

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-786

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Axcan Scandipharm

Helizide™ Capsules (Biskalcitrate, Metronidazole & Tetracycline Hydrochloride)

1.2.2 Updated Patent Information

Module 1

1.2.2 UPDATED PATENT INFORMATION

Two FDA 3542a forms are provided in this section for U.S. patents (i) Patent 6,350,468 and (ii) Patent 5,476,669.

Both patents cover the drug product Helizide™ Capsules (140 mg biskalcitrate, 125 mg metronidazole, 125 mg tetracycline hydrochloride) of NDA 50-786.

Patent 6,350,468 was previously submitted to NDA 50-786 as Amendment 6 on July 29, 2002.

Patent 5,476,669 was submitted in the original NDA submission for Helicide® Capsules (140 mg biskalcitrate, 125 mg metronidazole, 125 mg tetracycline hydrochloride), NDA 50-786 (formerly 21-362) dated September 28, 2001.

The two submissions mentioned above predated the current requirement for completed FDA forms 3542a and 3542. Therefore, in order to bring the current file up to date, a complete FDA form 3542a for each patent is being provided in this submission.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

50-786

NAME OF APPLICANT / NDA HOLDER

Axcan Scandipharm Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Helizide™

ACTIVE INGREDIENT(S)

biskalcitrate, metronidazole, tetracycline hydrochloride

STRENGTH(S)

biskalcitrate 140 mg, metronidazole 125 mg, tetracycline hydrochloride 125 mg

DOSAGE FORM

Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
US 6,350,468

b. Issue Date of Patent
2/26/2002

c. Expiration Date of Patent
12/14/2018

d. Name of Patent Owner
Inventor: Giovanni Sanso (Milan, IT)
Assignee: Axcan Pharma Inc. (the parent company of
Axcan Scandipharm Inc.) (Quebec, CA)

Address (of Patent Owner)
22 Inverness Center Parkway, Suite 310

City/State
Birmingham, AL

ZIP Code
35242

FAX Number (if available)
(205) 991-9547

Telephone Number
(205) 991-8085

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
22 Inverness Center Parkway, Suite 310

City/State
Birmingham, AL

ZIP Code
35242

FAX Number (if available)
(205) 991-9547

Telephone Number
(205) 991-8085

E-Mail Address (if available)
mparisher@Axcan.com

Mary Martha Parishier
In-house Counsel

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
 1 Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.
 Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
 Helizide™ (biscalcitrates, metronidazole, tetracycline hydrochloride) Capsules, in combination with omeprazole are indicated for the treatment of patients with Helicobacter pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

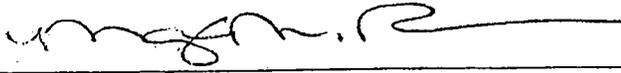
6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed
3/27/2006



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Mary Martha Parish
In-house Counsel

Address

22 Inverness Center Parkway, Suite 310

City/State

Birmingham, AL

ZIP Code

35242

Telephone Number

(205) 991-8085

FAX Number (if available)

(205) 991-9547

E-Mail Address (if available)

mparisher@Axcn.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



Axcam Scandipharm Inc.

HELICIDE® (Bismalate Potassium + Metronidazole + Tetracycline HCl) Capsules
New Drug Application
September 2001

NDA

SECTION 12: PATENT INFORMATION & CERTIFICATION

12.1 Patent Information

CONFIDENTIAL

001



Axcán Scandipharm Inc.

HELICIDE® (Biscalcitate Potassium + Metronidazole + Tetracycline HCl) Capsules
New Drug Application
September 2001

12.2 Patent Certification

Appears This Way
On Original

Patent Submission

Submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information please refer to 21 C.F.R. 314.53

Time Sensitive Patent Information pursuant to 21. C.F.R. 314.53 for NDA#

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: HELICIDE™
Active Ingredient(s):
Strength(s):
Dosage Form:
Approval Date: -----

A. This information should be provided for each individual patent submitted

U.S. Patent number: 5,196,205

Expiration Date: March 23, 2010

Type of Patent -- Indicate all that apply:

Drug Substance (Active Ingredient) ___Y___ X N
Drug Product (Composition/Formulation) ___Y___ X N
Method of Use X Y ___N___

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

- A method of preventing recurrence of duodenal ulcer associated with *Campylobacter pylori* infection in a patient suffering from duodenal ulcer disease associated with *Campylobacter pylori* infection

Names of Patent Owners: Exomed Australia Pty.Ltd.; Ostapat Pty. Limited; Gastro Services Pty. Limited; Capability Services Pty. Limited (all of New South Wales, Australia).

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Ronald P. Kananen

B. The following declaration statement is required by 21 C.F.R. 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 5,196,205 covers the composition, formulation and/or method of use of HELICIDE™ (name of drug product). This product is:

 currently approved under section 505 of the Federal Food, Drug and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed: Léon F. Gosselin

Date: Sept. 26, 2001

Title (optional): Léon F. Gosselin, President and CEO of AXCAN PHARMA INC.

Telephone number: (optional): (450) 467-5138

**Appears This Way
On Original**

Patent Submission

Submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act.

Time Sensitive Patent Information pursuant to 21. C.F.R. 314.53 for NDA#

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: HELICIDE™
Active Ingredient(s):
Strength(s):
Dosage Form:
Approval Date: -----

A. This information should be provided for each individual patent submitted

U.S. Patent number: 5,476,669

Expiration Date: March 23, 2010

Type of Patent -- Indicate all that apply:

Drug Substance (Active Ingredient) Y X N
Drug Product (Composition/Formulation) Y X N
Method of Use X Y N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

- A method of preventing recurrence of gastric ulcer and duodenal ulcer associated with *Campylobacter pylori* (Helicobacter pylori) infection in a patient suffering from gastric ulcer disease associated with *Campylobacter pylori* (Helicobacter pylori) infection

Names of Patent Owners: Exomed Australia Pty.Ltd.; Ostapat Pty. Limited; Gastro Services Pty. Limited; Capability Services Pty. Limited (all of New South Wales, Australia).

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Ronald P. Kananen

B. The following declaration statement is required by 21 C.F.R. 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 5,476,669 covers the composition, formulation and/or method of use of HELICIDE™ (name of drug product). This product is:

 currently approved under section 505 of the Federal Food, Drug and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed:

Léon F. Gosselin

Date:

Sept 26, 2001

Title (optional): Léon F. Gosselin, President and CEO of AXCAN PHARMA INC.

Telephone number: (optional): (450) 467-5138



AXCAN PHARMA INC.

597 boul Laurier
Mont-Saint-Hilaire QC J3H 6C4
Canada

Tél.: (450) 467-5138
1 (800) 565-3255
Fax: (450) 464-9979
www.axcan.com

The undersigned declares that U.S. Patent No. 6,350,468 covers the formulation, composition and/or use of HELICIDE (metronidazole, tetracycline hydrochloride, and biscaltrate potassium). This product is the subject of this application for which approval is being sought.

François Martin, MD, FRCP(C)

Name

Signature

Senior Vice President - Scientific Affairs

Title

25.07.2002

Date



1982-2002

20 ans à l'avant-garde
de la gastroentérologie

021

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 50-786 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 28, 2001 Action Date: September 28, 2006

HFD 590 Trade and generic names/dosage form: Pylera (biscalcitrates/metronidazole/tetracycline HCl)

Applicant: Axcan Pharmaceuticals, Inc. Therapeutic Class: Anti-infective

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _____

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Waived Studies

Age/weight range being waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 2 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. >2 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): September 30, 2011

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

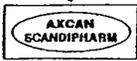
{See appended electronic signature page}

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

cc: NDA 50-786
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)



Axcan Scandipharm Inc.

HELIZIDE® (Bisacitrate Potassium + Metronidazole + Tetracycline HCl) Capsules
NDA 50-786

Amendment # 15: Response to Information Request, Revised Package Insert,
Revised Debarment Certification

September 26, 2003

8.1.3 Debarment Certification - Revised

* CONFIDENTIAL *

055

On behalf of Axcan Scandipharm Inc., I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with the HELICIDE NDA application.

J. S. Cipriano M.S., R.Ph.

John S. Cipriano M.S., R.Ph.
Director, Quality Assurance & Development
Axcan Scandipharm Inc.

9/24/03

Date



Axcen Scandipharm Inc.

HELICIDE® (Biscalcitrates Potassium + Metronidazole + Tetracycline HCl) Capsules
New Drug Application
September 2001

NDA 21-362

8.1.3 Debarment Certification

Note - Axcen rep who signed debarment is not a US national or resident. Proper US agent certification will arrive on 9/26/03, according to Can Reg.

9/29/03 - still have not received updated debarment. They say they mailed it on 9/26/03.

✓ received (see previous page)



AXCAN PHARMA INC.

597, boul. Laurier
Mont-Saint-Hilaire, QC J3H 6C4
Canada

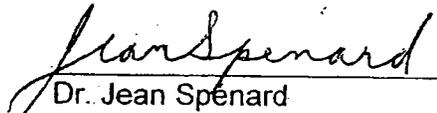
Tél.: (450) 467-5138

1 (800) 565-3255

Fax: (450) 464-9979

www.axcan.com

On behalf of Axcan Scandipharm Inc., I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA HELICIDE®.



