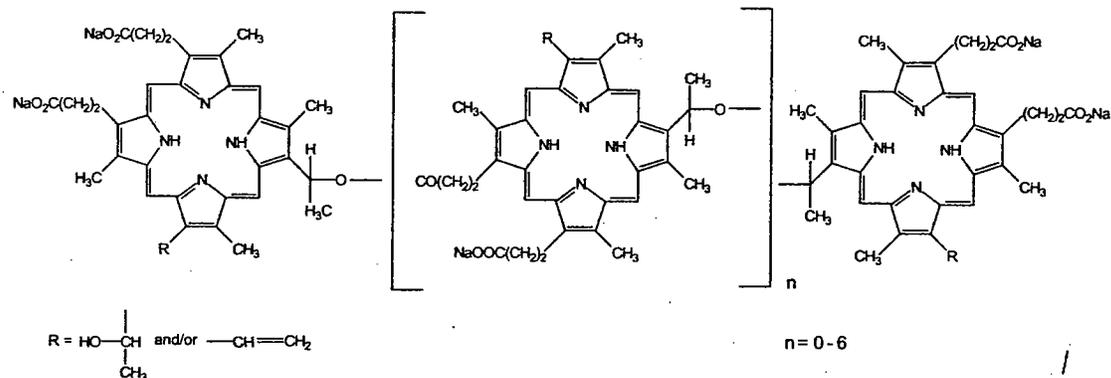
FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

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I. Background/Introduction

PHOTOFRIN[®] is a photosensitizing agent intended for use in the treatment of certain cancers and precancerous lesions. The active ingredient in PHOTOFRIN[®] is porfimer sodium. PHOTOFRIN[®] is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units, and is referred to as a polyhematoporphyrin of ethers/esters:



PHOTOFRIN[®] is used in combination with a Light Delivery System for Photodynamic Therapy (PDT) (See V. Device Component, below)

PHOTOFRIN[®] is currently approved by the Division of Oncologic Drug Products (HFD-150) for the following 3 indications: treatment of esophageal cancer (approved July 13, 1995), endobronchial cancer (approved January 9, 1998) and endobronchial nonsmall cell lung cancer (approved December 22, 1998). NDA 21-525 is a type 6 NDA seeking registration of PHOTOFRIN[®] (porfimer sodium) for the ablation of high-grade dysplasia (HGD) in Barrett's Esophagus (BE) among patients who are not considered to be candidates for esophagectomy. In addition to clinical data submitted in support of the safety and efficacy of the drug in the new indication, the NDA included updated summaries of the CMC, biopharm, and pharmacology/toxicology information previously included in NDA 20-451¹.

Barrett's Esophagus

- Barrett's Esophagus (BE) is a condition in which the normal stratified squamous epithelium, or mucosa lining the distal esophagus, is replaced over time by specialized (metaplastic) columnar epithelium. BE often develops during the process of healing after a **chronic injury to the esophageal mucosa**. In most patients with BE, chronic gastroesophageal reflux disease (GERD) is responsible for providing the abnormal environment leading to this injury (BE develops in ca. 10% of patients who have chronic GERD). Some patients may be **asymptomatic**, but the typical clinical manifestations of BE are heartburn and chronic esophageal reflux in mild cases, accompanied by dysphagia, gastrointestinal bleeding, nocturnal aspiration, and chronic obstructive pulmonary disease in more advanced cases.
- Patients with BE are at risk for development of dysplasia². Continued reflux causes initially mild (low-grade), and later, severe (**high-grade**) dysplasia.
- High-grade dysplasia (HGD) in BE is recognized as a major risk factor for **esophageal adenocarcinoma**, and is considered to be a **pre-malignant condition**³. Although variable depending

¹ Strongin B (Project Manager, HFD-180): Administrative Review of New Drug Application, July 1, 2002.

² Defined here as "unequivocally neoplastic epithelium confined within the basement membrane of the glands in which it arose"

³ The actual degree of estimated risk of adenocarcinoma for patients with HGD varies within the published literature. Endoscopic surveillance studies show the development of adenocarcinoma varies from one case in 16 to one case in 441 patient-years of follow-up.

on the publication, the available data indicate that the risk of adenocarcinoma in patients with HGD is about 30 to 170 times greater than in the normal population .

- The number of patients diagnosed with esophageal cancer each year is relatively small. However, these patients have an extremely poor prognosis (95% will die) with little hope of a cure. In addition, for reasons not yet understood, adenocarcinoma of the lower esophagus is one of the malignancies showing a rapid increase in incidence in the US.
- There is substantial debate within the medical community concerning the management of the patient whose endoscopic biopsies show **HGD without adenocarcinoma**. Some authors recommend **esophagectomy** for such patients, while others advocate continued endoscopic surveillance, or **“watchful waiting”**, until biopsy evidence of esophageal cancer is found. The proponents of esophagectomy for treatment of HGD argue that the high prevalence of associated invasive carcinoma in patients with HGD justifies resection. Reports indicate that invasive carcinoma can be found in 33% to 75% of patients who had esophagectomy for persistence of HGD. The concern among proponents of esophagectomy is that patients who choose endoscopic surveillance over surgery face an unacceptable risk for the development of cancer. This concern is based upon the notion that the progression from BE to adenocarcinoma is well known. However, the diagnosis of HGD presents a **clinical management challenge**, because **the natural history of this lesion is uncertain**. There seems to be strong evidence for sequential progression from LGD to HGD to invasive carcinoma. There is, however, no consensus concerning the frequency and timing of this progression.⁴ The pathologist's rating of dysplasia is always an issue when trying to compare results between studies.

A further caveat to the recommendation of prophylactic esophagectomy following diagnosis of HGD is the recognition of the number of HGD patients who do not show post-surgical evidence of cancer. Although it is true that cancer is post-surgically detected among approximately 50% of patients, it is also true that a significant percentage of esophagectomy patients **do not have cancer at the time the surgery is performed**. For example, in Heitmiller *et al.* (1996), 43% of patients were found to have invasive adenocarcinoma in the resected esophagus, while 57% were found to have HGD only . In a study by Edwards *et al.* (1996), 73% had post-surgical evidence of invasive carcinoma whereas 27% had HGD only. These studies suggest that a sizeable percentage of patients have esophagectomy **sooner than is perhaps needed**.

Esophagectomy is associated with high rates of mortality (4% to 7%) and morbidity (22% to 47%). Complications are varied. In a study by Rice *et al.* (1993), early post-surgical complications (<30 days after surgery) occurred among 44% of patients and included anatomic leak, pyloric channel ulcer and aspiration pneumonia. Late complications (>30 days following surgery) included esophageal strictures (accounting for 63.6% of complications), gastric outlet obstruction, recurrent aspiration and dumping syndrome. Among patients investigated by Reid (1991), 47% of patients developed post-operative complications. Post-surgical morbidity reported in various other investigations include cervical leak, chylothorax, colon necrosis, chest infections and small bowel infarction. According to Baba *et al.* (1997), quality of life can be adversely affected following esophagectomy. A questionnaire study of esophagectomy patients 10 years after surgery found that 20% of the survivors studied were not able to climb one flight of stairs without taking a rest. One-third of survivors also experienced dissatisfactory levels of daily food intake, resulting in no gain of body weight after discharge from the hospital.

Endoscopic Surveillance

The other main approach to the current management of patients with HGD in BE is continued endoscopic surveillance. The proponents of endoscopic surveillance point to some studies that show that the incidence of adenocarcinoma in patients with HGD is relatively low. For example, in a 7-year surveillance, 84% of HGD patients remained free of cancer while 16% developed cancer (Schnell *et al.*, 2001). **It is argued that those patients who do progress to adenocarcinoma can be detected at a potentially curative stage with a rigorous, systemic endoscopic biopsy protocol.** Endoscopic surveillance has the advantage of avoiding or delaying esophagectomy. In a study by Peters *et al.* (1994), the outcome of adenocarcinoma in endoscopically surveyed and non-surveyed patients was compared. Patients from surveillance programs were found to have a better post-surgical outcome and earlier stage tumors than patients who had not participated in a surveillance program. The American College of Gastroenterology practice guidelines for endoscopic surveillance of BE are:

⁴ In a study conducted by Ferguson *et al.* (1997), the incidence of progression from HGD to invasive carcinoma was 26% during a median follow-up period of two years. In another study, it was found that some patients with HGD did not progress to invasive adenocarcinoma for as long as 44 months following the diagnosis of HGD (Schnell *et al.*, 2001). A published comment to this latter study expressed concerns regarding the pathologist's rating of dysplasia (Spechler, 2001) [Ferguson MK, Naunheim KS. Resection for Barrett's mucosa with high grade dysplasia : implications for prophylactic phoytodynamic therapy. J Thorac Cardiovasc Surg 114(5):824-829(1997)].

<i>Dysplasia Grade</i>	<i>Surveillance Interval</i>
None	Every 2 to 3 years after two are negative
Low Grade	Every 6 months for 1 year, then every year
High Grade	Expert confirmation followed by either resection or continued surveillance every 3 months

By the time that HGD is diagnosed, the recommended surveillance is extensive, with current recommendations suggesting endoscopic examination every three months. This protocol is time-consuming, labor-intensive, and expensive, and is not without a certain degree of invasiveness and discomfort on the part of the patient (Provenzale, 2001). It also requires patient compliance in order to be successful. In addition, this technique of "watchful waiting" is not without risk in that cancer could be "missed" at an early stage. The "wait and see" approach may be even riskier in those patients who may be poor candidates for esophagectomy. Ultimately, continued surveillance is successful because it provides an opportunity to identify and treat adenocarcinoma at an early stage of development. However, the most commonly used and successful treatment for adenocarcinoma is, in fact, surgical resection. Patients that are not candidates for this surgery have significantly reduced options for treatment of their cancer. **This situation provides a strong rationale to developing alternative treatments that can be used to slow or reduce the progression to cancer in these patients.** Often, the "watchful waiting" approach is combined with medical therapy aimed at controlling GERD, such as treatment with proton pump inhibitors (PPIs). However, while it is possible that progression of dysplasia to cancer may be delayed by the use of medical therapy such as high dose omeprazole (Fennerty and Triadafilopoulos, 2001), **there is no convincing evidence of regression of dysplasia with medical therapy.** A recent survey of 26 studies using medical management of BE concluded that **regression of dysplasia with medical treatment was the exception rather than the rule** (Ormseth and Wong, 2001).

Other Therapeutic Options

There are few additional well-studied, generally accepted options for the treatment of HGD. Reports of several endoscopic ablation techniques such as the thermal Nd:YAG laser, argon and KTP lasers, and multipolar electrocoagulation have all shown regression, and in some cases, total reversal of BE (Sampliner *et al.*, 1996). However, these endoscopic ablation techniques have proven to be laborious, time consuming, and invasive. In addition, none of these techniques have been studied in randomized trials compared to a control group of endoscopic surveillance and/or omeprazole in patients with HGD to prove their efficacy in completely eradicating HGD, thus decreasing the risk of progression to cancer.

- The sponsor's proposed **photodynamic therapy with PHOTOFRIN[®]** may provide a new therapeutic alternative for HGD. Photodynamic therapy has been shown to eliminate dysplasia and superficial cancer, it may reduce Barrett's mucosa (Overholt *et al.*, 1993; Panjehpour *et al.*, 2000), it does not involve surgery, could be repeated, in many cases offers quick recovery and can be performed on an outpatient basis.
- This Supplemental NDA is being submitted in support of the following new indication for PHOTOFRIN[®]:

The ablation of high-grade dysplasia (HGD) in Barrett's Esophagus (BE) among patients who are not considered to be candidates for esophagectomy.

- PHOTOFRIN[®] PDT has been approved and marketed in Japan, Canada, the United States, the UK, Germany, and France for various treatments of cancer (including lung and esophageal). The first approval was in Canada in 1993.

II. Chemistry

PHOTOFRIN[®] (porfimer sodium) is a **photosensitizing agent**.⁵

PHOTOFRIN[®] is a complex mixture of monomeric porphyrins and oligomers of porphyrin units. □

⁵ Following reconstitution of the lyophilized product with 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, it is injected I.V. This is followed 40 to 50 h later by illumination of the tumor with laser light PHOTOFRIN[®] is a dark red to reddish brown 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 chemical complexity of the oligomeric mixture is further complicated by the dynamic aggregation/disaggregation exhibited by porphyrins in aqueous solution. These characteristics have precluded resolution of the oligomers present in PHOTOFRIN® by conventional analytical methods. All fractions resulting from attempts to fractionate PHOTOFRIN® and its precursor HpD by multiple gel chromatography or HPLC consisted of mixtures of oligomers, and were biologically active in a tumoricidal assay. Thus, no single components of PHOTOFRIN® can be isolated, and structure-function relationships cannot be determined for the complex components of PHOTOFRIN®.⁶

- In her review of the application, the Chemistry Reviewer, Dr. Marie Kowblansky, did not identify new CMC changes or additions specifically associated with this NDA 21-525. Dr. Kowblansky's recommendation for regulatory action is **approval**, with no post-approval commitments required (October 3, 2002).

III. Animal Pharmacology and Toxicology

The reviewer, Dr. Yash M. Chopra, noted that 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, which initiates the process of cell membrane damage, DNA fragmentation and apoptosis and, ultimately, destroys tumor cells. PHOTOFRIN®-PDT exerts direct action on the tumor cells. The sponsor noted that three additional nonclinical pharmacology studies were conducted and results submitted in support of NDA 21-525. These studies are related to the new devices that are required for light delivery for this indication.⁷ The sponsor noted that for the white balloon catheters, the energy density used for all of the treatments was 100 J/cm of diffuser and the power density was either 175, 230 or 267 mW/cm of diffuser. As the severity of the lesions produced was approximately the same in all of the treatment groups, **the PDT response was found to be independent of the power density used.** According to the sponsor, the additional data verified the concept that a single light dose (J/cm of diffuser) can be used for any of the 3, 5 and 7 cm white balloon-diffuser combinations. The power density does not have to be held constant, but can vary from 175 to 267 mW/cm of diffuser. This means that the treatment time can be varied depending on the laser power available and the size of the balloon catheter.

In his review, dated November 15, 2002, Dr. Chopra also presented a brief overview of Toxicology. From his review of this information, Dr. Chopra drew the following labeling recommendation: "Photofrin was not mutagenic in Chinese hamster ovarian cells gene mutation assay (CHO/HGPRT)".

- Dr. Chopra did not identify non-clinical safety issues relevant to the proposed clinical use. He recommended **approval** of the application.

IV. Pharmacokinetics and Pharmacodynamics

In their submission, the sponsor included discussion on several PK/PD topics, including absorption and distribution, metabolism, excretion, variations in special populations, potential for drug-drug interactions and pharmacodynamics. The FDA reviewer, Dr. Tien-Mien Chen, noted (review dated August 16, 2002) that the same dose (as that used for already approved indications) is proposed using the currently marketed 75 mg/vial, except for minor differences/changes in laser light (device) and timing of illumination. There were no new pharmacokinetic or other Phase I studies conducted by the sponsor that are included in NDA 21-525. The sponsor noted that human PKs had been studied in three clinical trials in cancer patients who

⁶ The monomeric porphyrins (Hp, Pp and HvdS) present in PHOTOFRIN® as a result of the synthetic process do not contribute to the phototherapeutic effect of the product, as they are cleared from the body within a few hours of administration, and are not present at the time of light treatment. ⁶ The active ingredient, porfimer sodium, consists of oligomeric species ranging from dimers to octomers, the majority of which are dimers and trimers.

