CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

Axcan Scandipharm, Inc.
Attention: Debbie O. Co, Ph.D.
4 Innovation Drive
Dundas, Ontario L9H 7P3
Canada

Dear Dr Co:

Please refer to your new drug application (NDA) dated May 24, 2002, received May 31, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHOTOFRIN® (porfimer sodium) for Injection.

We acknowledge receipt of your submissions dated September 26, October 23, and November 4, 2002 and January 28, February 18, April 4, May 13, June 3, July 29 and July 30, 2003.

Your submission dated January 28, 2003 was a complete response to our action letter dated November 29, 2002.

Please also refer to the April 6, 2003 supplemental new drug application NDA 20-451/S-012.

These new drug applications provide for the use of PHOTOFRIN® (porfimer sodium) for Injection for the ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy.

We completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For

administrative purposes, designate this submission"**FPL for approved NDA 21-525.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated July 29, 2003. This commitment is listed below.

1. You commit to completing the ongoing clinical study (PHO BAR 02) entitled, "A multicenter, partially blinded, randomized Phase III study of the efficacy and safety of photodynamic therapy (PDT) using PHOTOFRIN® (porfimer sodium) for Injection for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE): A 5-year follow-up".

   Final Report Submission: Within 24 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 20-451. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81)

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA (NDA 20-451) for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Project Manager at (301) 827-7473.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Joyce Korvick
8/1/03 02:15:12 PM
for Dr. Robert Justice

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NDA 20-451/S-012

Approvable Letter (s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-525

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

Dear Dr. Prokipcak:

Please refer to your new drug application (NDA) dated May 24, 2002, received May 31, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHOTOFRIN® (porfimer sodium) for Injection.

We acknowledge receipt of your submissions dated July 25, October 11, and November 4, 2002.

We also acknowledge receipt of your submissions dated September 26 and October 23, 2002. These submissions were not reviewed for this action. You may incorporate them by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

1. As stated in our letter dated January 24, 2001 regarding IND 61,011, "To qualify as a pivotal trial the primary response variable must reflect an improvement in the long-term clinical outcome. Partial histopathological responses to photodynamic therapy (PDT) might not reflect clinically meaningful long-term outcomes." The minimum follow-up of six months in study PHO BAR 01 in the original submission is not sufficient to establish that photodynamic therapy results in clinically meaningful long-term outcomes. The 24-month follow-up data from this study submitted in the final report on September 26, 2002 are required to make this determination.

2. Provide a listing by patient ID number of the patients who remained in complete response at the end of the 24-month follow-up period in PHO BAR 01. In addition, provide listings of patients who progressed to cancer, who received other treatments (specify), and who were discontinued from the study (specify the reasons). Include the length of follow-up in these listings.

3. In supporting Studies TCSC 93-07 and 96-01, patient ID numbers were not provided in Tables 3.7.3 and 3.9.1 in Volumes 1.42 and 1.47 respectively. These tables document Response Failures and Time to Progression to Cancer. The latter should be subsumed into the former, but the days to failure are different. Clarify if patients who progressed to cancer were included among those who were Response Failures.

4. The rates for Complete Response 1 or 2 or 3 in Studies TCSC 93-07 and 96-01 are 93.2% and 95.2% respectively (Volume 1.41, pp. 207, 208, 210; Volume 1.47, pp. 171-172). These rates are not consistent with the twelve-month response failure rates of 36.8% in Study TCSC 93-07 and 28.6% in Study TCSC 96-01 (Volume 1.86, p. 286; Volume 1.47, p. 250) or with the Time to Progression to Cancer in these studies (Volume 1.42, p.293; Volume 1.47, p. 255). Please clarify these discrepancies.

5. Perform a detailed analysis of the poorer response rate to PHOTOFRIN® for Injection photodynamic therapy (PDT) in older patients. Clarify if an age group exists for which PHOTOFRIN® for Injection PDT is contraindicated.

In addition, it will be necessary for you to submit draft labeling revised as follows:

Provide a revised proposed package insert to incorporate the results of the final study report for PHO BAR 01 submitted September 26, 2002 and the Safety Update submitted October 23, 2002.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Also, please be advised that we are tentatively planning to take this application to an advisory committee during the next review cycle.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
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
11/29/02 11:58:25 AM