Dr. Jean Spénard
Program Director, Clinical Research

September 25, 2001

Date

MEMORANDUM OF TELECONFERENCE

DHHS/Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Special Pathogen and Transplant Products

Date: September 28, 2006

Between: Irma Monaco, Manager, Regulatory Affairs (CMC)
CanReg, Inc.

And: Rebecca D. Saville, Regulatory Project Manager, HFD-590
DSPTP

Subject: PYLERA® (biskalcitrate/metronidazole/tetracycline HCl) Capsules
NDA 50-786
Foreign Marketing Status

On September 28, 2006, I called CanReg to inquire on the foreign marketing status of Pylera. CanReg emailed to me the following information to me:

Hi Rebecca,

Please note this product has not been marketed in any jurisdiction to date. A safety update on each of the individual components was provided in the complete response submitted March 26, 2006.

Foreign Marketing Status:

Canada

As of March 14, 2003, we received approval for HELICIDE from the Therapeutic Products Directorate of Health Canada. On September 5, 2003, a second approval was issued for the new name of HELIZIDE. In parallel, Axcan changed their biskalcitrate manufacturer to [REDACTED]. The new manufacturer has not yet been submitted for approval in Canada, thus, HELIZIDE was never marketed in Canada.

European Union

Marketing authorization is currently being sought in the [REDACTED]. Axcan has decided a decentralized procedure and is in discussions with the [REDACTED] and [REDACTED] regarding the filing of the application.

Thank you for all your help.

Irma

Irma Monaco
Manager, Regulatory Affairs (CMC)
CanReg Inc.
4 Innovation Drive
Dundas, Ontario L9H 7P3
Canada
Ph: (866) 722-6734, ext. 228
Fax: (905) 689-1465

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager, DSPTP

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

/s/

Rebecca Saville
9/28/2006 03:36:17 PM
CSO

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

This corrected version of the Regulatory Filing Review supersedes the version dated September 20, 2006. Corrections are highlighted below:

NDA # 50-786 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Pylera
Established Name: biscalcitate/metronidazole/tetracycline HCl
Strengths: 140 mg/ 125 mg/ 125 mg

Applicant: Axcan Scandipharm, Inc.
Agent for Applicant (if applicable): CanReg, Inc.

Date of Application:
September 28, 2001 (original), March 31, 2003 (1st resubmission), March 27, 2006 (2nd resubmission)
Date of Receipt of 2nd Resubmission: March 28, 2006
Date clock started after UN: March 28, 2006
Date of Filing Meeting: unknown
Filing Date: November 27, 2001
Action Goal Date (optional): User Fee Goal Date: September 28, 2006

Indication(s) requested:
In combination with omeprazole, Pylera is indicated for the treatment of patient with Helicobacter pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file? user feel not originally paid

Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the

User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain: Patent certification not included in application. Requested on September 7, 2006.
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
Labeling submitted electronically.
2. This application is an eNDA or combined paper + eNDA YES NO
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES No
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
No, BPCA and PREA did not apply when originally submitted
YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. **Drug name and applicant names are correct**

- List referenced IND numbers:
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Resubmission Meeting(s)? January 11, 2001 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? n/a YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application: n/a

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? n/a

YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

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ATTACHMENT

MEMO OF RESUBMISSION ACCEPTABILITY

DATE: April 12, 2006

NDA #: 50-786

DRUG NAMES: Pylera

APPLICANT: Axcan Pharmaceutical

BACKGROUND:

Pylera (formerly called Helicide and Helizide) oral capsules contain a combination of three drug substances, which are metronidazole, tetracycline HCl, and bismalcytrate potassium. Metronidazole and tetracycline are antimicrobials. NDA 12-623 Flagyl (metronidazole) was approved on July 18, 1963. Tetracycline was initially approved in 1957 and is considered an "old" antibiotic according to Hatchman-Wax Act. Bismalcytrate K is a bismuth complex, a type of bismuth salt, and is a new molecular entity. Its pharmacologic category is a mucosal protectant. Historically, bismuth salts have astringent, antacid, and mild bactericidal activity and have been used for the treatment of diarrhea, nausea, indigestion, and inflammatory diseases of the stomach and colon. A common example of a bismuth salt is Pepto-Bismol (bismuth subsalicylate).

Pylera, in combination with a proton pump inhibitor (PPI), omeprazole, is indicated for the eradication/treatment of *Helicobacter pylori* in patients with *H. pylori* infection in duodenal ulcer disease. The combination therapy of omeprazole, bismalcytrate K, metronidazole, and tetracycline HCl is abbreviated OBMT. The combination of metronidazole, tetracycline HCl, and a bismuth salt has been a therapeutic regimen usually used with H₂-agonists and is considered the gold standard therapy. An example is NDA 50-719 Helidac (bismuth subsalicylate/metronidazole/tetracycline), which consists of the 3 drug substances co-packaged together and used in conjunction with an H₂-agonist. Helidac was approved on August 15, 1996 for the eradication/treatment of *Helicobacter pylori* in patients with *H. pylori* infection in duodenal ulcer disease. If approved, Pylera will provide for the first product using the new bismuth complex bismalcytrate K and combining all 3 drug substances in one capsule as well as the first regimen using a PPI.

NDA 50-786 was originally dated September 28, 2001. Several studies were conducted under IND to support the efficacy and safety. Two Phase 1 clinical pharmacology (drug-drug interaction) studies and two Phase 3 clinical trials were conducted by the sponsor. In the Phase 3 North American trial (Protocol HPST99-CUS01), patients were randomized to OBMT or a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin and enrolled with a history of or current duodenal ulcer. The Phase 3 International trial (Protocol HPST99-INT01) differed from the North American trial in that all patients received OBMT. The main efficacy endpoint for both trials is the absence (eradication) of *H. pylori* after treatment. Eradication is defined, according to guidelines, as two negative ¹³C urea breath tests done at least 4 and 8 weeks after the end of treatment. Due to differences in the patient population enrolled in the two trials and the lack of a comparator arm in the International trial, the North American trial is considered pivotal and the International trial is considered supportive.

Other supportive clinical data include two pilot studies using bismalcytrate, metronidazole, and tetracycline (with or without omeprazole) dispensed as separate formulations in a blister pack., four clinical studies sponsored by independent investigators and conducted using a prototype single triple capsule with a slightly different drug content than Pylera, findings of safety and efficacy during the review for the Helidac (referenced under Section 505(b)(2) of the FD&C Act), and a literature review of the efficacy of OBMT therapy. The safety database contains data on 383 subjects exposed to OBMT from the two clinical pharmacology studies

and the two clinical studies. The applicant also cited FDA's prior findings of safety and efficacy during the review of NDA 50-719 Helidac for support of Pylera.

On April 19, 2002, deficiencies to DMF were conveyed to the DMF holder, and on June 18, 2002, deficiencies in the drug substance section and site inspections were conveyed to the applicant. These deficiencies included approvability issues; therefore, a nonapprovable letter was issued on August 12, 2002 after the applicant did not address the deficiencies during the first cycle of review. A class 2 complete response was submitted on March 31, 2003. During the second cycle of review, the information provided in the response was found to be inadequate and facility inspections yielded deficiencies related to GMP compliance. A nonapprovable letter was issued on October 2, 2003. In addition to requesting resolution of the facility deficiencies, additional safety information and updated foreign marketing status was requested. Although Pylera is approved in Canada under the trade name, HELIZIDE, the applicant is not marketing it because they changed manufacturing facilities for biscalcitrato and the new facility has not been approved yet. The applicant is also seeking approval in Europe.

On December 7, 2005, the applicant requested and was granted a meeting to discuss chemistry, manufacturing and control information to be submitted to address the deficiencies listed in the October 2, 2003 letter. On January 11, 2006, the applicant requested and was granted a second meeting to discuss the efficacy of Pylera in patients with [REDACTED]. On January 19, 2006, responses to the questions in the briefing package for the chemistry meeting were conveyed to the applicant. On February 6, 2006 and February 9, 2006, responses to the questions in the briefing package for the second meeting were conveyed to the applicant. A class 2 complete response was submitted on March 27, 2006 and received on March 28, 2006.

ATTENDEES: Gene Holbert, Ph.D., Chemistry Reviewer
 Rebecca Saville, Pharm.D., Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Joette Meyer
Secondary Medical:	
Statistical:	Karen Higgins
Pharmacology:	Steve Hundley
Statistical Pharmacology:	
Chemistry:	Gene Holbert
Environmental Assessment (if needed):	
Biopharmaceutical:	Seong Jang
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Pete Dionne
DSI:	
OPS:	
Regulatory Project Management:	Rebecca Saville
Other Consults:	DMETS DDMAC

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO

If no, explain:

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

Safety, Clinical Pharmacology, and Pharmacology/Toxicology

For biscalcitrates:

- FDA findings of safety during the review of NDA 50-719 Helidac (bismuth subsalicylate 262.4 mg/metronidazole 250 mg/tetracycline HCl 250 mg); approved August 15, 1996
- Published literature
- Summary of expert reports and toxicity studies for BARRIER (biscalcitrates K) available in Europe

For metronidazole:

- NDA 12-623 Flagyl (metronidazole)
- Published literature

For tetracycline:

- FDA findings of safety during the review of NDA 50-719 Helidac
- Published literature

For OBMT:

- Two Phase 1 clinical pharmacology studies and two Phase 3 clinical trials were conducted by the applicant
- FDA findings of safety during the review of NDA 50-719 Helidac
- Published literature

Efficacy and Microbiology

For OBMT:

- Phase 3 clinical study conducted by the applicant (Protocol HPST99-CUS01)
- Published literature

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions)? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

Tetracycline

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved?

YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)?

YES NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than ~~one~~ pharmaceutical alternative approved, consult your ~~ODE's~~ Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

YES NO

Please see response to Question #2.

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

Yes, please see response to Question #2.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Please see Background above.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).

YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

YES NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

YES NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)?

YES NO

(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III

certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

The BA study was a Phase I Protocol (HLD-P0-180) entitled "Comparative Bioavailability Study of Bismuth Following the Administration of Helicide (Combination of Metronidazole, Tetracycline, and Bismuth) with or without Omeprazole to Healthy Male Volunteers."

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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this page is the manifestation of the electronic signature.**

/s/

Rebecca Saville
9/28/2006 04:45:24 PM
CSO



NDA 50-786

Axcan Scandipharm, Inc.
c/o CanReg Inc.
Attn: Irma Monaco
Manager, US Regulatory Affairs
4 Innovation Drive
Dundas, ON L9H 7P3
Canada

Dear Ms. Monaco:

Please refer to NDA 50-786, submitted on September 28, 2001 and resubmitted on March 27, 2006, for Pylera™ (biscalcitrates, metronidazole, and tetracycline HCl) Capsules.

We have the following request pertaining to the above application:

You cannot rely upon the list of published literature or the reviews for the NDA 50-719 for Helidac. You will need to submit to your NDA the literature that FDA needs to support approval of Pylera. You do not need to send every supportive article you have found, but if any of the literature is necessary to support the approval of Pylera, you will need to submit it. You cannot incorporate the literature by reference to Helidac.

Please provide the actual articles; a list of articles is not sufficient.

Please refer to 21 CFR 314.430(e)(2) which states that "summaries do not constitute the full reports...on which the safety and efficacy of the drug may be approved." Reviews are summaries. The list of referenced literature would be part of that summary.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. Saville, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

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

/s/

Rebecca Saville
9/14/2006 11:23:13 AM
CSO
NDA 50-786 Information Request 9-14-06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-786

Axcan Scandipharm, Inc.
c/o CanReg, Inc.
Attn: Ms. Irma Monaco
Manager, Regulatory Affairs (CMC)
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Monaco:

We acknowledge receipt on March 28, 2006 of your March 27, 2006 resubmission to your new drug application for Helizide™ (biscaltrate potassium, metronidazole, and tetracycline HCl) Capsules. We also acknowledge receipt of your submission dated April 13, 2006.

We consider this a complete, class 2 response to our action letter dated August 12, 2002. Therefore, the user fee goal date is September 28, 2006.

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

7

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this page is the manifestation of the electronic signature.**

/s/

Rebecca Saville

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NDA 50-786 N 000 AZ 27-March-2006

User Fee ID 4217 pd. 10/23/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Axcan Scandipharm Inc.	DATE OF SUBMISSION 3/27/06
TELEPHONE NO. (Include Area Code) (800) 615-4393	FACSIMILE (FAX) Number (Include Area Code) (205) 991-8047
APPLICANT ADDRESS (Number, Street, City, State, County, ZIP Code or Mail Code, and U.S. License number if previously issued): 22 Inverness Center Parkway, Suite 310 Birmingham, AL 35242	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE CanReg Inc. 450 North Lakeshore Drive Mundelein, IL 60060 Ph: (866) 722-6734

RECEIVED

MAR 29 2006

CDER White Oak DRI

RECEIVED

MAR 29 2006

CDER / CDER
MAR 29 2006
CDER / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-786		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) biscalcitrates, metronidazole, tetracycline hydrochloride	PROPRIETARY NAME (trade name) IF ANY Helizide	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N/A	CODE NAME (If any)	
DOSAGE FORM: Capsules	STRENGTHS: 140 mg biscalcitrates, 125 mg metronidazole, 125 mg tetracycline hydrochloride	ROUTE OF ADMINISTRATION: Oral

PROPOSED INDICATION(S) FOR USE:
Indication of Helicobacter pylori infection.

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Helidac</u> Holder of Approved Application <u>PROCTER AND GAMBLE</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION
Complete Response to Action Letter, dated October 2, 2003.

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 9 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See addendum for establishment information and responses to FDA 483 issued 3/16/05.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

References to DMF No. (biskalcitrate potassium) have been removed. There are no other changes from the original NDA submission.

This application contains the following items: (Check all that apply)

- | | |
|-------------------------------------|--|
| <input checked="" type="checkbox"/> | 1. Index |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input checked="" type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) |
| <input checked="" type="checkbox"/> | 4. Chemistry section |
| <input checked="" type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| <input type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| <input type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| <input checked="" type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) Complete Response to Action Letter, dated October 2, 2003. |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

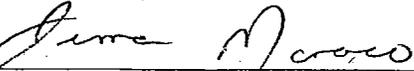
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE:



Irma Monaco
Manager, Regulatory Affairs (CMC)

3/27/06

ADDRESS (Street, City, State, and ZIP Code)

Telephone Number

22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

(800) 615-4393

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

USER FEE COVER SHEET

See Instructions on Reverse Side Before Competing This Form

1. APPLICANT'S NAME AND ADDRESS Axcan Scandipharm Inc. 22 Inverness Parkway, Suite 310 Birmingham, AL 35242	3. PRODUCT NAME HELICIDE® Capsules 4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
2. TELEPHONE NUMBER (Include Area Code) (800) 615-4393	6. LICENSE NUMBER / NDA NUMBER NDA 21-362
5. USER FEE I.D. NUMBER. N/A	

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input checked="" type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

A agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

~~Please~~ **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Jenna M. Jones for</i>	TITLE Becky Prokipcak, Ph.D U.S. Regulatory Affairs	DATE September 2001
---	---	------------------------



NDA 50-786

Axcan Scandipharm, Inc.
c/o CanReg Inc.
Attn: Irma Monaco
Manager, US Regulatory Affairs
4 Innovation Drive
Dundas, ON L9H 7P3
Canada

Dear Ms. Monaco:

Please refer to your meeting package for NDA 50-786, submitted on January 4, 2006 and received on January 5, 2006, for Helizide™ (biskalcitrate potassium, metronidazole, and tetracycline HCl) Capsules.

The Office of New Drug Chemistry Quality Assessment has reviewed the questions posed in your meeting package and has the following responses (following your questions in bold):

- 1. Based on the information presented, does the Agency agree that the company has demonstrated equivalence between Biskalcitrate from [redacted] and Biskalcitrate manufactured at the original site [redacted]?**

The Agency agrees that the information submitted demonstrates the equivalence of biskalcitrate from the two sources.

- 2. In addition to the information presented in question 1, Axcan Pharma Inc. intends to submit the following information in the amendment:**

- **Name and address of the new manufacturer for Biskalcitrate.**
- **Evidence of GMP Compliance (most recent FDA inspection observations).**
- **Complete description of the manufacturing process for Biskalcitrate. A summary of the minor process changes between the two sites can be found in Appendix 4.**
- **Updated specifications and tests methods for Helizide™ Capsules**
- **Updated specifications for Tetracycline HCl and Tetracycline capsule**
- **Biskalcitrate process validation protocol.**
- **Update of the drug substance information for Biskalcitrate.**
- **We propose that this data is submitted in CTD format. Please note that the original NDA was filed in the 'old' NDA format.**

Is this approach acceptable to the Agency?

The approach that you have proposed is acceptable.

- 3. The following changes have been made to the specifications for Biscalcitrates as compared to those submitted in amendment 10 in our NDA. Would the Agency please confirm that these changes are acceptable?**

The proposed changes in the acceptance criterion for Assay of _____ in Biscalcitrates are acceptable.

- 4. For Biscalcitrates, Metronidazole and Tetracycline HCl, Appendix 6 shows that the FDA proposed specification limits cannot consistently be met at 75 rpm (outside the error bars describing ± 3 standard deviations from the mean percent). Axcan's proposed specifications are based on batch analysis results and are also in accordance with The Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms (for rapidly dissolving drug product a NLT _____ in 60 minutes or less is used). Therefore Axcan believes that the new proposed dissolution specifications for Biscalcitrates, Metronidazole and Tetracycline HCl follow the recommendations of FDA's guidance.**

Are the new method and the specifications acceptable for the agency?

Your proposed dissolution method and specifications are acceptable.

- 5. Does the Agency intend to perform PAI's for all facilities involved with Helizide™?**

The Office of Compliance will decide whether or not to perform PAIs on all facilities listed in the application. However, the facilities should be ready for inspection on the day you submit the amendment to the NDA.