⁷ The data collected using the 5 and 7 cm black balloons and the 3, 5 and 7 cm white balloons with their corresponding diffusers, verified data from the pilot study in which a conversion factor of 1.5 was determined for converting the black balloon light dose (150 J/cm of diffuser) to an equivalent white balloon light dose (100 J/cm of diffuser).

were undergoing PDT (submitted in the original NDA) and in one clinical trial in healthy volunteers (a post-marketing study that was submitted in an Annual Report to the NDA). In addition to this previously submitted and reviewed information, Dr. Chen noted that five recent literature articles published between 1995 and 2001 describing the general PKs of the drug were submitted in NDA 21-525. From his review of this evidence, Dr. Chen concluded that the results were consistent with those previously reported. The MTL agrees with this conclusion. Nonetheless, two subject matters are briefly summarized below, not because they are issues, but for completeness (both subject matters are addressed in the approved labeling).

Potential for drug-drug interactions

PHOTOFRIN® is given as an injection in a hospital setting in the context of PDT. Patients receive a single injection, with repeat doses being at least 60 days (for cancer treatments) or 90 days (for treatment of high-grade dysplasia) apart. There have been no formal interaction studies of PHOTOFRIN® and any other drugs. However, it is possible that concomitant use of **other photosensitizing agents**⁸ could increase the photosensitivity reaction. In addition, there exists a theoretical possibility that there may be interactions with other drugs with significant biliary excretion such as **erythromycin, azithromycin and lansoprazole**. Compounds that quench active oxygen species or scavenge radicals such as **dimethyl sulfoxide, β-carotene, ethanol, formate and mannitol** would be expected to decrease PDT activity. According to the sponsor, 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 aggregation⁹, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

NOTE: The most likely new concomitant medication in the context of treatment of HGD is the use of PPIs especially omeprazole. PHOTOFRIN® and omeprazole differ significantly in their absorption, distribution, metabolism and excretion properties. The MTL agrees with the sponsor that PK interaction between these products is not expected to be of clinical concern.

Pharmacodynamics

As previously stated, PHOTOFRIN® is a photosensitizing agent that is used for the treatment (destruction) of neoplastic cells¹⁰. With PHOTOFRIN® PDT, light activation is performed at 40 to 50 h after I.V. injection, a time by which PHOTOFRIN® has cleared from a variety of normal tissues and has been retained by tissue, skin, and organs of the reticuloendothelial system. Red light at 630 nm wavelength is used for activation because this is the longest wavelength that can adequately activate PHOTOFRIN® and provide the greatest tissue penetration. Also, at this wavelength, the absorption of activating light by hemoglobin is minimal. The activation of PHOTOFRIN® results in the conversion of molecular oxygen to the highly reactive, short-lived singlet oxygen form. Tumor necrosis occurs via direct cytotoxicity and by ischemic necrosis because of the sensitivity of tumor microvasculature to PDT. Thrombogenic agents appear to be liberated locally and result in occlusion of tumor capillaries within 20 min. of photoactivation.

- The dose of PHOTOFRIN® used in all pivotal and non-pivotal studies (2 mg/kg body weight via the I.V. route) was determined empirically. This dose is intrinsically non-toxic and is consistently referred to throughout the PDT literature. This dose of PHOTOFRIN® has been used for more than 3,000 treatments as the standard dose, as is the 40- to 50-hour interval between injection and the non-thermal laser light dosing. The timing of light dosing is based on the clearance of PHOTOFRIN® from most tissues except skin and tumors. Total light dose delivered to tumor or dysplastic tissue is a key factor in efficacy and safety. According to the sponsor, the light doses recommended for use in HGD in BE are the lowest which achieved consistent efficacy and an acceptable safety profile.

Dr. Chen also pointed out that no new CPB labeling changes had been proposed and that the sponsor will fulfill OCPB Phase IV comment under previous NDA 20-451 regarding PK data in

⁸ e.g. tetracyclines, sulfonamides, phenothiazines, sulfonyleurea hypoglycemic agents, thiazide diuretics and griseofulvin

⁹ e.g., thromboxane A2 inhibitors

¹⁰ The drug is a complex mixture of porphyrin oligomers. 

In the oligomers, porphyrin units are joined by ether and/or ester linkages.

patients with hepatic impairments and in those that have received more than one course of therapy. Dr. Chen's conclusion was that the new indication is acceptable from the OCPB/DPE II viewpoint provided that the previous labeling changes (under NDA 20-451) as proposed by the Agency, dated 12/11/01, regarding PK section, which includes the results of gender analysis, are incorporated into the labeling. This wording is found in Dr. Chen's Biopharm review of the current NDA.

V. Device Component

PHOTOFRIN[®] was originally approved on December 27, 1995 as a **drug-device combination for PDT**. The approved indication was the palliation of esophageal cancers. For this indication, delivery of light to body cavities is accomplished using laser light passed through endoscopically placed fiber optics tipped with cylindrical diffusers. It is assumed that the esophagus is a hollow tubular organ and the fiber optic diffuser is placed in the center. This is a reasonable approximation when treating patients that have obstructing tumors and a narrowed lumen. It is worth noting, however, that the normal esophagus does not behave as a cylindrical tube. It tends to collapse when empty, resulting in a series of internal mucosal folds, which create a "hill-and valley" effect. This normal behavior is of greater concern when treating patients with dysplasia or superficial esophageal cancers, where the treatment area is more diffuse than that seen with a bulky tumor. Respiratory movements, esophageal motility and endoscope design all make it difficult to maintain a proper, central positioning of the fiber optic that is required for uniform light dosimetry. The internal mucosal folds further impair an even light distribution to the surface of the esophagus.

The sponsor notes that as part of the development of PHOTOFRIN[®] PDT for new indication (ablation of HGD in BE and superficial esophageal cancer), a new inflatable centering balloon was developed to improve light dosimetry. This new version of the device was tested by Dr. Overholt and associates at the Thompson Cancer Survival Center. Nonclinical testing was carried out in dogs, and prototype balloons were used in the early clinical trials on HGD in BE.

Preclinical Balloon Development

The original balloon developed consisted of a semiflexible tube with a central inner channel and an inflatable optically clear cylindrical balloon attached at the distal end. A removable stylet was placed in the central channel to add rigidity for positioning, and was replaced with the fiber optic diffuser for treatment. The balloon was positioned using a small endoscope alongside, and then inflated to expand the esophagus. The 25 mm diameter was sufficient to smooth out the mucosal folds and provide the modest friction against displacement, while avoiding undue pressure on the esophagus.

- The diffuser/balloon combination was assessed in preclinical pilot studies in dogs utilizing endoscopic observation and histological assessment. Treatment consisted of 2 or 4 mg/kg PHOTOFRIN[®], followed by light treatment 48 h later with a 3.6 cm balloon and a 1 cm diffuser. Endoscopic examination indicated that the balloon/diffuser combination using light doses of 300 and 600 J/cm produced complete, circumferential mucosal damage. In contrast, PDT responses were non-uniform and noncircumferential when animals were treated with only the cylindrical diffuser (no balloon).
- Necropsy findings supported the endoscopic observations. Necropsy data suggested that when the diffuser was used alone, it was positioned between folds of the collapsed esophageal wall, creating a "hill-and-valley" shadowing effect. Necrosis was greatest when the diffuser was in contact with the tissue and minimal in areas that were not exposed to direct light. In contrast, when the diffuser/balloon combination was used, necropsy data indicated that the PDT response was circumferential and uniform. The light-induced damage increased with increasing light dose, with moderate to severe damage at 300 and 600 J/cm of diffuser. Overall, these results highlighted the importance of the balloon for achieving a uniform light delivery to all affected areas of the esophagus.
- These early prototype devices used a balloon design that was entirely optically transparent. This design allowed light to be transmitted proximally and distally from the balloon, thereby extending the ablated length. To provide for more control over the section of esophagus to be treated, the balloons were modified to make them opaque at the ends. The new balloons were black at the ends ("black-capped") and transparent through the center, allowing for a 360 degree central "window".

- The "black-capped" balloon prototypes were tested in a third canine pilot study to assess light distribution characteristics. Endoscopic and necroscopy studies indicated that the balloon shading at the ends effectively prevented normal esophageal mucosa outside of the intended treatment area (**windowed area**) from being affected by the light exposure.
- After results from early clinical trials, further improvements were made to the balloon design. Bench testing and extensive light measurements of the "black-capped" balloon indicated a nonlinear light output across the window, resulting in a peak at the mid-point of the window. This peak in light intensity appeared to correspond to the position of stricture development in at least some patients. A new "white-capped" balloon, the one now intended for marketing, was developed to solve this problem¹¹.

Clinical Trials with PHOTOFRIN® PDT Using Prototype Balloons

The initial "black-capped" balloons developed in the non-clinical testing were used in the clinical trial, 93-07, conducted by Dr. Overholt at the Thompson Cancer Survival Center. At the time of study initiation, only 3 cm balloons were available. Therefore, multiple light sessions were required to treat segments that were longer than 3 cm in length. To do the re-treatment, the balloons were re-positioned along the esophagus. In the process, some areas of the esophagus received more than one light treatment. **Later analysis suggested that these overlap areas were particularly prone to esophageal strictures.** This led the sponsor to develop longer balloons (5 and 7 cm) for the treatment of longer esophageal segments. The sponsor further notes that although the location of the strictures was not always recorded in the case report forms, it was determined that two of the strictures corresponded to the middle of the 5 cm window. Further laboratory tests suggested that there was a peak in light intensity through the middle of the "black-capped" balloon that may have contributed to the strictures. Therefore, a further modification to the balloon was made to enhance the evenness of light output through the window. These new "white-capped" balloons became available after the initiation of the second clinical trial, 96-01.

The second study, 96-01, started with the use of 5 and 7 cm black-capped balloons. The use of the new "white-capped" balloons was added in a Protocol Amendment in April 1997. It is to be noted, however, that the use of multiple light doses (175 and 200 J/cm), two balloon lengths (5 and 7 cm), two types of balloon "caps" or shading, and treatment with and without steroids **makes it difficult to draw conclusions on which delivery system was associated with the higher rate of stricture formation.** Nonetheless, the improvements made in the Light Delivery System as a result of the Phase II trial experience were incorporated into the **pivotal clinical trial for HGD in BE, PHO BAR 01**¹².

- Overall, the incidence of strictures was higher in the first Phase II study, 93-07 (42% in all treated patients, 57% in HGD patients), than in Study 96-01 (36% in all patients and 26% in HGD patients), or in the pivotal controlled clinical trial, PHO BAR 01 (36%). It should be clearly stated that the progressive changes to the light delivery system throughout the clinical development **makes it difficult to extrapolate any correlations between particular devices used and stricture incidence.** However, it seems reasonable to propose that the PHO BAR 01 data, which were obtained using the light delivery system that is intended for marketing, may be more reflective of the potential risks for stricture development in the intended commercial use of PHOTOFRIN® for ablation of HGD in BE.

VI. EFFICACY: Summary/Conclusions

At a June 1, 2001, pre-NDA meeting with the sponsor, the Division acknowledged that there is no consensus in the GI community for treatment of HGD in BE patients. FDA also appreciated the difficulty of including a surgical (esophagectomy) arm in a clinical trial. It was concluded that the lack of an esophagectomy group meant that there were no data to support use of PDT over the use of esophagectomy in the test population and that the sponsor's data could only be used to support the PDT with PHOTOFRIN® for those patients with HGD in BE who are not candidates for esophagectomy. It should be

¹¹ The white-capped balloon has a reflective inner coating at the ends, allowing for a more uniform light output from the balloon. The white-capped balloons were compared to the black-capped balloons in dogs, and optimized to provide desired light delivery characteristics. Finally, the Polymer Technology Group (PTG) white-capped balloon was compared to the Wilson Cook (WC) white-capped balloon. The WC balloon is the one that is intended for marketing, and as such, was part of NDA 21-525 package.

¹² As previously mentioned, this study utilized the fibers and balloons that are intended for marketing for this indication, and were included in the current Drug-Device Application (PARTS II, III and IV).

noted that Dr. Overholt's data in his two uncontrolled clinical studies, performed in patients with various dysplastic changes in BE, were reanalyzed by the Sponsor, utilizing the same outcome criteria as those employed in PHO BAR 01. The reanalysis included only those patients with HGD.

NDA 21-525 is based upon one Phase III pivotal and two non-pivotal Phase II studies.

- The pivotal study (PHO BAR 01) is a multicenter, controlled, partially blinded, randomized, trial comparing the safety and efficacy of PHOTOFRIN® PDT plus omeprazole therapy [PHOTOFRIN® PDT + OME] to a surveillance arm consisting of omeprazole therapy alone in 208 patients with HGD in BE. This is an adequate study design because it allows assessment of the natural history of "untreated" HGD in BE. The sponsor notes that rigorous endoscopic surveillance allowed early detection of progression of HGD, so patients were not exposed to undue risk.
- One of the 2 supportive trials, TCSC 93-07 [n = 99], was a single center, investigator-sponsored, uncontrolled Phase II study set to evaluate the safety and efficacy of PHOTOFRIN® PDT in patients being treated for dysplasia or early adenocarcinoma in BE and to determine the required light dose to produce effective results.
- The other, Study TCSC 96-01 [n = 87], was a single center, Investigator-sponsored, partially blinded, randomized, Phase II parallel-group trial, designed to compare the incidence and severity of esophageal strictures between patients with BE who received steroid therapy after PHOTOFRIN® PDT and patients who received PHOTOFRIN® PDT alone for treatment of dysplasia and/or early adenocarcinoma of the esophagus.

The results of each of these three clinical trials, one pivotal, the other two supportive, are briefly summarized below. More details are found in Dr. E. Kamiskas' clinical (01/09/03) and Dr. Milton C. Fan's statistical (11/01/02) reviews of the initial application. The latter included a follow-up of only 6 months, which is too short to assess durability of response. The applicable was approvable. In Division Director's letter of November 29, 2002, the sponsor was informed that review of the 24-month follow-up data, which had been submitted towards the end of the first review cycle, was required to address issues regarding whether the duration of response is clinically meaningful and whether the reduction in HGD results in a significant reduction in the incidence of esophageal cancer, a very important Public Health issue.

- Because of the above, the emphasis in the current MTL review is on the 24-month efficacy data from the PHO BAR 01 study. Assessment of the 2 supportive studies is found in Drs. Kaminskas and Fan reviews of the 24-month efficacy data.

Controlled Study – PHO BAR 01

Of a total n of 208 patients, 138 were randomized to the PHOTOFRIN® PDT + OME treatment arm, and 70 to the OME Only treatment group, with a mean age of 66.1 (SD=10.9) and 3 (SD=11.1) years, respectively. Other characteristics of the study populations were similar between the two groups.¹³

The primary efficacy endpoint for this study was the **complete ablation of HGD**. Patients with ablation of HGD included those who scored **complete response 3 (CR3)** or better (that is, CR2 or CR1) on a rigorous endoscopic biopsy procedure. The definitions of the complete response levels were:

Complete response 1 (CR1): Complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium.

Complete response 2 (CR2): Ablation of all histological grades of dysplasia, including patients with indefinite grade of dysplasia, but some areas of Barrett's metaplastic epithelium still remain.

Complete response 3 (CR3): Ablation of all areas of high-grade dysplasia but some areas of low-grade dysplasia with or without areas which are indefinite for dysplasia, or areas of Barrett's metaplastic epithelium.

¹³ The MTL agrees with the sponsor that the patient population enrolled in this study is representative of the general population affected by advanced dysplasia. The demographics of esophageal adenocarcinoma are such that the male to female ratio is 7:1 (Sharma and Sampliner, 2001). It has also been reported that 95% of all esophageal adenocarcinomas occur in white males. Similarly, BE is a disease primarily affecting white men in the Western world; the male:female ratio is about 2-3:1 (Stein and Siewert, 1993).

The proportion of responders (**CR3 or better**) was significantly higher in the PHOTOFRIN® PDT + OME group as compared to those in the OME Only group (77% versus 39%, respectively; $p < 0.0001$) (Table 1). The proportion of responders slightly increased in the PHOTOFRIN® PDT + OME group in the Evaluable population (82%) as compared to the ITT population. No changes were observed in the OME Only group between the ITT and Evaluable populations.