- 6. Axcan understands this will be submitted as an amendment to the open NDA 50-786 and that the PDUFA date will be 180 days after submission. Does the Agency agree with this assessment?**

The review time for the amendment will be six months from the date of receipt.

We are providing the above information by email for your convenience. Contact me at 301-796-0804 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. Saville, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

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/s/

Rebecca Saville
1/19/2006 03:41:34 PM
NDA 50-786/MP

NDA 50-786

Dear Ms. Monaco:

Please refer to NDA 50-786 for Helizide (metronidazole, biskalcitrate potassium, and tetracycline hydrochloride) Capsules and Amendment #18, dated October 31, 2003.

We agree that should a new manufacturer for biskalcitrate potassium be obtained, the following information would be required:

- Physico-chemical comparison of material from each manufacturing site
- Full analytical testing of the API and drug product
- Comparative dissolution of the drug product from each site
- Long term and accelerated stability data
- API release specifications from the new manufacturing site.

We would accept a 6 month time period for the long term stability tests.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Andrei Nabakowski
11/26/03 10:26:09 AM
NDA 50-786/Helizide Amendment #18



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-786

Axcan Scandipharm, Inc.
c/o CanReg, Inc.
Attention: Becky Prokipcak, Ph.D.
Manager, US Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Prokipcak:

Please refer to your new drug application (NDA) dated September 28, 2001, user fee payment received on October 23, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Helizide (biskalcitrate potassium, metronidazole, tetracycline hydrochloride) Capsules.

This application is subject to the exemption provisions in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated:

July 29, 2002 (2)	August 19, 2002	September 26, 2002	October 30, 2002
November 27, 2002	June 9, 2003	July 16, 2003	August 6, 2003
August 8, 2003	September 26, 2003		

The March 31, 2003 submission constituted a complete response to our August 12, 2002 action letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

During a recent inspection for your NDA of the _____ our field investigator conveyed deficiencies to the facility's representatives. Some of these deficiencies had been noted in a previous inspection. Satisfactory resolution to these deficiencies is required before this application may be approved.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(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. This update should specifically include a summary of any hepatic adverse events.

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

2. Describe in detail any significant changes or findings in the safety profile.
3. Provide English translations of current approved foreign labeling not previously submitted.

In addition, it will be necessary to revise the package insert prior to approval. We anticipate that additional labeling discussions will take place prior to approval.

We have also noted that no USAN name has been established for biscalcitrato potassium. We have previously recommended that you obtain one, and if you have not yet applied for one, we recommend that you do so as soon as possible. We also recommend that either you or the DMF holder apply for a CAS registry number for biscalcitrato potassium since you will need one to obtain an USAN name. For further information and guidance, please refer to 21 CFR 299.4, the preface to the most recent edition of the "USP Dictionary of USAN and International Drug Names" (USP publisher) and the USAN website, <http://www.ama-assn.org/ama/pub/category/2956.html>.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. 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.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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

If you have any questions, contact Andrei Nabakowski, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Edward Cox
10/2/03 04:09:43 PM
for Mark J. Goldberger, MD, MPH



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2003

To: Becky Prokipcak	From: Andrei Nabakowski Division of Division of Special Pathogen and Immunologic Drug Products
Company: CanReg, Inc.	
Fax number: (905) 689-1465	Fax number: 301-827-2475
Phone number: (905) 689-3980 x232	Phone number: 301-827-2127
Subject: Dissolution recommendation for Helizide Capsules	

Total no. of pages including cover: 3

Document to be mailed: • YES NO

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other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 827-
2127. Thank you.

NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for Helizide (metronidazole, biscalcitrates potassium, and
tetracycline hydrochloride) Capsules and your August 8, 2003 submission regarding dissolution
data.

We recommend the final dissolution methods and specifications for each component of
Helizide® capsule as follows:

Biskalcitrate Potassium

Apparatus: USP apparatus II (paddle)
Dissolution medium: Water at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: Atomic absorption spectroscopy
Specification: Q = _____) at 20 min

Metronidazole

Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: HPLC with UV detection
Specification: Q = _____) at 30 min

Tetracycline HCl

Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: HPLC
Specification: Q = _____) at 20 min

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Andrei Nabakowski
10/1/03 03:50:51 PM
CSO
NDA 50-786 dissolution recommendation



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 25, 2003

To: Irma Monaco	From: Andrei Nabakowski Division of Division of Special Pathogen and Immunologic Drug Products
Company: CanReg, Inc.	
Fax number: (905) 689-1465	Fax number: 301-827-2475
Phone number: (905) 689-3980 x228	Phone number: 301-827-2127
Subject: Clarification of response to FDA chemistry questions of 9/4/03	

Total no. of pages including cover: 3

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Dear Ms. Monaco:

Please refer to NDA 50-786 for metronidazole, biskalcitrate potassium, and tetracycline hydrochloride capsules, our September 4, 2003 fax concerning your submission of March 31, 2003, and your September 24, 2003 faxed response. Our reviewer has the following request for information:

In "Request 2.2", please identify the _____

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
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Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Andrei Nabakowski
9/25/03 04:23:20 PM
CSO
NDA 50-786/Helizide

question

MEMORANDUM

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

DATE: September 12, 2003

TO: NDA 50-786 file
Helizide (biskalcitrate potassium/metronidazole/tetracycline hydrochloride) Capsules

THROUGH : Renata Albrecht, M.D.
Director, Division of Special Pathogen
and Immunologic Drug Products (DSPIDP) (HFD-590)

Mark Avigan, M.D.
Acting Division Director, Division of Drug Risk Evaluation (HFD-430)

FROM: Andrei Nabakowski, Pharm.D., Regulatory Project Manager, DSPIDP

SUBJECT: Preapproval Safety Conference for NDA 50-786/Helizide
(biskalcitrate potassium/metronidazole/tetracycline hydrochloride) capsules

The Division of Special Pathogen and Immunologic Drug Products and the Division of Drug Risk Evaluation have concurred that a Pre-approval Safety Conference is not required for NDA 50-786/Helizide (biskalcitrate potassium, metronidazole, and tetracycline hydrochloride capsules).

Any new potential human toxicity from biskalcitrate potassium would be from excessive systemic levels of bismuth. It is known that upon ingestion, biskalcitrate potassium is converted to potassium citrate, citric acid, and bismuth oxide (Bi_2O_3). Due to this conversion, biskalcitrate potassium may be compared to bismuth subsalicylate (BSS), approved for OTC use as the active ingredient in Pepto-Bismol. The maximum recommended over the counter dose for BSS is approximately 4 g daily, which corresponds to 2.3 g of bismuth. This level of bismuth is almost 5 times greater than the mg equivalents of Bi_2O_3 contained in the proposed daily oral dose of biskalcitrate potassium in Helizide capsules.

Therefore, while biskalcitrate potassium is officially designated a New Molecular Entity, it is believed that it will not have the potential for new toxicities that are clinically significantly different from similar bismuth-containing compounds.

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/s/

Andrei Nabakowski
9/12/03 07:35:48 PM
CSO
NDA 50-786

Rigoberto Roca
9/16/03 05:21:44 PM
MEDICAL OFFICER

Renata Albrecht
9/16/03 05:35:08 PM
MEDICAL OFFICER

Mark Avigan
9/16/03 05:38:36 PM
DRUG SAFETY OFFICE REVIEWER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 4, 2003

To: Becky Prokipcak	From: Andrei Nabakowski Division of Special Pathogen and Immunologic Drug Products
Company: Axcen Scandipharm	
Fax number: (905) 689-1465	Fax number: 301-827-2475
Phone number: (905) 689-3980 x232	Phone number: 301-827-2127
Subject: Chemistry questions for Helizide, NDA 50-786	

Total no. of pages including cover: 3

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NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for metronidazole, biskalcitrate potassium, and tetracycline hydrochloride capsules and your submissions dated October 30, 2002 and March 31, 2003. Our reviewing chemist has the following requests:

Concerning the submission of October 30, 2002:

1. Please submit a copy of the IUPAC reference to the Absolute Limit of Detection (see Appendix 6, page 99). Please also specify how the values for s and S in the equations on page 99 were obtained from the raw data.

2. _____

Please explain this discrepancy.

Concerning the submission of March 31, 2003:

Please refer to the validation of the "Assay of _____
_____ by HPLC (Volume 5, Appendix 11, pp. 15-16).

1. Are the biskalcitrate samples stable at this pH?
2. If not, what is the fate of bismuth?
3. Why is the citric acid retention time approximately 5 minutes in the System Suitability Standard and in Helizide powder, but 3.2 minutes in the biskalcitrate sample?