The secondary efficacy endpoints included the following variables¹⁴

- Quality of complete response
- Duration of complete response
- Time to progression to cancer
- Time to treatment failure (i.e., delaying need for esophagectomy or other intervening therapy)
- Survival time.

The analysis of **duration of CR** was to be restricted to complete responders. For all time to event endpoints, the primary analysis (based on a minimum of 6 months of follow-up) was to be considered as a preliminary analysis, with the final analysis to be based on the minimum 24-month follow-up data.

The **quality of response** in the PHOTOFRIN® PDT + OME group was significantly better than that measured in the OME Only group in both the ITT and Evaluable Populations (Table 2). Ca. half of the patients in each of these 2 Study Populations, who were treated with PHOTOFRIN® + OME, had a response of CR1 [proportion in the ITT = 0.522; proportion in the Evaluable population = 0.554].

Table 1

Study PHO BAR 01

Results of Primary Efficacy Evaluations– Overall CR3 or Better Clinical Response After a Minimum Follow-Up of 24 Months

Responders	Treatment Groups			p-value ^A
	PHOTOFRIN® PDT + OME	OME Only	ITT population ^C	
Numbers of patients	138	70		
CR3 or better ^B	n Proportion 95% CI	106 0.768 (0.698, 0.839)	27 0.386 (0.272, 0.500)	< 0.0001
		Evaluable population ^D		
Numbers of patients	130	69		
CR3 or better ^B	n Proportion 95% CI	106 0.815 (0.749, 0.882)	27 0.391 (0.276, 0.506)	< 0.0001

^A Fisher's Exact test.

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

^C 6 patients in the PHOTOFRIN® PDT + OME group and 3 in the OME Only group without post-baseline biopsy data are considered as non-responders.

^D 3 patients in the OME Only group without post-baseline biopsy data are considered as non-responders.

Data source: Panel 11.6 of the Final Clinical Report [V. 1.104 (V. 2 of Amendment 2) p. 103]

Table 2 also shows a proportion of 0.587 (95% CI=0.505, 0.669) responders in the PHOTOFRIN® PDT + OME group and a proportion of 0.623 (95% CI=0.540, 0.706) responders with a response of CR2 or better in the ITT and Evaluable populations, respectively. There was a much lower proportion of responders in

¹⁴ Data source: [V. 1.104 (V. 2 of Amendment 2) p. 030]:

the OME Only group: a proportion of 0.071 (95% CI=0.011, 0.132) and a proportion of 0.143 (95% CI=0.061, 0.225) in the ITT population with a response of CR1 and CR2 or better, respectively. The proportions of responders in the Evaluable population were similar¹⁵.

The median duration of response at CR1 was 316.0 days (95% CI=187.0), *¹⁶ in the PHOTOFRIN[®] PDT + OME group and 84.0 days (95% CI=77.0), * in the OME Only group (Table 3). The median duration of response at CR2 or better was 478.0 days (95% CI=187.0, *) in the PHOTOFRIN[®] PDT + OME group and 184.0 days (95% CI=91.0, *) in the OME Only group. The median duration of response at CR3 or better was 987.0 days (95% CI=444.0, *) in the PHOTOFRIN[®] PDT + OME group and 98.0 days (95% CI=91.0, 104.0) in the OME Only group.

For the CR3 or better response level, the last patient was censored at day 987 in the PHOTOFRIN[®] PDT + OME group and at day 280 in the OME Only group.

Median duration of response for all three response categories was three to 10 times longer in the PHOTOFRIN[®] PDT + OME group as compared to the OME Only group. The ITT and Evaluable populations for each treatment group were similar¹⁷.

Table 2
Study PHO BAR 01
Results of Secondary Efficacy Evaluations – Quality of Response
After a Minimum Follow-Up of 24 Months

Responders	Treatment Groups		p-value ^A
	PHOTOFRIN [®] PDT + OME	OME Only	
ITT population ^D			
Numbers of patients	138	70	
CR1 ^B	n 72 Proportion 0.522 95% CI (0.438, 0.605)	5 0.071 (0.011, 0.132)	< 0.0001
CR2 or better ^C	n 81 Proportion 0.587 95% CI (0.505, 0.669)	10 0.143 (0.061, 0.225)	< 0.0001
Evaluable population ^E			
Numbers of patients	130	69	
CR1 ^B	n 72 Proportion 0.554 95% CI (0.468, 0.639)	5 0.072 (0.011, 0.134)	< 0.0001
CR2 or better ^C	n 81 Proportion 0.623 95% CI (0.540, 0.706)	10 0.145 (0.062, 0.228)	< 0.0001

^A Fisher's Exact test.

^B CR1: See text.

^C CR2 or better: See text.

^D See Footnote to Table 1.

^E See Footnote to Table 1.

Data source: Panel 11.7 of the Final Clinical Report [V. 1.104 (V. 2 of Amendment 2) p. 104].

¹⁵ Source: [V. 1.104 (V. 2 of Amendment 2) p. 104]

¹⁶ where * means that the value cannot be estimated

¹⁷ Source: [V. 1.104 (V. 2 of Amendment 2) p. 106].

Table 3
Study PHO BAR 01
Results of Secondary Efficacy Evaluations - Median Duration of Response
After a Minimum Follow-Up of 24 Months

Responders	Treatment Groups			
	PHOTOFRIN® PDT + OME		OME Only	
ITT population				
CR1 ¹	Median (95% CI)	(days)	316.0 (187.0, *)	84.0 (77.0, *)
CR2 or better ²	Median (95% CI)	(days)	478.0 (187.0, *)	184.0 (91.0, *)
CR3 or better ³	Median (95% CI)	(days)	987.0 (444.0, *)	98.0 (91.0, 104.0)
Evaluable population				
CR1 ¹	Median (95% CI)	(days)	316.0 (187.0, *)	84 (77.0, *)
CR2 or better ²	Median (95% CI)	(days)	478.0 (187.0, *)	184.0 (91.0, *)
CR3 or better ³	Median (95% CI)	(days)	987.0 (444.0, *)	98.0 (91.0, 104.0)

*Value cannot be estimated.

¹ CR1: See text.

² CR2 or better: See text.

³ CR3 or better: Ablation of all areas of HGD (primary efficacy parameter).

Data source: Panel 11.9 of the Final Clinical Report [V. 1.104 (V. 2 of Amendment 2) P. 107].

Probability of Maintaining a Clinical Response¹⁸

- By the end of the 2-year follow-up period (730 days), the probability of maintaining the **CR3 or better** criteria was 52.7% in the PHOTOFRIN® PDT + OME group (median time 987 days) as compared to 12.8% (median time 98 days) in the OME Only group.
- **At the CR1 response level**, the probability of maintaining the criteria after two years was 45.8% in the PHOTOFRIN® PDT + OME group as compared to 33.3% in the OME Only group.
- **At the CR2 or better response level**, the probability of maintaining the criteria after two years was 47.5% in the PHOTOFRIN® PDT + OME group as compared to 42.9% in the OME Only group.
- All the above-mentioned differences were statistically significant.

Proportion of Patients Progressing to Cancer / Time to Progression to Cancer / Time to Treatment Failure / Survival Time

- At 24 months of follow-up, the proportion of patients progressing to cancer was significantly lower in the PHOTOFRIN® PDT + OME group (13%) than in the OME Only group (28%), $p < 0.006$.

¹⁸ Source: [V. 1.140 (V.1 of Amendment 7) p. 111

- In the PHOTOFRIN[®] PDT + OME group, a total of 18 patients (13%) had progressed to cancer¹⁹ from days 48 to 1044 in the ITT population by the end of the minimum follow-up of 2 years. Suspicious biopsy for cancer was unconfirmed for one patient. By the end of the minimum follow-up of 2 years, a total of 20 patients (28%) in the OME Only group had progressed to cancer from days 63 to 1092 in the ITT population. Suspicious biopsy for cancer was unconfirmed for 6 patients. The proportion of patients who progressed to cancer in the PHOTOFRIN[®] PDT + OME group was statistically lower than those in the OME Only group in the ITT population ($p = 0.0060$) and the Evaluable population ($p = 0.0061$)²⁰.
- Median Time to Treatment Failure (TTF)²¹ after PHOTOFRIN[®] PDT + OME or omeprazole alone was the day that the probability of documenting a progression to cancer or starting any intervening therapy was 50.0%. Median TTF could not be estimated for the PHOTOFRIN[®] PDT + OME group because the probability of treatment failure was less than 50.0% by the end of follow-up. Median TTF was estimated at **670.0 days** (95% CI=497.0, 827.0) for the OME Only group. Comparison between the two treatment arms using the log rank test showed that the need for esophagectomy or other intervening therapy was **significantly postponed** in the PHOTOFRIN[®] PDT + OME group compared to the OME Only group in the ITT and Evaluable populations ($p < 0.0001$)²².

The sponsor notes that the Kaplan-Meier method was used to present the distribution of TTF (their Figure 6.0-3, not reproduced in the current review, indicates when the differentiation of the two treatments occurred). Treatments began showing differences four months after start when the probability of treatment success in the PHOTOFRIN[®] PDT + OME group was 95.5% compared to 85.5% in the OME Only group. The treatment success in the OME Only group continued to decline at a faster rate than that which occurred in the PHOTOFRIN[®] PDT + OME group. Hence, by the end of the minimum follow-up of 2 years (730 days), the probability of treatment success was 75.0% in the PHOTOFRIN[®] PDT + OME group compared to 46.8% in the OME Only group. By the end of 3.5 years of follow-up (1280 days), the probability of treatment success was 51.8% in the PHOTOFRIN[®] PDT + OME group compared to 19.4% in the OME Only group²³.

Finally, survival time²⁴ could not be estimated for either treatment group because the probability of dying was less than 50.0% by the end of follow-up: two patients in the PHOTOFRIN[®] PDT + OME group died by day 631 (Patient 3002) and by day 643 (Patient 0704), and one patient in the OME Only group died by day 25 (Patient 3804). The last patient was censored at day 643 in the PHOTOFRIN[®] PDT + OME group; no patient was censored in the OME Only group. Comparison between the two treatment arms using the log Rank Test showed no statistical difference between the two treatment groups in the ITT ($p = 0.9880$) or Evaluable ($p = 0.9927$) study populations²⁵.

EFFICACY CONCLUSION

Efficacy has been shown based on results from pivotal Study PHO BAR 01 and the two supportive studies, TCSC 93-07 and TCSC 96-01. PHO BAR 01 was a multi-center, randomized, partially blinded, 2-arm study in patients with Barrett's esophagus and high-grade dysplasia who were all given omeprazole. The two arms of the study consisted of PHOTOFRIN PDT [$n = 130$] and aggressive surveillance [$n = 69$]. The primary efficacy endpoint, assessed after a minimum follow-up of 24 months, was the Complete Response (CR, complete ablation of HGD with re-growth of normal squamous epithelium.). PHOTOFRIN[®] PDT resulted in a CR in 82% of treated patients, compared with 39% in those treated with OME alone [$p <$

¹⁹ The secondary efficacy variable, time to progression to cancer (TTP), was defined as the period in days from the date of randomization until the date the progression to cancer was first documented.

²⁰ Source: [V. 1.104 (V. 2 of Amendment 2) p. 111-113]

²¹ The secondary efficacy variable, time to treatment failure (TTF), was defined as the period in days from the date of randomization until the date of the first documentation of progression of HGD to cancer or the start of any intervening therapy for HGD other than the randomized study treatment.

²² Source: V. 1.140 (V. 1 of Amendment 7) p. 114]

²³ Source: [V. 1.140 (V. 1 of Amendment 7) p. 116-117]

²⁴ The secondary efficacy variable, survival time, was defined as the time from randomization until the patient's death.

²⁵ Source: [V. 1.104 (V.2 of Amendment 2) p. 126; V. 1 of Amendment 7) p. 121]

0.0001]. Efficacy was supported by results of secondary efficacy endpoints which included quality of response, duration of response, time to treatment failure and time to progression to cancer. Because few patients died during the trial, survival time could not be assessed.

Results from studies TCSC 93-07 and 96-01 supported those in the PHO BAR 01 clinical trial.

VII. SAFETY: Summary/Conclusions

Only certain aspects of safety are highlighted in the current review. More Details are given in Dr. E. Kaminskas' reviews, dated 01/09/03 and 07/21/03. All patients who received at least one dose of PHOTOFRIN® or omeprazole were included in the safety summary.

All safety data from the controlled study PHO BAR 01 and the two uncontrolled studies TCSC 93-07 and TCSC 96-01 [V. 1.131 (V. 1 of Amendment 4) p. 002] were integrated in a summary consisting of the following four patient groups for the ITT and Safety populations: 1.HGD-PHOTOFRIN® PDT + OME patients [n = 224]; 2. HGD-OME Only patients [n = 70]; 3. Other-PHOTOFRIN® PDT patients [n = 100]; and 4. Total-PHOTOFRIN® PDT patients (HGD-PHOTOFRIN® PDT + OME patients + Other-PHOTOFRIN® PDT patients) [n = 324].

- Treatment with PHOTOFRIN® consisted of a 2 mg/kg I.V. dose slowly injected over 3 to 5 min., followed by 630 nm laser-light treatment 40 to 50 h after drug administration²⁶. Data on the overall duration of follow-up for all patients included in NDA 21-525²⁷ are summarized as follows:
 - Seventy five percent (299/394 patients, 75.9%) of the entire ITT study population was in the study for more than 12 months: 78.4% of patients (254/324) in the Total-PHOTOFRIN® PDT group and 64.3% of patients (45/70) in the HGD-OME Only group.
 - The mean duration on study in the Total-PHOTOFRIN® PDT patients group did not differ from that in the HGD-OME Only patients group.
 - The mean duration on study for the Total-PHOTOFRIN® PDT patients group was 18.96 months (SD=9.89) and ranged in duration from 0 to 44.3 months. The mean duration on study for the HGD-OME Only patients group was 18.63 months (SD=11.73) and ranged in duration from 0.2 to 39.8 months²⁸.
- The majority of patients in the Total-PHOTOFRIN® PDT group in the ITT population received one course of therapy (317/324 patients, 97.8%); 125 (38.6%) patients received Course 2, and 48 (14.8%) patients received Course 3.
- The number of courses of therapy was similar between the ITT and Safety populations²⁹. A summary of the extent of PHOTOFRIN® PDT exposure is shown in Table 4 (Safety population). The majority of patients in the Total-PHOTOFRIN® PDT group (HGD-PHOTOFRIN® PDT + OME and Other-PHOTOFRIN® PDT groups) in the Safety population received the recommended PHOTOFRIN® dose of 1.9950–2.0050 mg/kg: 74.8% (237/317 patients) in Course 1, 83.2% (104/125 patients) in Course 2, and 93.7% (45/48 patients) in Course 3³⁰.
- During Courses 1 and 2 of therapy, the majority of the laser light treatments received by patients in the Total-PHOTOFRIN® PDT patients group (HGD-PHOTOFRIN® PDT + OME and Other-PHOTOFRIN® PDT patients groups) in the Safety population used a 7 cm balloon window. During Course 1, 177 (54.8%) laser light treatments were performed with a 7 cm balloon window. Sixty four

²⁶ A second laser light application could be given to a previously treated segment that showed a "skip" area (i.e., an area that did not show sufficient mucosal response) 96 to 120 h after PHOTOFRIN® injection. Additional injection of PHOTOFRIN® was not performed until a 90-day period had passed, and only if follow-up endoscopy revealed HGD, LGD or Barrett's metaplasia, or to a new segment if the initial Barrett's segment was > 7 cm in length.

²⁷ Source: [V. 1.131 (V. 1 of Amendment 4) p. 010-020]

²⁸ Source: [V. 1.131 (V. 1 of Amendment 4) P. 024]

²⁹ Source: [V. 1.131 (V. 1 of Amendment 4) p. 026].

³⁰ Source: [V. 1.131 (V. 1 of Amendment 4) p. 026-027]

(19.8%) and 73 (22.6%) laser light treatments were performed with a 3 cm and 5 cm balloon window, respectively. During Course 2, laser light treatments using a 3 cm, 5 cm, and 7 cm balloon windows were performed 14 (12.1%), 26 (22.4%), and 75 (64.7%) times, respectively. During Course 3 of therapy, 12 (25.5%) laser light treatments were performed with a 3 cm balloon window, 17 (36.2%) were performed with a 5 cm balloon window, and 18 (38.3%) with a 7 cm balloon window. A 2 cm balloon window was occasionally used especially during Course 1 (8 laser light treatments, 2.5%)³¹.

Table 4
NDA 21-525
Summary of Extent of Photodynamic Therapy Treatment
(Safety Population)

		Treatment Groups					
		HGD ^A PHOTOFRIN [®] PDT + OME [n = 219]			Other ^B PHOTOFRIN [®] PDT [n = 99]		
		Course 1 n = 219	Course 2 n = 115	Course 3 n = 45	Course 1 n = 99	Course 2 n = 10	Course 3 n = 3
PHOTOFRIN [®] Dose (mg/kg)							
1.4970-1.9949	n (%)	20 (9.1)	8 (7.0)	1 (2.2)	9 (9.2)	1 (10.0)	0
1.9950-2.0050	n (%)	171 (78.1)	99 (86.1)	43 (95.6)	66 (67.3)	5 (50.0)	2 (66.7)
2.0051-2.2380	n (%)	28 (12.8)	8 (7.0)	1 (2.2)	23 (23.5)	4 (40.0)	1 (33.3)
Laser Light Sessions							
Utilisation of balloon ¹							
Number of patients	n	219	115	45	98 ^C	10	3
Yes	n (%)	209 (95.4)	107 (93.0)	41 (91.2)	86 (87.8)	8 (80.0)	2 (66.7)
No	n (%)	10 (4.6)	8 (7.0)	4 (8.9)	12 (12.2)	2 (20.0)	1 (33.3)
Length of balloon window ²							
Number of treatments	n	224	107	45	99	9	2
2 cm	n (%)	5 (2.2)	0	0	3 (3.0)	1 (11.1)	0
3 cm	n (%)	39 (17.4)	13 (12.1)	12 (26.7)	25 (25.3)	1 (11.1)	0
5 cm	n (%)	42 (18.8)	24 (22.4)	17 (37.8)	31 (31.3)	2 (22.2)	0
7 cm	n (%)	137 (61.2)	70 (65.4)	16 (35.6)	40 (40.4)	5 (55.6)	2 (100)
Unknown	n (%)	1 (0.4)	0	0	0	0	0
Balloon light dose delivered ³							
Number of applications	n	261	123	50	122	11	6
< 129 J/cm	n (%)	18 (6.9)	8 (6.5)	0	4 (3.3)	0	1 (16.7)
129-131 J/cm	n (%)	120 (46.0)	74 (60.2)	33 (66.0)	0	0	0
> 131 J/cm	n (%)	123 (47.1)	41 (33.3)	17 (34.0)	118 (96.7)	11 (100)	5 (83.3)

^A Includes all HGD patients from PHO BAR 01 [n=133], TCSC 93-07 [n=44], and TCSC 96-01 [n=42].

^B Includes patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma at baseline from TCSC 93-07 [n=55] and TCSC 96-01 [n=44].

^C Missing information for Patient 055 (TCSC 93-07)

¹ Percentages are based on the number of patients in each course.

² Ibid.

³ Ibid.

Source: [V. 1.131 (V. 1 of Amendment 4) p. 026-027]

- The PDT light doses used across studies largely varied due to the TCSC 93-07 study's objective to determine the required light dose to produce effective results. Because of this, larger range of PDT light doses were used (300, 450, or 600 J/cm). In the Total-PHOTOFRIN[®] PDT patients group, 241 PDT (62.9%) was administered with a light dose greater than 131 J/cm, ranging from 132 to 500 J/cm, during Course 1. The sponsor notes that subsequently, most PDT was administered with a light dose of 130 J/cm: 55.2% in Course 2, and 58.9% in Course 3. Less than 6% of the PDT was administered with a light dose less than 129 J/cm, 35-128 J/cm³².

³¹ Source: [V. 1.131 (V. 1 of Amendment 4) P. 027]

³² Source: [V. 1.131 (V. 1 of Amendment 4) p. 027-028]

- **Concomitant medications** were classified using the WHO Drug Dictionary³³. Patients in the Total-PHOTOFRIN® PDT patients group commonly used more concomitant medications in the following therapeutic classes than patients in the HGD-OME Only patients group: Alimentary tract and metabolism (97.8% versus 59.4%), Nervous system (94.3% vs. 66.7%), Systemic hormonal preparations excluding sex hormones and insulins (45.6% vs. 24.6%), and Blood and blood-forming organs (39.3% vs 24.6%). Patients in the HGD-OME Only patients group commonly used more concomitant medications in the following therapeutic class than patients in the Total-PHOTOFRIN® PDT patients group: Cardiovascular (72.5% vs. 64.2%) and Musculoskeletal (37.7% vs. 26.4%) systems³⁴.
- The treatment groups were comparable in terms of **baseline characteristics**. In the HGD patients who received PHOTOFRIN®, 85% were male and the mean age was 66 y. There was a predominance of Caucasians in the clinical studies, with only two black and three Asian patients participating. The age and race distributions were similar among all HGD patients in the clinical studies. The gender distribution varied among the sub-groups of the two TCSC studies with a higher ratio of female patients. At baseline, the median duration of BE was 18.8 months (ranging from 0.8 to 328.8 months) and 19.2 months (ranging from 0.9 to 141.7 months) in the Total-PHOTOFRIN® PDT patients group and the HGD-OME Only patients group, respectively. The duration of HGD was 6 months or less in 43.8% and 70.0% of the patients in the Total-PHOTOFRIN® PDT patients group and HGD-OME Only patients group, respectively for the ITT population. The duration of HGD was unknown for a large proportion of the patients (38.4%) in the Total-PHOTOFRIN® PDT patients group. The median duration of HGD was 3.5 months (ranging from 0.1 to 40.7 months) and 4.1 months (ranging from 0.4 to 72.4 months) in the Total-PHOTOFRIN® PDT patients group and HGD-OM Only group, respectively³⁵. The length of BE as determined by endoscopy was categorized as ≤ 6 cm and > 6 cm. Patients in the HGD-OM Only patients group were evenly distributed between the two categories while the proportion of patients in the Total-PHOTOFRIN® PDT patients group was slightly higher in the > 6 cm category. The length of BE as determined by the histology was also categorized as ≤ 6 cm and > 6 cm. Results showed a higher proportion of patients in the ≤ 6 cm category in both groups: 51.3% of the patients in the HGD-PHOTOFRIN® PDT + OME vs 60.0% of the patients in the HGD-OME Only group³⁶. The most frequent endoscopic conditions found at baseline included hiatal hernia (38.6% in the Total-PHOTOFRIN® PDT patients group and 82.9% in the HGD-OME Only patients group) and nodules (27.5% in the Total-PHOTOFRIN® PDT patients group versus 27.1% in the HGD-OME Only patients group)³⁷. Esophageal strictures were detected in 4.3% of the patients in the Total-PHOTOFRIN® PDT and the HGD-OME Only patients groups. Results of the Safety population did not differ from those observed in the ITT population³⁸.
- Almost all patients who participated in these three clinical studies developed at least one treatment emergent adverse event (TEAE). Table 5 displays **TEAE incidence rates** per study and per integrated treatment group; this table includes information on all patients who received PHOTOFRIN®, including those with LGD and early cancer
- A total of 316 (99%) patients in the Total-PHOTOFRIN® PDT patients group reported 2747 TEAEs. Treatment emergent AEs occurring in ≥10% of patients were reported as Gastrointestinal Disorders (267 patients, 84%); General Disorders and Administration Site Conditions (201 patients, 63%); Skin

³³ During the study, 318 (100%) patients in the Total-PHOTOFRIN® PDT patients group and 67 (97.1%) patients in the HGD-OME Only patients group took at least one concomitant medication.

³⁴ Source: [V. 1.131 (V. 1 of Amendment 4) p. 028]

³⁵ Source: [V. 1.131 (V. 1 of Amendment 4) p. 031]

³⁶ In most patients, HGD extended over multiple levels: 62.9% of patients in the HGD-PHOTOFRIN® PDT + OME group compared to 61.4% of patients in the HGD-OME Only group. Extent of HGD did not differ between the two groups and between the ITT and Safety population. Source: [V. 1.131 (V. 1 of Amendment 4) p. 031]

³⁷ The incidence of esophageal ulcers was similar between the Total-PHOTOFRIN® PDT patients group and the HGD-OME Only patients group (6.5% vs 4.3%).

³⁸ Source: [V. 1.131 (V. 1 of Amendment 4) p. 033]

- and Subcutaneous Tissue Disorders (149 patients, 47%); Respiratory, Thoracic and Mediastinal Disorders (89 patients, 28%); and Metabolism and Nutrition Disorders (69 patients, 22%).
- The most commonly reported TEAEs were nausea (124 patients, 39%), photosensitivity reaction (117 patients, 37%), chest pain of non-cardiac origin (111 patients, 35%), vomiting (107 patients, 34%), esophageal stenosis acquired, which includes esophageal narrowing and esophageal strictures (95 patients, 30%), dysphagia (77 patients, 24%), pyrexia (60 patients, 19%), constipation (54 patients, 17%), pleural effusion (40 patients, 13%), chest discomfort (35 patients, 11%), and dehydration (32 patients, 10%)³⁹.

Table 5
NDA 21-525
Treatment Emergent Adverse Event (TEAE)
(Safety Population)

Patients experiencing	CLINICAL TRIALS			
	93-07	96-01	PHO BAR 01	
	PHOTOFRIN® Patients [n=99] ^A n (%)	PHOTOFRIN® Patients [n=86] ^B n (%)	PHOTOFRIN® PDT+OME [n=133] ^C n (%)	OME Only [n=69] ^D n (%)
TEAEs	98 (99)	85 (99)	132 (99)	51 (74)
associated TEAEs	94 (95)	83 (96)	125 (94)	9 (13)
serious TEAEs	19 (19)	10 (12)	50 (38)	19 (28)
serious associated TEAEs	9 (9)	7 (8)	16 (12)	1 (1)
TEAEs leading to withdrawal	2 (2)	1 (1)	4 (3)	1 (1)
TEAEs leading to death	1 (1)	0	1 (1) ^E	1 (1)
Patients experiencing	TREATMENT GROUPS ^F			
	HGD ^G PHOTOFRIN® PDT + OME [n=219]	HGD ^H OM Only [n=69]	Other ^J PHOTOFRIN® PDT [n=99]	Total PHOTOFRIN® PDT [n=318]
TEAEs	217 (99.1)	51 (73.9)	99 (100)	316 (99.4)
associated TEAEs	206 (94.1)	9 (13.0)	97 (98.0)	303 (95.3)
serious TEAEs	63 (28.8)	19 (27.5)	17 (17.2)	80 (25.2)
serious associated TEAEs	25 (11.4)	1 (1.4)	8 (8.1)	33 (10.4)
TEAEs leading to withdrawal	5 (2.3)	1 (1.4)	2 (2.0)	7 (2.2)
TEAEs leading to death	2 (0.9)	1 (1.4)	0	2 (0.6)

^A Includes all patients in the Safety population from TCSC 93-07: HGD patients [n=44] and patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma at baseline [n=55]

^B Includes all patients in the Safety population from TCSC 96-01: HGD patients [n=42] and patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma at baseline [n=44]

^C Includes all HGD patients in the Safety population from PHO BAR 01 [n=133]

^D Includes all HGD patients in the Safety population from PHO BAR 01 [n=69]

^E Patient 3002 not included because events were not reported as an AE for unknown reason

^F As per ISS report

^G Includes all HGD patients in the Safety population from PHO BAR 01 [n=133], TCSC 93-07 [n=44], and TCSC 96-01 [n=42]

^H Includes all HGD patients in the Safety population from PHO BAR 01 [n=69]

^I Includes patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma at baseline in the Safety population from TCSC 93-07 [n=55] and TCSC 96-01 [n=44]

^J Patient 023 (LGD) who experienced an unrelated TEAE 15 months after the end of the study was included in the ISS Report as opposed to the individual TCSC 96-01 Clinical Study Report that covered a 12-month follow-up period

Patients are counted only once per body system and preferred term

Percentages are based on the number of patients in the Safety population in each group

Source: [V. 13 p. 122; V. 42 p. 223; V. 47 p. 182; V. 1.131 (V. 1 of Amendment 4) p. 034]

- A total of 51 (74%) patients in the HGD-OME Only patients group reported 330 TEAEs. Treatment emergent AEs occurring in ≥10% of patients were mostly reported as Gastrointestinal Disorders (25

³⁹ Source: [V. 1.131 (V. 1 of Amendment 4) p. 035]

patients, 36%), Respiratory, Thoracic and Mediastinal Disorders (21 patients, 30%), and General Disorders and Administration Site Conditions (17 patients, 25%). **The most commonly reported TEAEs were chest pain of non-cardiac origin (8 patients, 12%) and diarrhea (7 patients, 10%)**⁴⁰.

- The sponsor notes that the majority of TEAEs in the Total-PHOTOFRIN[®] PDT patients group were of mild (1450 events, 53%) or moderate (919 events, 33%) intensity. More than half of TEAEs (1744 events, 63%) were considered to be associated with treatment. The majority of the 1744 TEAEs for the Total-PHOTOFRIN[®] PDT patients group that were considered associated with treatment were of mild (937 events, 54%) or moderate (574 events, 33%) intensity. The majority of TEAEs associated with treatment was reported as Gastrointestinal Disorders (246 patients, 77%), General Disorders and Administration Site Conditions (173 patients, 54%), and Skin and Subcutaneous Tissue Disorders (141 patients, 44%). The most commonly reported TEAEs associated with treatment were nausea (117 patients, 37%), photosensitivity reaction (117 patients, 37%), chest pain of non-cardiac origin (101 patients, 32%), vomiting (96 patients, 30%), esophageal stenosis acquired, which includes esophageal narrowing and esophageal strictures (95 patients, 30%), dysphagia (76 patients, 24%), pyrexia (54 patients, 17%), pleural effusion (37 patients, 12%), constipation (32 patients, 10%) as well as chest discomfort and dehydration⁴¹.
- The majority of TEAEs for the HGD-OME Only patients group were of mild (194 events, 59%) or moderate (85 events, 26%) intensity. A total of 16 (5%) events were considered to be associated with treatment. Of the 16 TEAEs that were considered to be associated with treatment, 11 events (69%) were mild, and four (25%) events were moderate in intensity. The majority of TEAEs associated with treatment was reported as Gastrointestinal Disorders (6 patients, 9%)⁴².
- The proportion of events of severe/very severe intensity was similar between the Total-PHOTOFRIN[®] PDT patients group (354/2747 events, 13%) and the HGD-OME Only patients group (48/330 events, 14%). However, 65% (229/354 events) of the events reported as being severe/very severe in the Total-PHOTOFRIN[®] PDT patients group were considered to be associated with treatment compared to 2% (1/48 events) in the HGD-OME Only patients group.
- In the Total-PHOTOFRIN[®] PDT patients group, the events associated with treatment that were mostly severe/very severe were odynophagia (13/19 events, 68%), atrial fibrillation (3/5 events, 60%), dyspepsia (7/15 events, 47%), dysphagia (35/86 events, 41%), overall abdominal pain (7/17 events, 41%), joint contracture (1/3 events, 33%), chest pain of non-cardiac origin (36/111 events, 32%), and decreased joint range of motion (2/8 events, 25%).
- Overall, **two cases of esophageal perforation** were reported. One case of esophageal perforation associated with the PHOTOFRIN[®] PDT + OME treatment was life threatening (Patient 0602). The other case, Patient 096 from TCSC 93-07, the perforation of the esophagus was severe and associated with the Nd:YAG laser treatment. In the HGD-OME Only patients group, there was only one case of nausea associated with treatment that was severe; three events not associated with treatment were life-threatening (two cases of cerebrovascular accident and one case of myocardial infarction)⁴³.