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Andrei Nabakowski

9/4/03 02:45:39 PM

USO

DA 50-786 chem questions 9-4-03



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 20, 2003

To: Becky Prokipcak	From: Andrei Nabakowski
Company: Axcan Scandipharm	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (905) 689-1465	Fax number: 301-827-2475
Phone number: (905) 689-3980 x232	Phone number: 301-827-2127
Subject: NDA 50-786/Helicide dissolution data question	

Total no. of pages including cover: 3

Document to be mailed: • YES NO

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NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for metronidazole, biskalcitrate potassium, and tetracycline hydrochloride capsules and your August 8, 2003 submission. Our reviewer has the following request for information:

Have Helicide lots 9E520, 9E521, and 9E522 been tested for bioequivalence? If so, please provide supporting documentation.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Andrei Nabakowski
8/20/03 02:03:32 PM
CSO
NDA 50-786/Helicide



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2003

To: Becky Prokipcak	From: Andrei Nabakowski
Company: Axcan Scandipharm	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (905) 689-1465	Fax number: 301-827-2475
Phone number: (905) 689-3980 x232	Phone number: 301 827-2127

Subject: Response to email question about USAN name and NDA approval

Total no. of pages including cover: 3

Document to be mailed: • YES NO

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NDA 50-786

Dear Ms. Prokipcak:

This message is in response to our phone conversation of July 15, 2003 concerning the United States Adopted Name Council (USAN) name for "biscalcitrates potassium" for NDA 50-786 (metronidazole, biscalcitrates potassium, and tetracycline hydrochloride capsules). Specifically, you had asked if the NDA might not be approved if an adopted name had not yet been secured for "biscalcitrates potassium".

Please refer to 21CFR 299.4, and particularly section (d), which states that "All applicants for new-drug applications and sponsors for 'Investigational New Drug Applications' (IND's) are encouraged to contact the USAN Council for assistance in selection of a simple and useful name for a new chemical entity. Approval of a new-drug application providing for the use of a new drug substance may be delayed if a simple and useful nonproprietary name does not exist for the substance and if one is not proposed in the application that meets the above-cited guidelines. Prior use of a name in the medical literature or otherwise will not commit the Food and Drug Administration to adopting such terminology as official."

You should be aware that if an NDA were approved without an USAN approved name and the proposed name was later disapproved by USAN, we would require all labeling and packaging to be changed to the approved name.

I am providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Andrei Nabakowski
7/23/03 01:07:31 PM
CSO
NDA 50-786



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: July 21, 2003

To: Becky Prokipcak	From: Andrei Nabakowski
Company: Axcan Scandipharm	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (905) 689-1465	Fax number: 301-827-2475
Phone number: (905) 689-3980 x232	Phone number: 301 827-2127
Subject: NDA 50-786 Helicide information request	

Total no. of pages including cover: 3

Comments:

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NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for metronidazole, biskalcitrate potassium, and tetracycline hydrochloride capsules and Amendment #8 dated October 30, 2002. Our reviewing chemist has the following requests:

1.

2. Page 81 of the amendment lists Annex 1 through Annex 10 with no referencing page numbers. Please provide a sheet which lists the corresponding page number for each Annex.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Andrei E. Nabakowski
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
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/s/

Andrei Nabakowski
7/21/03 03:52:52 PM
CSO
NDA 50-786/Helicide



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 22, 2003

To: Becky Prokipcak Manager, U.S. Regulatory Affairs	From: Matthew A. Bacho Regulatory Project Manager
Company: Axcan Scandipharm Inc. c/o CanReg, Inc.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
Fax number: (905) 689-1465	Fax number: (301) 827-2475
Phone number: (905) 689-3980	Phone number: (301) 827-2127
Subject: Information request (NDA 50-786)	

Total no. of pages including cover: 3

Reviewers: Norman Schmuff, Ph.D., Chemistry Team Leader/Gene Holbert, Ph.D., Chemistry Reviewer/Philip Colangelo, Ph.D., Pharm.D., Acting Clinical Pharmacology & Biopharmaceutics Team Leader/Seong Jang, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

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NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for metronidazole, biscalcitate potassium, and tetracycline hydrochloride capsules and your class 2 resubmission of March 31, 2003. Our reviewing chemist and clinical pharmacologist would like to make the following requests:

1. We have noted that no USAN name has been established for biscalcitate potassium. If you have not applied for one, we recommend that you do so as soon as possible. We also recommend that either you or the DMF holder apply for a CAS registry number for biscalcitate potassium since you will need one to obtain an USAN name. For further information and guidance, please refer to 21 CFR 299.4, the preface to the most recent edition of the "USP Dictionary of USAN and International Drug Names" (USP publisher) and the USAN website, <http://www.ama-assn.org/ama/pub/category/2956.html>. It is our understanding that the USP will not publish a monograph without an USAN name.
2. We have reviewed the information that was submitted on October 30, 2002, and the dissolution data from one batch of Helizide[®] capsules:

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Matthew Bacho
5/22/03 01:27:21 PM
CSO
NDA 50-786



NDA 50-786

Axcan Scandipharm Inc.
c/o CanReg, Inc.
Attention: Becky Prokipcak, Ph.D.
Director, U.S. Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Dr. Prokipcak:

We acknowledge receipt on April 2, 2003, of your March 31, 2003 resubmission to your new drug application for Helicide® Capsules (metronidazole, tetracycline hydrochloride, and biscalcitrates potassium).

We consider this a complete, class 2 response to our August 12, 2002 action letter. Therefore, the user fee goal date is October 2, 2003.

If you have any questions, call me at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Matthew Bacho
5/16/03 02:17:07 PM
NDA 50-786



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 16, 2002

To: Becky Prokipcak Manager, U.S. Regulatory Affairs	From: Matthew A. Bacho Regulatory Project Manager
Company: Axcan Scandipharm Inc. c/o CanReg, Inc.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
Fax number: (905) 689-1465	Fax number: (301) 827-2475
Phone number: (905) 689-3980	Phone number: (301) 827-2127
Subject: Comments regarding (NDA 50-786)	

Total no. of pages including cover: 3

Reviewers: Norman Schmuff, Ph.D., Chemistry Team Leader/Gene Holbert, Ph.D., Chemistry Reviewer

Document to be mailed: YES NO

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NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for metronidazole, biscalcitrates potassium, and tetracycline hydrochloride capsules and to your facsimile transmission of November 27, 2002 (receipt date of hard copy in Division Document Room: December 11, 2002). Our reviewing chemist would like to make the following comments:

Question #12 from our August 23, 2002 memorandum was intended to refer to biscalcitrates drug substance. We recommend that you develop a [REDACTED] for the assay of biscalcitrates drug substance. The HPLC assay method described for [REDACTED] studies will be adequate for analyzing [REDACTED]. It needs to be validated and additional details (e.g., chromatographic conditions such as column, mobile phase, sample preparation, flow rate, column temperature, etc.) will be needed for review, but it provides no information on the stability of the biscalcitrates complex itself. The issue at hand concerns the stability of the biscalcitrates complex, and we are of course open to any suggestions that you might have in this regard.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Diana Willard
12/16/02 01:37:17 PM
CSO
for Matt Bacho (NDA 50-786)



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

FACSIMILE TRANSMITTAL SHEET

DATE: August 29, 2002

To: Becky Prokipcak Manager, U.S. Regulatory Affairs	From: Matthew A. Bacho Regulatory Project Manager
Company: Axcan Scandipharm Inc. c/o CanReg, Inc.	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
Fax number: (905) 689-1465	Fax number: (301) 827-2475
Phone number: (905) 689-3980	Phone number: (301) 827-2127
Subject: Comments regarding the proposed tradenames, "Helicide" and "Helizide" (NDA 50-786)	

Total no. of pages including cover: 5

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NDA 50-786

Dear Ms. Prokipcak:

Please refer to NDA 50-786 for metronidazole, bismaltrate potassium, and tetracycline hydrochloride capsules and your request for a review of the proposed tradenames, "Helicide" and "Helizide." We have completed our review and have the following comments:

A. "Helicide"

The Division of Special Pathogen and Immunologic Drug Products and the Division of Medication Errors and Technical Support (DMETS) do not recommend the use of the proprietary name, "Helicide." Our primary concern is with potential confusion with the proprietary name, Helidac, which already exists in the United States marketplace. Helidac is a potential look alike name that could be confused with "Helicide" and result in medication errors and health consequences.

Helidac is the proprietary name for a product containing three generic medications, bismuth subsalicylate, metronidazole and tetracycline. These three medications in combination with an H₂ antagonist have been approved for the treatment of *Helicobacter pylori*. Helidac and "Helicide" can look alike when scripted with each name beginning with the letters "Heli." When it is scripted, only the last syllable in each name may help to differentiate the products. However, the last syllable of each name contains the letter "d" followed by either an "ac" or "e." These trailing letters are sometimes not clearly distinguishable, adding to the possibility of a misinterpretation of the name.

These products also share a number of similar characteristics. These include the same indication for use (eradication of *H. Pylori*), frequency of administration (four times a day), route of administration (oral), prescriber population, and patient population. Since both medications share the same prefix "Heli," the medications could be stored next to each other on a pharmacy shelf. The prescription directions for Helidac need to include information on 3 medications taken in different quantities four times a day. Therefore, most physicians would only prescribe the Helidac with the directions "ud" or "as directed." Since Helidac contains three dosage forms (tablets and capsules) a physician would probably not write the quantity of medication but indicate the duration of treatment. A Helidac prescription could be written as "Helidac sig: ud for 14 days." Whereas, a "Helicide" prescription could be written as "Helicide sig: ud for 10 days." Two of the medications, metronidazole and tetracycline, are in both products, but the strength of these medications is different. This may not appear to be a safety issue, but the duration of therapy to treat *H. pylori* is different for the two products (14 days versus 10 days). This could result in a shortened and possibly ineffective course of therapy or an unnecessarily longer course of therapy. Another safety concern is the fact Helidac contains bismuth subsalicylate. If Helidac were dispensed instead of "Helicide," a patient with an allergy to salicylates could have a severe reaction. Due to the potential look alike similarities of Helidac and "Helicide," there is an increased potential for a medication error and medical consequences.

We also had concerns about the promotional aspect of "Helicide." The prefix "Heli" refers to *Helicobacter* and the suffix "cide" means "to kill." This suggests the product is 100% effective, which overstates the proven benefits of the product.

B. "Helizide"

We considered the name "Helizide" to look different from Helidac with the distinguishing feature of the letters "zi", most notably the letter "z." If scripted, the portion of the letter "z" below the line creates a distinctive appearance. If printed, the area required for writing the letter "z" and the letter itself creates a distinctive appearance. This appearance is enhanced with the addition of the letter "i" that follows the letter "z." When scripted or printed, the combination of letters "zi" help differentiate the names.

However, we are concerned these two products will be in close proximity to each other on a pharmacy shelf. A pharmacist or technician could possibly read the prescription correctly, but select the wrong product. Labeling is an important feature that can help differentiate the products. We recommend that you review and compare the labeling of the product Helidac with respect to the proposed labeling for "Helizide." You should implement any possible labeling changes that will differentiate the products, and prevent medication errors. We recommend the following changes to the labeling:

[Container Label]

1. Increase the prominence of the proprietary name, established name, and product strength.
2. Include the dosage form "capsule" in the established name.
3. The "Rx only" statement separates the proprietary name and established name. Move the "Rx only" statement to a different location on the principal display panel.
4. Remove the statement on the principal display panel, "For information see package insert." This information is stated on the side panel.
5. Revise the dosage statement to include the dosing of omeprazole. Revise to read "in conjunction with omeprazole 20 mg twice a day."
6. We note this product will be packaged in bottles containing 120 capsules. We consider this packaging "unit of use," which may be dispensed directly to a patient. Consequently you should comply with the child-resistant packaging requirements of 16 CFR 1701.1.

[Package Insert]

7. The "Information for Patients" subsection that appears following the "Dosage and Administration" should also appear in the "Precautions" section.

This decision is considered preliminary. The proprietary name and its associated labels and labeling will be re-submitted for review and consult upon submission of your response to the August 12, 2002 action letter and 90 days prior to approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names.

Finally, we strongly recommend that you apply to the U.S. Adopted Names Council for a USAN name for lyophilized biscalcitrates potassium drug substance. Please refer to 21 CFR 299.4 for further information. Application forms and information may be found at the USAN web site: <http://www.ama-assn.org/ama/pub/category/2956.html>. Please note that you will also need to obtain a Chemical Abstracts Service (CAS) name and registry number for the USAN application process.

NDA 50-786

Page 3

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

{See appended electronic signature page}

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Matthew Bacho
8/29/02 11:23:09 AM
CSO
NDA 50-786

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 15, 2002

NDA NUMBER: 50-786

NAME OF DRUG: Helicide (primary) or Helizide (secondary) Capsules
(biscalcitrates potassium, metronidazole, and tetracycline hydrochloride capsules)
140 mg/125 mg/125 mg

NDA SPONSOR: Axcan Scandipharm Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590) for an assessment of the proposed proprietary names, Helicide. This proposed tradename was submitted with NDA 50-786. DMETS also reviewed the container label and package insert labeling. Before this consult was completed DMETS received a second proposed proprietary name, Helizide, to be evaluated from the Division of Special Pathogen and Immunologic Drug Products (HFD-590).

PRODUCT INFORMATION

"Helicide" / "Helizide" contains the active ingredients biscalcitrates potassium, metronidazole, and tetracycline. These three active ingredients have been manufactured into a hard gelatin capsule, size 0, for oral administration. These three active ingredients taken in combination with omeprazole are indicated for the eradication of *H. pylori* in patients with *H. Pylori* infection and duodenal ulcer disease. The recommended dose is three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to "Helicide" / "Helizide" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's

¹ MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).

² Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.

³ The Drug Product Reference File [DPR], Established Evaluation System [EES], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.

trademark electronic search system (TESS) was conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names "Helicide" and "Helizide". Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified three proprietary names that were thought to have the potential for confusion with "Helicide". These products are listed in Table 1, along with the dosage forms available and usual dosage. DDMAC had concerns with the promotional aspects of the name "Helicide".

TABLE 1

Product Name	Generic name, Dosage form(s), Strength	Usual adult dose*	Other**
Helicide	Bismuth Potassium, Metronidazole, Tetracycline Hydrochloride Capsules, 140 mg (equivalent to 40 mg bismuth oxide), 125 mg, 125 mg	Treatment of H. pylori: Three (3) capsules taken orally 4 times a day after meals and at bedtime. To be taken in conjunction with omeprazole 20 mg twice a day.	
Remicade	Infliximab, Powder for injection, lyophilized, 100 mg in 20 mL single use vials	Initial treatment of Rheumatoid Arthritis: 3 mg/kg given as an IV infusion followed with additional doses at 2 and 6 weeks after the first infusion.	L/A per DMETS
Halcion	Triazolam, Tablets, 0.125 mg and 0.25 mg	Treatment of Insomnia: Take 0.125 mg to 0.5 mg orally at bedtime.	S/A and L/A per DMETS
Helidac	Bismuth Subsalicylate Tablets, 262.4 mg Metronidazole Tablets, 250 mg Tetracycline Capsules, 500 mg	Treatment of H. Pylori: Take 525 mg bismuth subsalicylate, 250 mg metronidazole and 500 mg tetracycline orally 4 times a day at meals and at bedtime. Also take a prescribed H ₂ antagonist therapy as directed.	L/A per DMETS
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

⁴WWW location <http://tess.uspto.gov/bin/lookup.exe?f=tess&state=k0n826.1.1>

⁵Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

The Expert Panel identified two proprietary names that were thought to have the potential for confusion with "Helizide". These products are listed in Table 2, along with the dosage forms available and usual dosage. DDMAC did not have any concerns with the promotional aspects of the name "Helizide".

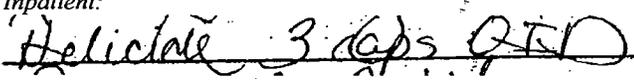
TABLE 2

Product Name	Generic name, Dosage form(s), Strength	Usual adult dose*	Other**
Helizide	Bismaltrate Potassium, Metronidazole, Tetracycline Hydrochloride Capsules, 140 mg (equivalent to 40 mg bismuth oxide), 125 mg, 125 mg	Treatment of H. pylori: Three (3) capsules taken orally 4 times a day after meals and at bedtime. To be taken in conjunction with omeprazole 20 mg twice a day.	
Hydra-Zide	Hydralazine Hydrochloride and Hydrochlorothiazide, Capsules 25 mg/25 mg; 50 mg/50 mg; and 100 mg/50 mg	Treatment of essential hypertension: Take 1 capsule orally two times a day.	S/A and L/A per DMETS
Helidac	Bismuth Subsalicylate Tablets, 262.4 mg Metronidazole Tablets, 250 mg Tetracycline Capsules, 500 mg	Treatment of H. Pylori: Take 525 mg bismuth subsalicylate, 250 mg metronidazole and 500 mg tetracycline orally 4 times a day at meals and at bedtime. Also take a prescribed H ₂ antagonist therapy as directed.	L/A per DMETS
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Helicide and Helizide with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 107 health care professionals (nurses, pharmacists, and physicians) for Helicide and 105 health care professionals (nurses, pharmacists, and physicians) for Helizide. This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Helicide and Helizide. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

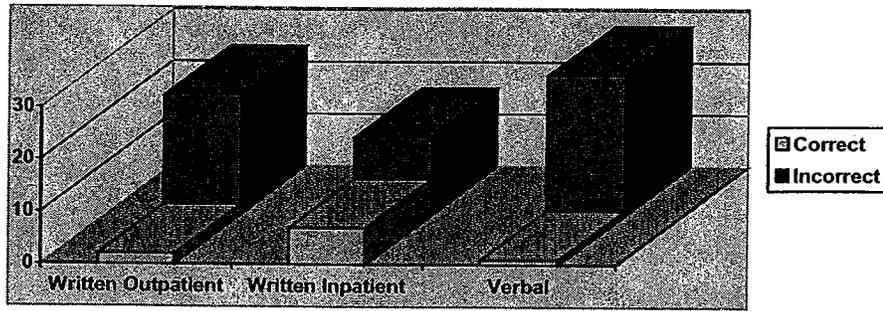
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Outpatient:</p> 	<p>Outpatient:</p> <p>Helicide 3 caps 4 times a day Number 120</p>
<p>Inpatient:</p> 	

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Outpatient:</p> 	<p>Outpatient:</p> <p>Helicide 3 po 4 times a day Dispense Number 60</p>
<p>Inpatient:</p> 	

2. Results

Results of the **Helicide** exercises are summarized below:

Study	No. of participants	# of responses (%)	"Helicide" response	Other response
Written: Outpatient	33	25 (76%)	2 (8%)	23 (92%)
Inpatient	35	22 (63%)	7 (32%)	15 (68%)
Verbal: Outpatient	39	28 (72%)	1 (4%)	27 (96%)
Total:	107	75 (70%)	10 (13%)	65 (87%)



Among participants in the written outpatient prescription study, 2 of 25 respondents (8%) interpreted the name correctly. Incorrect interpretations included Hebride (4), Hebiide (4), Hebside (3), Hebriide (2), Hebicide (2), Actacide (1), Helissole (1), Hebude (1), Hebreide (1), Hebiicle (1), Hebside (1), Helizide (1), and Hebriicle (1).