Dr. Kaminskas, the MO Reviewer, discusses the following **Most Frequent Adverse Events**

Photosensitivity

The majority of **skin photosensitivity reactions** occurred within 90 days following PHOTOFRIN[®] injection. Photosensitivity reactions occurred in 37% of the patients who received PHOTOFRIN[®] PDT treatment.

The majority of the photosensitivity reactions were of **mild** (174/250 events, 70%) or **moderate** (59/250 events, 24%) intensity, and 246 (98%) events were considered to be associated with treatment. The

⁴⁰ Source: [V. 1.131 (V. 1 of Amendment 4) p. 035]

⁴¹ Source: [V. 1.131 (V. 1 of Amendment 4) p. 037]

⁴² Source: [V. 1.131 (V. 1 of Amendment 4) p. 037]

⁴³ Source: [V. 1.131 (V. 1 of Amendment 4) p. 037]

reaction was typically characterized by skin disorder, sunburn, and rash, and affected mostly exposed areas such as the face, hands, and neck. Swelling, erythema, blisters, itching, and burning sensation were associated symptoms. Fifteen patients⁴⁴ reported severe reactions that all resolved⁴⁵.

Esophageal Stenosis Acquired

As pointed out in his review, Dr. Kaminskas, the MO FDA reviewer, identified esophageal strictures as being the most important treatment-related adverse events. He summarized the data in 2 Tables, one listing the proportion of patients experiencing strictures, the other listing the proportion of patients undergoing dilations because of esophageal stricture. The present review presents these data in consolidated Table 6.

- In all three studies, all esophageal narrowing and stenosis data were collected under the term “esophageal stricture” regardless of subsequent management⁴⁶.
- In the controlled study PHO BAR 01, about half of the investigators performed esophageal dilations whether or not an esophageal stricture was observed as per DMSC recommendations. The disparity in practice makes the interpretation of the data difficult.

For the purpose of better summarizing the incidence of the event, esophageal stricture data were divided into two categories: undilated esophageal stenosis (hereinafter referred to as “esophageal narrowing”) and dilated esophageal stenosis (hereinafter referred to as “esophageal stricture”).

Table 6
NDA 21-525
Summary of Esophageal Narrowing, Esophageal Strictures, and Dilations
(data from Endoscopic and AE Evaluations in Clinical Trials)

		Clinical Trials			
		93-07	96-01	PHO BAR 01	
		PHOTOFRIN® Patients ^A n (%)	PHOTOFRIN® Patients ^B n (%)	PHOTOFRIN® PDT+OME ^C n (%)	OME Only ^C n (%)
Endoscopic and Adjunctive Therapy Evaluation					
ITT population [n]		99	86	138	70
Patients with any treatment emergent narrowing	n (%)	28 (28)	10 (12)	38 (28)	4 (6)
baseline strictures	n (%)	6 (6)	1 (1)	0	0
treatment emergent strictures	n (%)	42 (42)	31 (36)	49 (36)	0
Course					
1	n (%)	36 (36)	26 (30)	11 (8)	
2	n (%)	4 (4)	5 (6)	31 (22)	
3	n (%)	2 (2)	0	7 (5)	
Dilations					
1 to 2	n (%)	12 (12)	14 (16)	12 (9)	0
3 to 5	n (%)	13 (13)	12 (14)	8 (6)	0
6 to 10	n (%)	7 (7)	5 (5)	14 (10)	0
>10	n (%)	10 (10)	0	15 (11)	0
AE Evaluation¹					
Safety population [n]		99	86	133	69
Patients with any treatment emergent esophageal stenosis acquired	n (%)	31 (31)	12 (14.0)	53 (40)	1 (1)

^A HGD patients [n=44] and patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma [n=55]

^B HGD patients [n=42] and patients with Barrett's metaplasia, indefinite dysplasia, LGD, and adenocarcinoma [n=44]

^C HGD patients

¹ Overestimated because figures include esophageal narrowing and esophageal strictures

NOTE: Percentages are based on the number of patients in the ITT population in each group for the Endoscopy and Adjunctive Therapy data and on the number of patients in the Safety population for the AE data.

Patients are counted only once

Source: [V. 1.104 (V. 2 of Amendment 2) p. 144, 165; V. 42 p. 227-228; V. 47 p. 187-188]

⁴⁴ Patients 0309, 0601, 0701, 0712, 0725, 2403, 2404, 1801, 1812, 3201, 3202, 3204, 7901, and 7902 from PHO BAR 01 and 035 from TCSC 93-07.

⁴⁵ Source: [V. 1.131 (V. 1 of Amendment 4) p. 038]

⁴⁶ As per the Data and Safety Monitoring Committee members (DSMC), an esophageal stricture was defined as a fixed lumen narrowing with solid food dysphagia.

The MO Reviewer also noted that re-treatment of a mucosal segment with PDT was associated with development of esophageal strictures. Strictures developed in 44.2% of patients who had a mucosal segment treated twice and in 23.5% of patients who did not have a same segment re-treated. Overall, 28% of the patients in the PHOTOFRIN® PDT + OME group and 6% of those in the OME Only group developed an esophageal narrowing that did not require dilation during the study⁴⁷.

- Finally, the sponsor notes that in the PHOTOFRIN® PDT + OME group, patients were rather evenly distributed among the four categories in terms of dilation frequency. The majority of esophageal strictures were successfully manageable through scope dilations⁴⁸.

Chest Pain

Under this heading, Dr. Kaminskas mentioned that the number of patients reporting this symptom increased shortly after PDT and then declined over a 4-week period. The proportion of patients reporting mild, moderate or severe chest pain was 129 to 30%, 34 to 41%, and 12%, respectively.

Odynophagia and dysphagia

As also noted by Dr. Kaminskas, the proportion of patients reporting mild, moderate, or severe odynophagia, was 11 to 19%, 15 to 18%, and 5%, respectively. Ca. the same proportion of patients reported dysphagia. While odynophagia remitted over 4 weeks following PDT, dysphagia remitted over 6 months.

Deaths, Withdrawals due to AEs and SAEs

A total of 5 patients died; 3 in the PHO BAR 01 controlled study and 2 in the TCSC 93-07 uncontrolled study. No patient died in the uncontrolled TCSC 96-01 study. The summary of deaths is given in Table 7. None of the deaths, in the 2 clinical trials was assessed as related to test medication.

Table 7

NDA 21-525

**Summary of Deaths
(PHO BAR 01, TCSC 93-07)**

Study Number	Study Center	Patient No (Initials)	Treatment	Cause	Causal relationship
PHO BAR 01 (Controlled study)	Thompson Cancer Survival Center Knoxville, TN, USA	0704 (ERT)	PHOTOFRIN® PDT + OME	Systemic disease: metastatic breast cancer with aortic valve stenosis, deep vein thrombosis, and pulmonary embolism (AEs leading to death)	NO
TCSC 93-07 (Uncontrolled study)	Thompson Cancer Survival Center Knoxville, TN, USA	057 (JPR)	PHOTOFRIN® PDT	Pleural effusion with associated atelectasis; cardiac arrest	NO
		072 (JP)	PHOTOFRIN® PDT	Enterococcal meningitis (AEs leading to death)	NO
PHO BAR 01 (Controlled study)	Duke University Medical Center, Durham, NC, USA	3002 (BLH)	PHOTOFRIN® PDT + OME	Tamponnade following coronary bypass surgery	NO
PHO BAR 01 (Controlled study)	Parkland Memorial Hospital, Dallas, TX, USA	3804 (NES)	OME Only	Stroke (AEs leading to death)	NO

NOTE: For confidentiality purposes, the name of the individual investigators at the listed study sites was omitted.
Source: [V. 1.131 (V. 1 of Amendment 4) p. 042]

⁴⁷ Source: [V. 1.104 (V. 2 of Amendment 2) p. 144]

⁴⁸ Source: [V. 1.104 (V. 2 of Amendment 2) p. 165]

- A total of 8 patients withdrew from these studies due to AEs: 5 in the PHO BAR 01 study, 2 in TCSC 93-07, and 1 in the TCSC 96-01 study. Details of these discontinuations are found in Dr. Kaminskas' review.
- In the Total-PHOTOFRIN[®] PDT patients group, 80 (25%) reported 240 SAEs. Most SAEs in the Total-PHOTOFRIN[®] PDT patients group were reported by only one or two patients in each instance. SAEs experienced by more than two patients in the Total-PHOTOFRIN[®] PDT patients group were reported in Gastrointestinal disorders (28 patients, 9%), Cardiac disorders (18 patients, 6%), Respiratory, thoracic and mediastinal disorders (17 patients, 5%), General disorders and administrative site conditions (16 patients, 5%), Neoplasms benign, malignant and unspecified (11 patients, 3%), Metabolism and nutrition disorders (10 patients, 3%), Vascular disorders (9 patients, 3%), Nervous system disorders (6 patients, 2%), Investigations (6 patients, 2%), Hepatobiliary disorders (4 patients, 1%), Blood and lymphatic system disorders (3 patients, 1%), and Psychiatric disorders (3 patients, 1%).
- The majority of SAEs in the Total-PHOTOFRIN[®] PDT patients group were of severe/very severe (118 events, 49%) or moderate (84 events, 35%) intensity, and 72 (30%) SAEs were considered to be associated with treatment.
- The majority of the 72 SAEs that were considered associated with the PHOTOFRIN[®] PDT treatment was of severe/very severe (38 events, 53%) or moderate (28 events, 39%) intensity.
- The majority of SAEs associated with treatment was reported as Gastrointestinal Disorders (18 patients, 6%).
- The most commonly reported SAE associated with treatment was dehydration (7 patients, 2%).
- The HGD-OME Only patients group had a similar incidence of SAEs (19 patients, 28%) than the Total-PHOTOFRIN[®] PDT patients group (80 patients, 25%). In the HGD-OME Only patients group, the only SAE reported by more than two patients were chest pain of non-cardiac origin (4 patients, 6%), myocardial infarction (3 patients, 4%), arthralgia (3 patients, 4%), and cholelithiasis (3 patients, 4%). The majority of SAEs were of severe (38 events, 66%) intensity, and only four SAEs (7%) were considered to be associated with the OME Only treatment.
- SAEs associated with treatment were reported as Gastrointestinal Disorders (1 patient, 1%) and Blood and Lymphatic System Disorders (1 patient, 1%). The SAE associated with treatment were reported as nausea (1%), melaena (1%), esophagitis ulcerative (1%), and anaemia (1%).

Clinical Laboratory Evaluation

There were no findings of concern. In the clinical trials, most (90.9% to 100%) abnormalities in hematology seen at baseline and at Month 3 were not clinically significant. Shifts from clinically significant at baseline to not clinically significant at Month 3 occurred in 0-1.9% of the patients in Course 1 and 2; however, this shift occurred in 3-6.1% of the patients in Course 3. In the OM only group, there were no shifts from clinically significant at baseline to not clinically significant at Month 3. Clinically significant abnormalities at both measurements were observed in 1.4-2.0% of the patients in the PHOTOFRIN[®] PDT + OME group only and involved the BUN, creatinine, and glucose parameters. In both treatment groups, most (94.1-100%) abnormalities in serum chemistry from baseline to worst measurement were not clinically significant. Clinically significant abnormalities at both measurements occurred at 0.8% for BUN, creatinine and glucose in the PHOTOFRIN[®] PDT + OME group only⁴⁹.

SAFETY CONCLUSION.

Treatments with PHOTOFRIN[®] are relatively safe. The most commonly reported treatment emergent AEs were nausea (39%), photosensitivity reaction (37%), chest pain of non-cardiac origin (35%), vomiting (34%), esophageal stenosis acquired, which includes esophageal narrowing and esophageal strictures (30%), dysphagia (24%), pyrexia (19%), constipation (17%), pleural effusion (13%), chest discomfort (11%), and dehydration (10%).

⁴⁹ Source: V. 1.104 (V. 2 of Amendment 2) p. 174]

In his MO Review, Dr. Kaminskas notes that variations in the frequency of the most common AEs among the 3 clinical trials addressed in his review, may have been due to the relatively small number of patients. They may have also been influenced by local variations in care among sites. He further notes that one center (Thompson Cancer Survival Center in Knoxville, TN) contributed ca. 69% of the total safety population. It is indeed possible that patients' experiences at that one center may have influenced the relative frequency of at least some of the AEs.

There is no question that the main safety issue with PDT is the development of esophageal strictures. The incidence of strictures may have decreased with improvements of the light delivery system, but at 36% in the PHO BAR 01 trial, it is still very high. As summarized in Table 6, the number of dilations for strictures (Table 6) is also relatively high, although, according to the sponsor, the rate of stricture development seems comparable to that which occurs following esophagectomy (a range of 9% to 63% in some studies).

VIII. Other

Other components of NDA 21-525 are adequately addressed in Dr. Kaminskas' review. They include: Important milestone in Product Development, Post-marketing Experience, Literature review, Overview of methods Used to Evaluate Data Quality and Integrity, Evaluation of Financial Disclosure, Evaluation of Pediatric Program and Labeling Recommendations.

IX. Recommendations from June 26, 2003 Advisory Committee Meeting

NDA 21-525 was discussed at the Gastrointestinal Drugs Advisory Committee meeting of June 26, 2003. In response to Question 1, about the appropriate patients for PHOTOFRIN PDT, since the diagnosis of HGD was confirmed by the Central Reference Laboratory in only half of the patients with that diagnosis, the Committee expressed concern over the ability to accurately diagnose HGD.

The Committee voted Yes = 7 and No = 3 to the question of whether diagnosis of HGD should be confirmed by a reference laboratory of acknowledged experts before PHOTOFRIN PDT is undertaken. The Committee's discussion and deliberations included the need for an expert pathologist, as well as the importance of a reference laboratory. It was recommended that slides could be read by a panel of pathologists with the expertise and experience to diagnose HGD. Also discussed was a certification program associated with an educational program. The Committee's voting regarding questions on efficacy, safety, and follow-up, is summarized in Table 8.

Table 8
AC Meeting of 6/25/ 2003: Answers to Questions on Efficacy, Safety and Follow-up

	YES	NO	Abstain
EFFICACY			
• Do the applicant's data demonstrate efficacy of PHOTOFRIN PDT in complete ablation of high-grade dysplasia in Barrett's esophagus?	9	0	1
• Is a 2-year F/U period adequate to demonstrate cancer risk reduction in high-grade dysplasia patients treated with PHOTOFRIN PDT?	5	5	0
• Considering rewording of the proposed indication	9	1	0
SAFETY			
• Is the safety profile of PHOTOFRIN PDT acceptable?	10	0	0
FOLLOW-UP			
• Is a maximum of 5 years of follow-up for patients in the two arms of the study adequate to demonstrate cancer risk reduction in high-grade dysplasia patients?	9	1	0

--Among the responses provided by the Committee were: 1) The delayed time of progression may be over 2 years and the need to follow up over a longer period; and 2) The effect of follow-up on reducing the period prevalence of the disease.

--The Committee provided the following two responses in answer to the question of how frequently should patients who have undergone PHOTOFRIN PDT be monitored by esophagoscopy: 1) Every 3 months for 1 year, followed by 2) Every 6 months for the second year; and 3) Annually thereafter.

--According to the Committee, practitioner training should be required; there is need for a formal education program.

X. Overall Conclusions (Benefit/Risk Relationship)

Barrett's Esophagus (BE) is a condition in which the normal stratified squamous epithelium, is replaced over time by specialized (metaplastic) columnar epithelium. BE usually develops during the process of healing after a chronic injury, such as GERD, to the esophageal mucosa. Patients with BE are at risk for development of dysplasia, a pre-malignant condition that may culminate in esophageal adenocarcinoma. The latter, which occurs in 0.2 to 2 % of patients, is the most serious and most feared complication of BE⁵⁰. Patients who have progressed to high-grade dysplasia (HGD) have a greater than 30% incidence of invasive adenocarcinoma. The incidence of mortality is extremely high (95%) in patients with invasive adenocarcinoma.

The appropriate management of HGD in BE without pre-operative evidence of adenocarcinoma is controversial. Currently, esophagectomy constitutes a proposed standard practice of care although yet to be studied in randomized clinical trials. Since there is no consensus about this approach, there is substantial debate concerning the management of patients whose endoscopic biopsies show HGD without adenocarcinoma. One school of thought recommends esophagectomy for such patients, arguing that the high rate of invasive cancer in patients with HGD warrants resection. (Altorki, *et al.*, 1990; Edwards, *et al.*, 1996; Provenzale and Wong, 1995; Stein and Siewert, 1993) Although a benefit of esophagectomy is the complete removal of abnormal and cancerous cells, partial esophagectomy is not always a curative procedure as recurrent metaplasia and dysplasia in esophageal remnant have been reported⁵¹. In addition, esophagectomy may be associated with decreased physical functioning and reduction in quality of life. Taking another approach are advocates of continued endoscopic surveillance until biopsy evidence of esophageal cancer is found (Levine, *et al.*, 1993; Reid, *et al.*, 1988; Schnell, *et al.*, 1996; Schnell, *et al.*, 2001; van Sandick, *et al.*, 1998). These proponents argue that those HGD patients who do progress to adenocarcinoma can be detected at a curative stage with a rigorous systemic endoscopic biopsy protocol⁵². **There is no evidence of regression of dysplasia with drug therapy alone. Therapy with high dose of proton pump inhibitors does not eliminate Barrett's epithelium.** There have been only sporadic reports of the disappearance of HGD with medical therapy (Gore, *et al.*, 1993; Weinstein, *et al.*, 1996). Reports of several experimental endoscopic ablation techniques such as the thermal Nd:YAG laser, argon and KTP lasers, and multipolar electrocoagulation have all shown regression and in a few cases, total reversal of BE (Sampliner, *et al.*, 1996) but these endoscopic ablation techniques have proven to be laborious, time consuming and invasive.

In the sponsor's NDA 21-525, a statistically significant proportion of patients in the PHOTOFRIN[®] PDT + OME group showed a response at level CR3 or better (primary efficacy parameter) of 77% and 81% for the ITT and Evaluable populations, respectively, as compared to 39% in the OME Only group for the ITT and Evaluable populations ($p < 0.0001$). By the end of the minimum follow-up of 2 years, a total of 18 patients (13%) in the PHOTOFRIN[®] PDT + OME group had progressed to cancer as compared to 20 patients (28%) in the OME Only group in the ITT population. The rate of patients who progressed to cancer in the PHOTOFRIN[®] PDT + OME group was statistically lower than those in the OME Only group ($p = 0.0060$, ITT Population).

There are, however, risks associated with this treatment. In PHO BAR 01, the pivotal/critical trial, the most commonly reported treatment emergent AEs associated with treatment were photosensitivity reaction (68%), esophageal stenosis acquired, which includes esophageal narrowing and esophageal strictures (40%), vomiting (32%), chest pain of non-cardiac origin (20%), and pyrexia (20%). The incidence of any treatment emergent esophageal strictures in the PHOTOFRIN[®] PDT + OME group was 36% with most esophageal strictures reported during Course 2 (22%) of treatment. By contrast, the OME Only group presented no treatment emergent esophageal strictures.

In spite of the above, in the MTL's opinion, the benefit of retarding cancer development in a high-risk population prevails over the manageable risk of developing esophageal strictures.

⁵⁰ The approximate risk of adenocarcinoma for BE patients is 1% per year, 40 to 100 times the average risk of esophageal adenocarcinoma (Botterweck, *et al.*, 2000; Desoubeaux, *et al.*, 1999; Haggitt, 1992; O'Connor, *et al.*, 1999; Sarr, *et al.*, 1985).

⁵¹ In addition, the procedure has a substantial (3-7%) mortality rate (Levine, *et al.*, 1993) and a significant (15-32%) short-term morbidity rate, as well as long-term morbidity rate (75%), among patients who are generally in poor overall health due to prior interventions or limited cardiac and pulmonary function (Gomes, 1992). Patients of esophagectomy are also at risk due to the eventual functional sequelae associated with the tissue loss at surgery.

⁵² The risk involved with this approach is that invasive cancer may be missed. However, when a strict biopsy protocol (4 quadrant, 2 cm level) is used as proposed in a surveillance program, only 10 to 17% remain undiagnosed.

It is concluded that, in this instance, the potential benefits outweigh the potential risks. The MTL agrees with the sponsor and the MO Reviewer, that PDT with PHOTOFRIN® offers an alternative form of therapy for patients at risk for adenocarcinoma and for whom surgical treatment may not be an option.

PDT is non-invasive, non-mutilating, can be repeated, has relative discrimination between normal and abnormal cells, offers quick recovery in most patients and can be performed on an outpatient basis. In addition, in a certain proportion of patients, PDT can eliminate dysplasia and Barrett's mucosa

XI Medical Team Leader Recommendations on Approvability

In tandem with the recommendations from all other disciplines (Chemistry, Pharmacology/Toxicology, Biopharmaceutics and Statistics), NDA 21-525 [PHOTOFRIN® (porfimer sodium)] should be **approved**.

The indication should read:

"Photodynamic therapy with PHOTOFRIN® is indicated for the ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy".

**Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader
HFD-180**

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/s/

Hugo Gallo Torres
7/28/03 03:21:24 PM
MEDICAL OFFICER

Strongin, Brian K

From: Perez, Thomas
Sent: Tuesday, July 01, 2003 12:01 PM
To: 'Byroni Cryer'; 'Camilleri, Michael'; 'David Colin Metz'; 'George S. Goldstein'; 'Joel Richter'; 'John LaMont'; 'Maria. Sjogren'; 'Michael. Wolfe'; 'Robert Levine'; 'Ronald Fogel'; Abrams, Thomas W; Axelrad, Jane A; Bachorik, Lawrence L; Brodsky, Jason D; CDER EXSEC; Chen, Min Chu; Cruzan, Susan M; Cunningham, Rose E; Frost, Kathleen R; Henderson, Deborah J; Kweder, Sandra L; Lumpkin, Murray; Osborne, Walter; Sherman, Linda A; Skladany, Linda Arey; Smith, Nancy D (CDER); Stone, Bradford; Temple, Robert; Toigo, Theresa A; Woodcock, Janet; CDER-HFD-21; CDER-OND-180-ALL; Houn, Florence; 'otis_brawley@emoryhealthcare.org'; 'amangel@rti.org'; 'sbswensen1@aol.com'; 'jcara@dmc.org'; 'kelsend@mskcc.org'; 'john.carpenter@ccc.uab.edu'; Weichung Joe Shih (E-mail); 'jwg2@cornell.edu'; 'George S. Goldstein'
Subject: Flash Minutes for GIDAC June 25 & 26 meeting.

Hello everyone,

Attached are the flash minutes for the June 25 & 26 Gastrointestinal Drugs AC meeting . Please let me know if you have any comments.

Thank you
Tom



Flash
minutes.doc (55 K)

Thomas H. Perez, MPH
Health Science Administrator
US Food and Drug Administration
Center for Drug Evaluation and Research
Advisors and Consultants Staff
5630 Fishers Lane, HFD 21
Rockville, MD 20852
(p) (301) 827-6758
(f) (301) 827-6801
perezth@cder.fda.gov

Transcript and Quick minutes

Sponsor's Briefing Material

FDA'S Briefing Material

4 PAGES REMOVED. SEE THE
ADVISORY COMMITTEE MEETING
INFORMATION LOCATED ON THE FDA
WEBSITE BELOW:

<http://www.fda.gov/ohrms/dockets/ac/>

Division of Gastrointestinal and Coagulation Drug Products**REGULATORY PROJECT MANAGER REVIEW**

Application Number: NDA 21-525

Name of Drug: PHOTOFRIN® (porfimer sodium) for Injection

Applicant: Axcan Scandipharm, Inc.

Material Reviewed:

Submission Dates: April 4, 2003

Receipt Dates: April 10, 2003

Background and Summary

NDA 21-525, submitted May 24, 2002, provides for PHOTOFRIN® in combination with laser light for the ablation of high-grade dysplasia in Barrett's esophagus among patients who refuse esophagectomy and who are in overall good health. This application is a Type 6 NDA since PHOTOFRIN® is approved (NDA 20-451, Division of Oncologic Drug Products) for the following indications: 1) 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; 2) reductions of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC); and treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated. Corresponding applications have been submitted to the Center for Devices and Radiological Health. An approvable letter dated November 29, 2002 listed clinical deficiencies, requested new proposed labeling, and a safety update. On January 28, 2003 the sponsor submitted a complete response to the November 29, 2002 approvable letter. On April 4, 2003 the sponsor submitted revised labeling incorporating changes proposed in response to a November 27, 2002 letter from the Center for Devices and Radiological Health. In this review, the currently approved labeling (20000072-02, approved July 6, 2000 in NDA 20-451/SLR-006) was compared to the proposed labeling (2000072-03) and the differences are noted below. Please note that these identifiers were not included on the electronic copies of the currently approved and proposed package inserts submitted April 22, 2003 but were supplied via e-mail dated July 15, 2003 from the sponsor.

Review

The sponsor's proposed changes to the currently approved package insert are identified on the underline/strikeout version of the labeling submitted April 4, 2003. No additional

changes were identified.

Internal labeling discussions and discussions with the sponsor will be conducted to determine the acceptability of the sponsor's proposed labeling.

Conclusions

The proposed changes to the package insert will be the subject of internal labeling discussions and discussions with the sponsor. If appropriate, the agreed-upon labeling will be attached to the action letter to be sent by the end of this review cycle on July 25, 2003.

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Regulatory Project Manager

Supervisory Comment/Concurrence:

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff

Drafted: BKS/July 9, 2003
Revised/Initialed: JD/July 18, 2003
Finalized: BKS/July 18, 2003
Filename: PHOTOFRIN Labeling Review.doc

PM LABELING REVIEW

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/s/

Brian Strongin
7/18/03 03:30:41 PM
CSO

Julieann DuBeau
7/21/03 07:37:35 AM
CSO

4 Page(s) Withheld



 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



NDA 21525

2-13-03

Axcan Scandipharm, Inc.
c/o CanReg, Inc.
Attention: Becky Prokipcak, Ph.D.
4 Innovation Drive
Dundas, Ontario L9H 7P3
Canada

Dear Dr. Prokipcak:

We acknowledge receipt on February 3, 2003 of your January 28, 2003 resubmission to your new drug application for PHOTOFRIN® (porfimer sodium) for Injection.

We consider this a complete, class 2 response to our November 29, 2002 action letter. Therefore, the user fee goal date is August 3, 2003.

If you have any questions, call me at (301) 827-7473.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
2/13/03 12:30:43 PM

5 Page(s) Withheld



§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Division Director Memorandum

NDA: 21-525

Drug: PHOTOFRIN® (porfimer sodium) Injection

Applicant: Axcan Scandipharm, Inc.

Date: November 29, 2002

The submission is a type 6 NDA for the use of Photofrin injection in combination with a laser light delivery system as photodynamic therapy (PDT) of high-grade dysplasia in patients with Barrett's esophagus who are not candidates for esophagectomy. Three studies were submitted in support of the application:

- PHO BAR 01 is a multicenter, randomized (2:1), controlled trial in 208 patients with Barrett's esophagus and high-grade dysplasia. One hundred thirty-eight patients were randomized to PDT plus omeprazole and 70 were randomized to omeprazole alone. The primary efficacy endpoint in this trial was complete ablation of high-grade dysplasia and regrowth of normal squamous epithelium (CR1), or of normal epithelium with some areas of Barrett's metaplasia (CR2), or of normal epithelium with some areas of low-grade dysplasia, metaplasia, or indefinite for dysplasia (CR3). Seventy-two percent of the patients randomized to PDT plus omeprazole had a complete response (CR1 or CR2 or CR3) compared to 31% of patients randomized to omeprazole ($p < 0.0001$). The highest quality response (CR1), replacement of high-grade dysplasia by normal epithelium, occurred in 41% of patients randomized to PDT plus omeprazole and in only 4% of patients randomized to omeprazole ($p < 0.0001$). With a minimum duration of follow-up of only 6 months, the durability of these responses cannot be adequately assessed. Because of the short follow-up, the medians for time to progression to cancer, time to treatment failure, and survival could not be estimated. Eleven percent of the PDT plus omeprazole group progressed to cancer compared to 20% in the omeprazole group.

A final study report with a minimum follow-up of 24 months was submitted on September 26, 2002. The data in this report will need to be reviewed in the second review cycle before it can be concluded that the promising results described above are clinically meaningful. It should be noted that in a March 5, 2001 telecon the applicant was informed that "6-month follow-up data may be inadequate to assess the impact of treatment." In addition, an advice letter dated January 25, 2001 stated that "the primary response variable must reflect an improvement in long-term clinical outcome."

- TCSC 93-07 is a single center, investigator-sponsored Phase II study in which 99 patients were treated with different light doses and light delivery systems. Forty-four patients in this study had high-grade dysplasia. Since the results with the different light treatments were similar, the response data were combined. With 6 months of follow-up, a CR1 or CR2 or CR3 occurred in 89% of patients with high-grade dysplasia. With 12 months of follow-up, a CR1 or CR2 or CR3 occurred in 93% of

patients and the median duration of response was 391 days. The median time to progression to cancer and survival had not been reached.

- TCSC 96-01 is a single center, randomized study of the effect of steroid therapy on the incidence of esophageal stricture in 87 patients treated with PDT. Forty-two patients in this study had high-grade dysplasia. Since the results with or without steroid treatment were similar, the response data were combined. With 6 months of follow-up, a CR1 or CR2 or CR3 occurred in 88% of patients with high-grade dysplasia. With 12 months of follow-up, a CR1 or CR2 or CR3 occurred in 95% of patients and the median duration of response had not been reached. The median time to progression to cancer and survival had also not been reached.

The major adverse events are summarized in Dr. Kaminskas' review. When PDT groups from all 3 studies were combined (N=318), adverse events were reported in 98%. The most common were gastrointestinal and included nausea in 39%, vomiting in 32%, esophageal stricture in 29%, dysphagia in 20%, and odynophagia in 15%. For body as a whole, chest pain was reported in 48%, fever in 22% and pain in 19%. Photosensitivity reactions occurred in 44% and skin disorder in 4%. For a complete list see pages 57 and 58 of the Clinical Review. Esophageal stricture is the adverse event of greatest concern. The incidence of esophageal stricture following PDT as assessed by endoscopy was 35% in study PHO BAR 1, 42% in study 93-07 and 36% in study 96-01. It was characterized as mild in 44%, moderate in 43% and severe in 12%. Of the patients requiring dilations, 35% required 1-2, 29% required 3-5, 22% required 6-10, and 15% required >10.

Conclusions: The application is approvable. The preliminary efficacy data suggest that PDT is effective in the treatment of high-grade dysplasia associated with Barrett's esophagus. However, the minimum follow-up in the original submission was too short to determine whether the duration of response is clinically meaningful. Also, high-grade dysplasia is a surrogate endpoint for the development of cancer. Although time to progression to cancer was a secondary endpoint, the development of esophageal cancer is the outcome of greatest interest. The additional follow-up may clarify whether the reduction in high-grade dysplasia results in a significant reduction in the incidence of esophageal cancer. Review of the 24-month follow-up data will be required to address these issues. Esophageal stricture is the adverse event of greatest concern. An advisory committee meeting during the second review cycle to discuss the application and the risk:benefit ratio is under consideration.

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
11/29/02 04:49:55 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER'S REVIEW

A Medical Team Leader's Review will be prepared for the second review cycle.