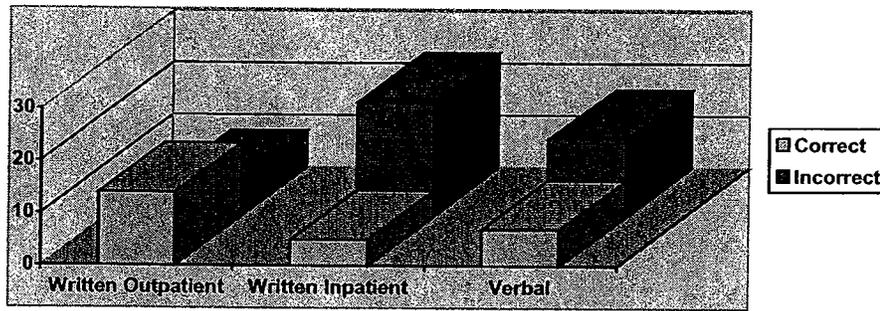
Among participants in the written inpatient prescription study, 7 of 22 respondents (32%) interpreted the name correctly. Incorrect interpretations included Helicine (5), Helicione (4), Helidone (1), Helicime (1), Heliciore (1), Heliciene (1), Heliclione (1), and Helicone (1).

Among participants in the verbal outpatient prescription study, 1 of 28 respondents (4%) interpreted the name correctly. Incorrect interpretations included Hilaside (6), Hilacide (4), Hillicide (3), Hilliside (2), Hiliside (2), Helocide (2), Hillaside (2), Ilaside (1), Hilicide(1), Halicide (1), Hilocide (1), Heliside (1), and Halazide (1).

None of the misinterpreted names is a currently marketed drug product.

Results of the **Helizide** exercises are summarized below:

Study	No. of participants	# of responses (%)	"Helizide" response	Other response
<i>Written:</i> Outpatient	34	21 (62%)	14 (67%)	7 (33%)
Inpatient	39	27 (69%)	5 (19%)	22 (81%)
<i>Verbal:</i> Outpatient	32	22 (69%)	7 (32%)	15 (68%)
Total:	105	70 (67%)	26 (37%)	44 (63%)



Among participants in the written outpatient prescription study, 14 of 21 respondents (67%) interpreted the name correctly. Incorrect interpretations included Heligide (1), Halizide (1), Helijide (1), Helixide (1), Heliside (1), Melizide (1), and Hiclizide (1).

Among participants in the written inpatient prescription study, 5 of 27 respondents (19%) interpreted the name correctly. Incorrect interpretations included Helezide (6), Hilizide (7), Hetezide (3), Hitizide (2), Hitirizide (1), Hiteride (1), Hlizide (1), and Heterzide (1).

Among participants in the verbal outpatient prescription study, 7 of 22 respondents (32%) interpreted the name correctly. Incorrect interpretations included Halazide (5), Halizide (3), Helazide (2), Helaside (1), Helicide (1), Halzide (1), Hializide (1), and Hellazide (1).

None of the misinterpreted names is a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary names, "Helicide" and "Helizide", the primary concerns raised by the DMETS expert panel were related to sound alike and/or look alike names that already exist in the US marketplace. The products considered having the greatest potential for confusion with "Helicide" were Remicade, Halcion and Helidac, and with "Helizide" were Hydra-Zide and Helidac.

1. Assessment of Helicide

Remicade is the proprietary name for infliximab and is indicated to treat rheumatoid arthritis and Crohn's disease. Infliximab is only available as a lyophilized powder for intravenous infusion. When scripted Remicade and Helicide have the potential to look alike. If the "R" is not scripted clearly it can look like a "H" and the "icade" can look similar to "icide". However, Remicade and Helicide have a number of characteristics to aid in differentiating the products. These include the product strength, package configuration, indications for use, usual dose, frequency of administration, route of administration, dosage form, prescriber population, and patient population. Remicade would not be dispensed for administration at home. Therefore, the potential for error would occur either in a clinic or a hospital. Remicade would also need specific dosing instructions, an order written "as directed" would not be appropriate for this medication. Remicade could be dosed from

3 mg/kg to 10 mg/kg, thus any question in the directions would require clarification. The risk of dispensing the wrong medication is low based on the many differences between the medications.

Halcion is the proprietary name for triazolam and is indicated to treat insomnia. Halcion is available as 0.125 mg and 0.25 mg tablets. The recommended dose to treat insomnia can be a dose of 0.125 mg to 0.5 mg administered at bedtime. Halcion and Helicide can sound alike when spoken and look alike when scripted. The first syllable in each name can sound and look similar. Each name also contains 3 syllables which contributes to a rhyming quality with the names when spoken. However, Halcion and Helicide have a number of characteristics to aid in differentiating the products. These include the product strength (0.125 mg or 0.25 mg vs. 140 mg/125 mg/125 mg), indication for use (insomnia vs. H. Pylori), usual dose (1 or 2 vs. 3), dosage form (tablets vs. capsules) and frequency of administration (at bedtime as needed vs. four times a day). Both medications could be stored in close proximity to each other on a pharmacy shelf. However, Halcion is a controlled substance and would probably be stored in a locked safe. Since Halcion is available in two strengths a prescription would require an appropriate strength. The administration directions for these two medications are very different. Halcion directions could be 1 or 2 tablets at bedtime as needed, while Helicide directions should include the wording, 3 capsules four times a day. To treat H. pylori with Helicide for 10 days, a patient would require 120 capsules. To treat insomnia with Halcion, the recommended initial duration should be limited to 7 to 10 days of therapy, which would require only a small quantity of medication from 7 to 20 tablets. Although it is possible for the names to be confused, the risk of dispensing the wrong medication is low based on the differences between the medications.

Helidac is the proprietary name for a product containing three generic medications, bismuth subsalicylate, metronidazole and tetracycline. The three medications are packaged into blister cards. Each blister card contains a combination of tablets and capsules to provide a one day supply of treatment. Fourteen blister cards, patient instructions and patient reminders are packaged in a carton to supply a 14 day course of therapy. These three medications in combination with an H₂ antagonist have been approved for the treatment of H. Pylori. Helidac and Helicide can look alike when scripted with each name beginning with the letters "Heli". When scripted only the last syllable in each name may help to differentiate the products. However, the last syllable of each name contains the letter "d" followed by either an "ac" or "e". These trailing letters are sometimes not clearly distinguishable adding to the possibility of a misinterpretation of the name. A handwriting sample is included below for review and comparison.

A handwriting sample showing the words "Helidac" and "Helicide" written in cursive script. The words are written in black ink on a white background. The letters are connected and fluid, with the "d" and "ac" or "e" endings being particularly similar in appearance.

These products also share a number of similar characteristics. These include the same indication for use (eradication of H. Pylori), frequency of administration (four times a day), route of administration (oral), prescriber population, and patient population. Since both medications share the ~~same~~ prefix "Heli", the medications could be ~~stored next to each~~ other on a pharmacy shelf. The prescription directions for Helidac need to include information on 3 medications taken in different quantities four times a day. Therefore,

most physicians would only prescribe the Helidac with the directions "ud" or "as directed". Since Helidac contains three dosage forms (tablets and capsules) a physician would probably not write the quantity of medication but indicate the duration of treatment. A Helidac prescription could be written as "Helidac sig: ud for 14 days". Whereas, a Helicide prescription could be written as "Helicide sig: ud for 10 days". Two of the medications, metronidazole and tetracycline, are in both products, but the strength of these medications is different. This may not appear to be a safety issue, but the duration of therapy to treat H. pylori is different for the two products (14 days vs. 10 days). This could result in a shortened and possibly ineffective course of therapy or an unnecessary longer course of therapy. Another safety concern is the fact Helidac contains bismuth subsalicylate. If Helidac was dispensed instead of Helicide, a patient with an allergy to salicylates could have a severe reaction. Due to the potential look alike similarities of Helidac and Helicide, there is an increased potential for a medication error and medical consequences.