*Appears This Way
On Original*

MEMORANDUM OF TELECON

DATE: November 29, 2002

APPLICATION NUMBER: NDA 21-525 Photofrin® (porfimer sodium) Injection

BETWEEN:

Name:

Michelle Depot, Ph.D., Project Manager, Axcan
Francois Martin, M.D., Senior Vice President, Scientific Affairs, Axcan
Jean Spenard, Ph.D., Director, Programs, Axcan
Mary Speagle, Executive Director, CanReg Inc., Regulatory Consultant to Axcan
Anne Tomalin, President, CanReg Inc., Regulatory Consultant to Axcan
Becky Prokipcak, Ph.D., Director, CanReg Inc.; Regulatory Consultant to Axcan

Phone: (877) 228-3370; Code # 2 7
Representing: CanReg, Inc. (for Axcan Scandipharm, Inc.)

AND

Name:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Robert Justice, M.D., M.S., Division Director
Edward Kaminskas, M.D., Medical Reviewer
Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

SUBJECT:

To discuss review issues related to the action concerning NDA 21-525.

BACKGROUND:

On May 24, 2002, NDA 21-525 was submitted by Axcan Scandipharm, Inc. for the study of Photofrin® (porfimer sodium) Injection in the ablation of high-grade dysplasia in Barrett's Esophagus. The NDA was filed in the Division of Gastrointestinal and Coagulation Drug Products (hereafter, Division) as a priority review application with a user fee action goal date of November 30, 2002.

THE CALL:

Dr. Justice informed the sponsor that the Division has completed review of NDA 21-525, as amended, and it is approvable. Therefore, the Division will issue an Approvable Letter to be sent to the sponsor before close of business today. Dr. Justice stated that a major issue in the review of the application is that the minimum follow-up of six months in the original submission is not sufficient to establish that photodynamic therapy results in clinically meaningful long-term outcomes. Dr. Justice stated that the 24-month follow-up data submitted in the final report on September 26, 2002 was not reviewed for this action and would be reviewed during the next review cycle.

The sponsor asked if referencing the 24-month follow-up data with the responses to the other deficiencies listed in the action letter would be sufficient for a complete response triggering the 6-month review clock.

Dr. Justice stated that the sponsor may incorporate the 24-month follow-up data by specific reference as part of the complete response and that a review of the resubmission would probably be shorter than 6 months depending on the data submitted. Dr. Justice asked the sponsor when the Division could expect a response.

The sponsor indicated that depending on the nature of the deficiencies, a response would probably be submitted before December 25, 2002.

Dr. Justice advised the sponsor that the Division plans to present issues related to risk vs. benefit of the drug to an advisory committee during the next review cycle. This advisory committee meeting would likely take place in April or May of 2003, assuming the Division receives the complete response in December 2002.

The sponsor acknowledged that the application would be presented to an advisory committee.

The sponsor asked if a letter would be coming today from the Division of General, Restorative and Neurological Devices.

Dr. Justice stated that the project manager would check whether that division plans to send a letter today and would convey the response to the sponsor.

The call was ended.

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/s/

Paul Levine
12/3/02 07:39:08 AM
CSO

Robert Justice
12/3/02 09:58:36 AM
MEDICAL OFFICER

6 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

DSI CONSULT: Request for Clinical Inspections

Date: September 9, 2002

To: Khin Maung U, M.D., GCPB Reviewer/HFD-46

From: Brian Strongin, R.Ph., M.B.A., Review Division PM
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Request for Clinical Inspections
NDA 21-525
Axcan Scandipharm, Inc.
PHOTOFRIN® (porfimer sodium) for Injection

Protocol/Site Identification:

As discussed with you, the following protocol/site essential for approval has been identified for inspection.

Indication	Protocol #	Site (Name and Address)
Ablation of high-grade dysplasia in Barrett's Esophagus	PHO BAR 01	Bergein F. Overholt, M.D. Gastrointestinal Associates, PC 801 Weisgarber Road Knoxville, TN 37909

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspection be performed and the Inspection Summary Results be provided by (inspection summary goal date) **November 25, 2002**. We intend to issue an action letter on this application by (action goal date) **November 29, 2002**.

Should you require any additional information, please contact Brian Strongin, R.Ph., M.B.A.

Concurrence: (if necessary)

{See appended electronic signature page}

Joyce Korvick, M.D.
Medical Team Leader

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/s/

Joyce Korvick
9/12/02 04:58:28 PM

Brian Strongin
9/12/02 08:49:43 AM



NDA 21-525

8-16-02

Axcan Scandipharm, Inc.
c/o CanReg, Inc.
Attention: Becky Prokipcak, Ph.D.
4 Innovation Drive
Dundas, Ontario L9H 7P3

Dear Dr. Prokipcak:

Please refer to your May 24, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHOTOFRIN® (porfimer sodium) for Injection.

We are reviewing the clinical pharmacology and biopharmaceutics section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

We refer to the following commitment to NDA 20-451, also for PHOTOFRIN for Injection, acknowledged in the December 27, 1995 letter from the Division of Oncology Drug Products (HFD-150):

Commitment 2

Conduct Phase 4 studies to gather further pharmacokinetic data in patients with hepatic impairment and in patients who have received more than one course of therapy. Pharmacokinetics will also be characterized in male and female patients.

We also refer to your May 14, 2001 submission to NDA 20-451 requesting release from Commitment 2 and to the December 11, 2001 fax from Paul Zimmerman of HFD-150 to Kathryn Dunn of CanReg stating that the exemption could not be granted. Please provide an update on the status of Commitment 2 for NDA 20-451.

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
8/16/02 04:00:15 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2002

To: Becky Prokipcak, Ph.D	From: Brian Strongin, R.Ph., M.B.A.
Company: CanReg, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (847) 837-8825	Fax number: (301) 443-9285
Phone number: (905) 689-3980, ext 232	Phone number: (301) 827-7310
Subject: Medical information request for NDA 21-525, PHOTOFRIN for Injection	

Total no. of pages including cover: 2

Comments:

Please submit a response to the attached questions ASAP. Thanks.

Document to be mailed: YES NO

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Please provide the following information regarding PHO BAR 01:

1. Clarify which patients were enrolled in which centers.
2. Provide the response rate for the primary efficacy endpoint if Dr. Overholt's patients were excluded.
3. Clarify if updated follow-up data will be provided (and if so, when) to allow calculation of a more complete value for duration of response.

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/s/

Brian Strongin
7/23/02 03:54:18 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2002

To: Becky Prokipcak, Ph.D	From: Brian Strongin, R.Ph., M.B.A.
Company: CanReg, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (847) 837-8825	Fax number: (301) 443-9285
Phone number: (905) 689-3980, ext 232	Phone number: (301) 827-7310
Subject: Statistical information request for NDA 21-525, PHOTOFRIN for Injection	

Total no. of pages including cover: 2

Comments:

Please provide the information requested in the attachment on diskette ASAP. Submit this as a statistical amendment to your NDA and clearly mark it a REVIEW AID on the cover letter so that it will not be processed in the electronic document room. Thanks.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Please provide the following efficacy data sets on diskette for Study PHO BAR 01. Submit these data sets on diskette as an amendment to NDA 21-525. In the cover letter clearly mark this as a REVIEW AID so that it will not be processed in the electronic document room. Thanks.

1. Primary efficacy data set
2. Secondary efficacy data set

These data sets should contain the following variables: •

1. unique patient ID
2. center number
3. gender
4. race
5. age
6. treatment group
7. other important demographic/prognostic variables
8. last visit (hour or day) completed for the patient.
9. time in study
10. completer? (1 = yes patient completed whole study, 0 = patient discontinued early)
11. protocol violation indicator (1 = yes, 2 = no)
12. reason for discontinuing the study
13. visit (hour or day) where zero denotes the time of randomization
 - this variable is present when the data was collected at several visits.
14. LOCF indicator variable (1 = record contains the last efficacy value on study; 0 = not the last value)
15. Raw and derived data for the efficacy variables
 - Derived data (e.g. complete response)
 - Baseline should be included with each record as well as for the time 0 record

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/s/

Brian Strongin
7/10/02 11:06:54 AM
CSO



NDA 21-525

7/10/02

Axcan Scandipharm, Inc
c/o CanReg, Inc.
Attention: Becky Prokipcak, Ph.D.
4 Innovation Drive
Dundas, Ontario L9H 7P3

Dear Dr. Prokipcak:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: PHOTOFRIN® (porfimer sodium) for Injection

Review Priority Classification: Priority (P)

Date of Application: May 24, 2002

Date of Receipt: May 31, 2002

Our Reference Number: NDA 21-525

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 30, 2002 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be November 30, 2002.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Attention: Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
7/10/02 10:20:34 AM

7/1/02

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-525

Name of Drug: PHOTOFRIN® (porfimer sodium) for Injection

Sponsor: Axcan Scandipharm, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: May 24, 2002

Receipt Date: May 31, 2002

Filing Date: July 30, 2002

User-fee Goal Date: November 30, 2002

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

Other Background Information: PHOTOFRIN is currently approved by The Division of Oncologic Drug Products (HFD-150) for the following indications:

1. 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
2. Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC)
3. Treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated.

NDA 21-525 is a Type 6 NDA providing for ablation of high-grade dysplasia in Barrett's Esophagus. The NDA includes updated summaries of the CMC, biopharm, and pharmacology/toxicology information included in NDA 20-451. A pre-NDA meeting was held June 1, 2001.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 1.1, unnumbered pages 1 – 4
2. Form FDA 356h (original signature)	X		Volume 1.1, unnumbered pages 5 – 6
a. Establishment information	X		Included by reference to NDA 20-451 on Form FDA 356h
b. Reference to DMF(s) & Other Applications	X		Included by reference to NDA 20-451 on Form FDA 356h
3. User Fee FDA Form 3397	X		Volume 1.1, unnumbered page 7
4. Patent information & certification	X		Volume 1.1, page 256
5. Debarment certification (Note: Must have a definitive statement)	X		Volume 1.1, page 258
6. Field Copy Certification		X	Will request a certification or the location of this information in the submission.
7. Financial Disclosure	X		Volume 1.100
8. Comprehensive Index	X		Volume 1.1, page 001
9. Pagination	X		Acceptable. Each volume is paginated separately.
10. Summary Volume	X		Volume 1.1
11. Review Volumes	X		All disciplines have received the appropriate review volumes.
12. Labeling (PI, container, & carton labels)			
a. unannotated PI	X		Volume 1.1, page 016
b. annotated PI	X		Volume 1.1, page 053

c. immediate container		X	Not necessary
d. carton		X	Not necessary
e. patient package insert (PPI)		X	Not necessary
f. foreign labeling (English translation)		X	Will request if necessary.
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		In the Electronic Document Room, under NDA 21525, in the CRT folder
14. Case Report Forms (paper or electronic, for death & dropouts due to adverse events)	X		<u>Paper</u> : Volume 1.96, page 1 to Volume 1.99, page 117 <u>Electronic</u> : In the Electronic Document Room, NDA 21525, in the CFT Folder

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Volume 1.1, page 121
2. Foreign Marketing History	X		Volume 1.1, page 135
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 1.1, page 140
b. Nonclinical Pharmacology/Toxicology	X		Volume 1.1, page 142
c. Human Pharmacokinetic & Bioavailability	X		Volume 1.1, page 164
d. Microbiology		X	N/A

e. Clinical Data & Results of Statistical Analysis	X	Volume 1.1, page 171
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X	Volume 1.1, page 239
5. Summary of Safety	X	Integrated Summary of Safety: Volume 8, page 106
6. Summary of Efficacy	X	Integrated Summary of Efficacy: Volume 8, page 084

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		<u>Clinical Section:</u> Volume 8, page 002 <u>Statistical Section:</u> Volume 52, page 002
2. Controlled Clinical Studies			
a. Table of all studies	X		<u>Clinical Section:</u> Volume 1.8, page 001 <u>Statistical Section:</u> Volume 1.52, page 001
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		See Attachment Number 1
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Volume 1.08, page 034
3. Integrated Summary of Efficacy (ISE)	X		Volume 1.08, page 084
4. Integrated Summary of Safety (ISS)	X		Volume 1.08, page 106
5. Drug Abuse & Overdosage Information		X	N/A

6. Integrated Summary of Benefits & Risks of the Drug	X	Volume 1.08, page 157
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	X	The pivotal and supporting studies enrolled primarily male, Caucasian patients only.

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	X		Request for a waiver of the requirement for a pediatric assessment in Volume 1.1, page 259.
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in MS WORD		X	Will request from the sponsor.
b. Stability data in SAS data set format (only if paper submission)		X	N/A
c. Efficacy data in SAS data set format (only if paper submission)		X	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)	X		Claiming 7-year exclusivity in the cover letter.

Y=Yes (Present), N=No (Absent)

^a GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND

ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^b"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^c"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

^d"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

^e"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

NDA 21-525 is filable from an administrative perspective. The following information was requested from Axcan Scandipharm, Inc. on July 1, 2002: 1) a certification that a copy of the NDA was sent to the appropriate field office; and 2) a copy of the proposed unannotated package insert on diskette in WORD 97 with additions and deletions highlighted. The need for analyses of gender, race, and age safety and efficacy data and an audit of clinical studies by the Division of Scientific Investigations will be discussed at the 45-Day Planning/Filing meeting on July 9, 2002.

ATTACHMENTS

Attachment #1

ATTACHMENT 1

Controlled and Uncontrolled Clinical Studies

PHO BAR 01

Study Report	Volume 1.13, page 001 (duplicate in Statistical section)
Synopsis	Volume 1.13, page 003 (duplicate in Statistical section)
List of Investigators	Volume 1.13, page 021 (duplicate in Statistical section)
Protocol	Volume 1.15, page 003 (duplicate in Statistical section)
Related Publications	Volume 1.20, page 184 (duplicate in Statistical section)

TCSC 93-07

Study Report	Volume 1.42, page 001 (duplicate in Statistical section)
Synopsis	None Submitted
List of Investigators	Single center study, Volume 1.42, page 1 (duplicate in Statistical section)
Protocol	Volume 1.42, page 024 (duplicate in Statistical section)
Related Publications	Volume 1.42, page 133 (duplicate in Statistical section)

TCSC 96-01

Study Report	Volume 1.47, page 001 (duplicate in Statistical section)
Synopsis	None Submitted
List of Investigators	Single center study, Volume 1.47, page 001 (duplicate in Statistical section)
Protocol	Volume 1.47, page 026
Related Publications	Volume 1.47, page 095

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/s/

Brian Strongin :
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CSO

BACKGROUND:

The NDA for Photofrin® was approved on December 27, 1995, under NDA 20-451, as a drug and device combination for the palliation of completely obstructing esophageal cancers. On January 9, 1998, Photofrin was approved, for the treatment of micro-invasive endobronchial non-small cell lung cancer for whom surgery and radiation is not indicated, and on December 22, 1998, it was approved for palliation of obstructive endobronchial non-small-cell lung cancer.

On September 26, 2000, IND 61,011 was submitted by Axcan Scandipharm, Inc. for the study of Photofrin® in the ablation of high grade dysplasia in Barrett's Esophagus.

In an advice letter, dated January 24, 2001, comments and recommendations resulting from the review of the IND were conveyed to the sponsor. On March 5, 2001, representatives from CanReg, Inc. (a subsidiary of Axcan Scandipharm, Inc.) met with the FDA via telephone to discuss these comments.

On January 29, 2001, the sponsor submitted a pre-NDA meeting request to discuss the development of Photofrin®.

MEETING PURPOSE:

To answer questions from the sponsor and provide guidance concerning the submission of an NDA for Photofrin®.

DISCUSSION:

The sponsor provided an overview of the regulatory background, including discussions with the Division of Oncologic Drug Products (HFD-150), and an overview of the preliminary results of the primary analysis for protocol PHO BAR 01 (see attached slides).

The sponsor was notified that the Agency's is concerned that an esophagectomy group was not included in the clinical trial and that the data might not justify the use of photodynamic therapy (PDT) over esophagectomy. In addition, the sponsor was notified that the Agency's is concerned about the risks to patients resulting from possible delays in surgery caused by photodynamic therapy. The Agency suggested that photodynamic therapy be used in those patients who are not candidates for esophagectomy.

FDA's Response to Questions from Sponsor

QUESTION #1: For the Preclinical section of the PHOTOFRIN® sNDA, it is our intention to include the following studies:

- Three studies designed to measure the light delivery and lesion development from the new balloon catheters compared to earlier balloon devices.
- Two genotoxicity studies measuring mutations in the HGPRT locus after exposure of Chinese Hamster Ovary (CHO) cells to PHOTOFRIN® in the presence and absence of light irradiation. These study reports were submitted to the NDA in an Annual Report, and will be included in this sNDA for convenience of review.
- A study assessing the dermal sensitization potential of the new balloon system.

The original NDA 20-451 will be cross-referenced for the rest of the preclinical data. Will the Agency please confirm that this approach is acceptable for the application?

FDA's Response: Additional information is needed before comments can be provided.

Additional Comments: The sponsor indicated that three studies had been submitted to the IND. These studies included two mutagenicity studies and one study on the early stage development of the balloon.

The sponsor was asked what changes in balloon size had occurred since the early development. The sponsor stated that the size of the balloon had not changed.

The sponsor asked if the Oncology Division would review the pharmacology and toxicology data. The sponsor was informed that the GI Division would review the data and may consult with other Divisions, as needed.

The sponsor agreed to include in the NDA submission to the GI Division, a summary of the pharmacology and toxicology data previously submitted with cross-references to the original submission.

QUESTION #2: Biopharmaceutical studies were included with the original NDA. An additional study comparing the pharmacokinetics of PHOTOFRIN® in healthy males and females (PHO PK 001) was conducted as a Phase IV commitment and submitted to the Agency on May 4, 2000, and a summary of this study will be submitted with the sNDA. No new biopharmaceutical studies are planned for the sNDA. Will the Agency confirm that this approach is acceptable?

FDA Response:

OCPB Comments:

1. Please update the status of Phase IV comments for NDA 20-451 on gathering PK data/information in hepatic impairment and PDT treatment of more than one course.
2. Since this is a new indication in a different population with a different disease, please clarify if supportive PK data is available, including:
 - a. the PK data in the dose range/regimen employed in the clinical trial(s) for this target population, and
 - b. the PK data on effects of co-administration of drugs, e.g., commonly used in this population and based on information on the metabolism via hepatic cytochrome P-450 enzyme systems (please see "In Vivo Drug Metabolism/Drug Interaction Studies" guidance).

Additional Comments: The sponsor presented updated information about the phase 4 commitments (see slides attached) .

The sponsor agreed to include in the NDA submission to the GI Division, a summary of the pharmacokinetic data previously submitted.

In addition, the sponsor indicated that no PK data/information was obtained from the clinical trial. The sponsor further indicated that on 05/09/01, a waiver for phase-4 studies on multiple dosing and hepatic dysfunction had been requested through the Division of Oncologic Drug Products.

QUESTION #3: No changes to the Chemistry and Manufacturing of PHOTOFRIN® are planned as a result of this new indication. Therefore, we intend to cross-reference NDA 20-451 for CMC information. Will the Agency confirm that this is acceptable?

FDA's Response: Yes, this appears to be acceptable. A summary of the information cross-reference in NDA 20-451 should be provided with the submission of the new NDA.

Additional Comments: The sponsor agreed to include in the NDA submission a summary of the CMC data previously submitted and CMC information submitted in response to Phase 4 commitments.

QUESTION #4: As discussed previously with the Division of Gastrointestinal and Coagulation Drug Products, Axcan intends to submit this sNDA for use of PHOTOFRIN® in patients with high grade dysplasia who are not candidates for esophagectomy. Our proposed labeling would include the following indication:

"PHOTOFRIN® (porfimer sodium) is indicated for the ablation of high-grade dysplasia (HGD) in Barrett's Esophagus (BE) among patients who are not considered to be candidates for esophagectomy."

Would the Agency please confirm that this indication is acceptable, and that the endpoints of the PHO BAR 01 clinical trial are sufficient to support this indication?

FDA's Response: The proposed indication and endpoints appears to be acceptable. However, we are unable to provide additional comment until all of the data from the clinical trials have been reviewed.

Additional Comments: The sponsor presented information on an alternative indication (see slide attachment).

The sponsor was informed that the Agency is concerned about the difference between the study population and the intended treatment population. The proposed indication and labeling would have to reflect this difference.

The sponsor asked for the Agency's comment about the use of Photofrin® as adjunctive therapy in the management of high grade dysplasia in Barrett's Esophagus and whether this issue would be taken to an advisory committee.

The sponsor was informed that the Agency is concerned about the misconception in clinical practice that Photofrin® is a better treatment option for high grade dysplasia in Barrett's Esophagus. Therefore, the proposed labeling would have to be clear on the proper use of the drug. The sponsor was further informed that the determination of whether or not this issue would be presented to an Advisory Committee is premature at this time.

QUESTION #5: The Clinical Section of the application will rely on one North American pivotal study, and two supportive studies, as discussed previously with the Division. Will the Division please confirm that this approach is acceptable?

FDA's Response: Additional information about the planned studies is required to determine the acceptability of this approach.

QUESTION #6: In the sNDA, Axcan will base the primary analysis for the PHO BAR 01 study on data collected up to a minimum of 6 months of follow-up after the last patient enrolled in the study, as per Protocol. The submission will include data from a median follow-up of 11 months. Surveillance of patients will continue, and Axcan will submit data on patients collected up to a minimum of 24 months of follow-up as a post-approval commitment. Will the Agency confirm that this approach is acceptable for this defined patient population?

FDA's Response: Additional information is required to determine the acceptability of this approach.

QUESTION #7: It is our intent to submit the PHOTOFRIN® sNDA in hard copy. Will the Agency please confirm that an electronic NDA is not required for this submission?

FDA's Response: The agency does not currently require that a sponsor provide an electronic submission of an NDA.

QUESTION #8: We intend to request a pediatric waiver for PHOTOFRIN® for this indication, given that the disease is limited to an adult population. Will the Agency please comment on whether this is acceptable?

FDA's Response: Yes, a pediatric waiver for PHOTOFRIN® is acceptable.

QUESTION #9: It is our intent to submit a request for Orphan Drug Designation to the Office of Orphan Product Development. If this designation is granted, will the Agency confirm that the fee for this submission will be waived?

FDA's Response: Yes, if the application meets the criteria for Orphan Drug Designation then the User Fee will be waived.

QUESTION #10: It is our intent to request a priority review for PHOTOFRIN® for the proposed indication. Will the Agency comment on whether this would be agreed to?

FDA's Response: The determination for priority review will be made at the time the application is filed and will be based upon the criteria indicated in the *Priority Review Policy, MaPP 6020.3*.

QUESTION #11: Since the time required for review for the PMA portion of the submission will be shorter than that required for the drug portion, will the Agency comment on the acceptability of submitting the drug portion first, followed by the submission of the device portion? Axcan understands that approval of the PHOTOFRIN® sNDA will depend on the approval of both components.

FDA's Response: Both the drug portion and the PMA (device) portion of the application should be included with the submission of the NDA. In addition, we recommend that the PMA portion of the NDA be contained in a separate volume within the NDA, and 6 desk copies of this section be provided as part of the NDA submission.

QUESTION #12: The data in the PMA portion of the submission will support the utility of the Barrett's Light Delivery System in conjunction with the Diomed 630 PDT Laser. Will the Agency confirm that this is acceptable?

FDA's Response: Yes, this is acceptable.

CONCLUSION

1. The sponsor agreed to include in the NDA submission to the GI Division, a summary of the pharmacology and toxicology data previously submitted with cross-references to the original submission.
2. The sponsor agreed to include in the NDA submission to the GI Division, a summary of the pharmacokinetic data previously submitted.
3. The sponsor agreed to include in the NDA submission a summary of the CMC data previously submitted and CMC information submitted in response to Phase 4 commitments.

11 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

Lilia Talarico
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MEMORANDUM OF TELECON

DATE: March 05, 2001

APPLICATION NUMBER: IND 61,011; Photofrin® (porfimer sodium) Injection

BETWEEN:

Name: Patrick Colin, Ph.D., Vice President, Clinical Research
Michelle Depot, Ph.D., Project Manager
Francois Martin, M.D., Senior Vice President, Scientific Affairs
Becky Prokipcak, Ph.D., Project Manager
Jean Spenard, Ph.D., Program Director, Clinical Research
L J Consultant
L J Consultant

Phone: (905) 689-3980 ext. 232

Representing: CanReg, Inc. (for Axcan Scandipharm, Inc.)

AND

Name:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Lilia Talarico, M.D., Division Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Mark Avigan, M.D., Medical Reviewer
Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

SUBJECT:

To answer the sponsor's questions and provide guidance concerning the Agency's advice letter, dated January 24, 2001.

BACKGROUND:

The NDA for Photofrin® was approved on December 27, 1995, under NDA 20-451, as a drug and device combination for the palliation of completely obstructing esophageal cancers. On January 9, 1998, Photofrin was approved, for the treatment of micro-invasive endobronchial non-small cell lung cancer for whom surgery and radiation is not indicated, and on December 22, 1998, it was approved for palliation of obstructive endobronchial non-small-cell lung cancer.

On September 26, 2000, IND 61,011 was submitted by Axcan Scandipharm, Inc. for the study of Photofrin® in the ablation of high grade dysplasia in Barret's Esophagus.

In a letter, dated January 24, 2001, comments and recommendations resulting from the review of the IND were conveyed to the sponsor.

THE CALL:

The sponsor provided an overview of the regulatory background for Photofrin, including an overview of previous discussions with the Division of Oncologic Drug Products (HFD-150).

The sponsor was asked to clarify the details of the follow-up process for patients, including what was being followed and for how long.

The sponsor stated that patient follow up occurred at 6, 12, 18, and 24 months. Surveillance biopsies were done at 6 months at the treatment site and other sites.

The sponsor was informed that 6 months follow-up may be inadequate to assess the impact of the treatment. A follow-up time frame of 5 years or more was recommended, but follow-up of at least 2-3 years would be acceptable.

The sponsor stated that a median time for follow-up on patients participating in the main study was 11 months. In addition, there are 2-4 years of follow-up data available for some patients.

The sponsor was informed that the Agency is concerned that the use of histopathological effects for measuring clinical benefit might be a surrogate endpoint. The appropriateness of this endpoint is questionable considering the difference in the natural course of high-grade dysplasia (HGD) from low-grade dysplasia (LGD) in the occurrence of cancer. The measurement should be linked to a clinical meaningful outcome. Therefore, the Agency recommends that procedures be implemented to distinguish between high-grade dysplasia and de novo low-grade dysplasia with advancement of disease.

In addition, the sponsor was informed that the Agency is concerned that photodynamic therapy (PDT) might be a cosmetic effect on treatment rather than changing the course of the disease. The sponsor was informed that the Agency is most interested in assessing whether there is a long-term sustained response to therapy.

The sponsor stated that the primary endpoint for treatment was complete ablation of HGD. Data from the clinical trial indicate that response to therapy is sustained.

The sponsor was informed that the Agency is concerned about a possible bias in entry criteria and was asked to clarify the entry criteria for patients.

In addition, the Agency stated that long-term clinical measures are extremely important in making relative comparison to esophagectomy. The absence of a long-term comparison study of esophagectomy to PDT for HGD might present problems in considering the "whole picture" and would prevent the sponsor from making superiority claims of PDT over esophagectomy.

The sponsor stated that there is no consensus on the treatment of patients with HGD. Consequently, study patients were offered, at entry, the options of surgical (esophagectomy) or non-surgical (surveillance) participation in the program. The sponsor indicated that the lack of data comparing the PDT to esophagectomy could be handled in labeling.

In addition, the sponsor stated that patients in the clinical trial have been randomized to omeprazole (10% PDT arm and 19% omeprazole arm representing 208 patients for 1 year). This data might provide more compelling support.

The sponsor indicated that it plans to request a pre-NDA meeting and would consider the Agency's comments in preparation for that meeting.

The call was ended

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/s/

Paul. Levine

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CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-525	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: PHOTOFRIN® (porfimer sodium) for Injection		Applicant: Axcan Scandipharm, Inc.
RPM: Brian Strongin, R.Ph., M.B.A.		HFD-180 Phone # 7-7473
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		6
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		
		August 3, 2003
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid user Fee
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
❖ Exclusivity (approvals only)		
• Exclusivity summary		X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		July 1, 2002
General Information		
• Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)		N/A
• Status of advertising (approvals only)		<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> (N/A) Reviewed for Subpart H
• Public communications		
• Press Office notified of action (approval only)		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable

<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input checked="" type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A - Package Insert
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	X - Package Insert (July 30, 2003 submission)
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X - Package Insert (May 24, 2002 submission)
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) 	(DDMAC Review: July 9, 2003; RPM Review July 21, 2003)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	N/A
<ul style="list-style-type: none"> Reviews 	N/A
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	N/A
Outgoing correspondence (i.e., letters, E-mails, faxes)	X
Memoranda and Telecons	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	N/A
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	June 1, 2001
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	N/A
<ul style="list-style-type: none"> Other 	March 5, 2001 (Telecon regarding the Agency's January 24, 2001 Advice letter)
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	June 26, 2003
<ul style="list-style-type: none"> 48-hour alert 	X
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	X (July 28, 2003, July 29, 2003)
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	X (November 14, 2002; July 21, 2003; July 22, 2003)
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	N/A
Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	X (See Medical Officer's Review dated July 21, 2003)
Pediatric Page (separate page for each indication addressing status of all age groups)	X

❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
Statistical review(s) (<i>indicate date for each review</i>)	X (November 1, 2002; June 23, 2003)
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	X (August 16, 2002; November 5, 2002)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (November 5, 2002)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	X (10/3/02)
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	X (10/3/02)
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	N/A
❖ Facilities inspection (provide EER report)	N/A
❖ Methods validation	(X) Completed N/A () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	X (November 15, 2002)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

7/2/02

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-525	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: PHOTOFRIN ® (porfimer sodium) for Injection		Applicant: Axcan Scandipharm, Inc.
RPM: Brian Strongin, R.Ph., M.B.A.		HFD-180 Phone # 7-7473
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		6
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		
		August 3, 2003
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None
		Subpart H
		<input type="checkbox"/> 21 CFR 314.510 (accelerated approval)
		<input type="checkbox"/> 21 CFR 314.520 (restricted distribution)
		<input type="checkbox"/> Fast Track
		<input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid user Fee
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
❖ Exclusivity (approvals only)		
• Exclusivity summary		X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		July 1, 2002
General Information		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)		N/A
• Status of advertising (approvals only)		<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable

<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input checked="" type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A - Package Insert
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	X - Package Insert (July 30, 2003 submission)
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X - Package Insert (May 24, 2002 submission)
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) 	(DDMAC Review: July 9, 2003; RPM Review July 21, 2003)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	N/A
<ul style="list-style-type: none"> Reviews 	N/A
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	N/A
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	June 1, 2001
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	N/A
<ul style="list-style-type: none"> Other 	March 5, 2001 (Telecon regarding the Agency's January 24, 2001 Advice letter)
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	June 26, 2003
<ul style="list-style-type: none"> 48-hour alert 	X
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	X (July 28, 2003, July 29, 2003)
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	X (November 14, 2002; July 21, 2003; July 22, 2003)
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	N/A
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	X (See Medical Officer's Review dated July 21, 2003)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X

❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	X (November 1, 2002; June 23, 2003)
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	X (August 16, 2002; November 5, 2002)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (November 5, 2002)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	X (10/3/02)
❖ Environmental Assessment	
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❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

7/2/02

SAFETY UPDATE REVIEW

See the Medical Officer's Review Dated July 21, 2003

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On Original**