2. Assessment of Helizide

Hydra-Zide is the proprietary name for a combination product containing hydralazine and hydrochlorothiazide and is indicated to treat hypertension. Hydra-Zide is available in 3 strengths of 25 mg/25 mg, 50 mg/50 mg, and 100 mg/50 mg. The recommended administration schedule is one capsule twice a day with the dosage adjustment based upon response. Hydra-Zide and Helizide can sound alike when spoken and look alike when scripted. Each name begins with the letter "H", ends with "zide" and contains 3 syllables. When spoken these features contribute to a similar rhyming quality. The "dra" can be a distinguishing sound differentiating the names. The hyphen and capital Z found in the proprietary name Hydra-Zide would not always be scripted by the general practitioner. Therefore, when scripted this would result in both names beginning with a capital "H" and ending with "zide". However, when scripted the "ydr" in Hydra-Zide and the "el" in Helizide can have a distinctively different appearance. Hydra-Zide and Helizide have a number of characteristics to aid in differentiating the products. These include the product strength (25 mg/25 mg, 50 mg/50 mg, or 100 mg/ 50 mg vs. 140 mg/125 mg/125 mg), indication for use (hypertension vs. H. pylori), usual dose (1 vs. 3), and frequency of administration (two times a day vs. four times a day). Both products would be stored at room temperature on a pharmacy shelf. However the products should be separated from each other since one name begins with "He" and the other with "Hy". Since Hydra-Zide is available in three strengths a prescription would require an appropriate strength. The directions for each product (1 po bid vs. 3 po qid) could be easily scripted by a practitioner and would help differentiate the products. Although it is possible for the names to be confused, the risk of dispensing the wrong medication is low based on the many different characteristics between the medications.

Helidac is the proprietary name for a product containing three generic medications, bismuth subsalicylate, metronidazole and tetracycline. Additional information on Helidac was presented above with the evaluation for Helicide. Helidac and Helizide can look similar when scripted with each name beginning with the letters "Heli". Only the last syllable in each name differentiates the products. However, the last syllable of each name contains the letter "d" followed by either an "ac" or "e". These trailing letters are sometimes not clearly distinguishable adding to the possibility of a misinterpretation of the name. This was illustrated with the Helidac / Helicide handwriting sample above. The distinguishing feature of the name Helizide is the letters "zi, but most notably the letter "z". If scripted, the portion of the letter "z" below the line creates a distinctive appearance. If printed, the area required writing the letter "z" and the letter itself create a distinctive

appearance. This appearance is enhanced with the addition of the letter "i" that follows the letter "z". The combination of letters "zi" help differentiate Helizide from Helidac if the names are scripted or printed. These products share a number of similar characteristics. These include the same indication for use (eradication of H. Pylori), frequency of administration (four times a day), route of administration (oral), prescriber population, and patient population. Since both medications share the same prefix "Heli", the medications could be stored next to each other on a pharmacy shelf. The prescription directions for Helidac need to include information on 3 medications taken in different quantities four times a day. Therefore, most physicians would only prescribe the Helidac with the directions "ud" or "as directed". Since Helidac contains three dosage forms (tablets and capsules) a physician would probably not write the quantity of medication but indicate the duration of treatment. A Helidac prescription could be written as "Helidac sig: ud for 14 days". Whereas, a Helizide prescription could be written as "Helizide sig: ud for 10 days". Two of the medications, metronidazole and tetracycline, are in both products, but the strength of these medications is different. This may not appear to be a safety issue, but the duration of therapy to treat H. pylori is different for the two products (14 days vs. 10 days). Another safety concern is the fact Helidac contains bismuth subsalicylate. If Helidac was dispensed instead of Helizide, a patient with an allergy to salicylates could have a severe reaction. Although the two products have many common characteristics, the names of the products do not sound alike and the letters "zi", most notably the "z", in Helizide are the distinguishing feature that differentiate the names when scripted. These characteristics can decrease the potential risk of a medication error between these two products.

The DDMAC representative had concerns of the promotional aspect of Helicide. The prefix "Heli" referring to Helicobacter and the suffix "cide" meaning "to kill". This suggests the product is 100% effective, which overstates the proven benefits of the product. The DDMAC representative did not have any concerns of the promotional aspect of Helizide.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS has reviewed the container label, and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. We have identified areas of improvement, in the interest of minimizing potential user error and patient safety.

A. Container Label

1. Increase the prominence of the proprietary name, established name and product strength.
2. Include the dosage form "capsule" in the established name.
3. The "Rx only" statement separates the proprietary name and established name. Move the "Rx only" statement to a different location on the principal display panel.
4. Remove the statement on the principal display panel, "For information see package insert." This information is stated on the side panel.
5. Revise the dosage statement to include the dosing of omeprazole. ~~Revise to read~~ "in conjunction with omeprazole 20 mg twice a day."

6. We note this product will be packaged in bottles containing 120 capsules. We consider this packaging unit of use, which may be dispensed directly to a patient. Therefore, please ensure they are distributed with a child-resistant closure (CRC).

B. Insert Labeling

1. The "Information for Patients" subsection that appears following the "Dosage and Administration" should also appear in the "Precautions" section.

IV. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Helicide. The primary concern is with potential confusion with the proprietary name, Helidac that already exist in the United States marketplace. Helidac is a potential look alike name that could be confused with Helicide and result in medication errors and health consequences.

Helidac is the proprietary name for a product containing three generic medications, bismuth subsalicylate, metronidazole and tetracycline. The three medications are packaged into blister cards. Each blister card contains a combination of tablets and capsules to provide a one day supply of treatment. Fourteen blister cards, patient instructions and patient reminders are packaged in a carton to supply a 14 day course of therapy. These three medications in combination with an H₂ antagonist have been approved for the treatment of H. Pylori. Helidac and Helicide can look alike when scripted with each name beginning with the letters "Heli". When scripted only the last syllable in each name may help to differentiate the products. However, the last syllable of each name contains the letter "d" followed by either an "ac" or "e". These trailing letters are sometimes not clearly distinguishable adding to the possibility of a misinterpretation of the name. A handwriting sample is included below for review and comparison.

A handwritten sample showing the words "Helidac" and "Helicide" written in cursive. The two words are very similar in appearance, illustrating the potential for confusion between them.

These products also share a number of similar characteristics. These include the same indication for use (eradication of H. Pylori), frequency of administration (four times a day), route of administration (oral), prescriber population, and patient population. Since both medications share the same prefix "Heli", the medications could be stored next to each other on a pharmacy shelf. The prescription directions for Helidac need to include information on 3 medications taken in different quantities four times a day. Therefore, most physicians would only prescribe the Helidac with the directions "ud" or "as directed". Since Helidac contains three dosage forms (tablets and capsules) a physician would probably not write the quantity of medication but indicate the duration of treatment. A Helidac prescription could be written as "Helidac sig: ud for 14 days". Whereas, a Helicide prescription could be written as "Helicide sig: ud for 10 days". Two of the medications, metronidazole and tetracycline, are in both products, but the strength of these medications is different. This may not appear to be a safety issue, but the duration of therapy to treat H. pylori is different for the two products (14 days vs. 10 days). This could result in a shortened and possibly ineffective course of therapy or an unnecessary longer course of

therapy. Another safety concern is the fact Helidac contains bismuth subsalicylate. If Helidac was dispensed instead of Helicide, a patient with an allergy to salicylates could have a severe reaction. Due to the potential look alike similarities of Helidac and Helicide, there is an increased potential for a medication error and medical consequences.

The DDMAC representative had concerns of the promotional aspect of Helicide. The prefix "Heli" referring to Helicobacter and the suffix "cide" meaning "to kill". This suggests the product is 100% effective, which overstates the proven benefits of the product.

DMETS considered the name Helizide to look different from Helidac with the distinguishing feature of the letters "zi", most notably the letter "z". If scripted, the portion of the letter "z" below the line creates a distinctive appearance. If printed, the area required writing the letter "z" and the letter itself creates a distinctive appearance. This appearance is enhanced with the addition of the letter "i" that follows the letter "z". When scripted or printed the combination of letters "zi" help differentiate the names.

However, DMETS is concerned these two products will be in close proximity to each other on a pharmacy shelf. A pharmacist or technician could possibly read the prescription correctly, but select the wrong product. Labeling is an important feature that can help differentiate the products. DMETS recommends the sponsor review and compare the labeling of the product Helidac with respect to the proposed labeling for Helizide. The sponsor should implement any possible labeling changes that will differentiate the products, and prevent medication errors.

In addition, we provide the following recommendation on labeling revisions that may minimize potential user error:

A. Container Label

1. Increase the prominence of the proprietary name, established name and product strength.
2. Include the dosage form "capsule" in the established name.
3. The "Rx only" statement separates the proprietary name and established name. Move the "Rx only" statement to a different location on the principal display panel.
4. Remove the statement on the principal display panel, "For information see package insert." This information is stated on the side panel.
5. Revise the dosage statement to include the dosing of omeprazole. Revise to read "in conjunction with omeprazole 20 mg twice a day."
6. We note this product will be packaged in bottles containing 120 capsules. We consider this packaging unit of use, which may be dispensed directly to a patient. Therefore, please ensure they are distributed with a child-resistant closure (CRC).

B. Insert Labeling

1. The "Information for Patients" subsection that appears following the "Dosage and Administration" should also appear in the "Precautions" section.

V. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, "Helicide", but has no objection to the use of the proprietary name, "Helizide". The name, "Helizide" must be reevaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends the sponsor review and compare the labeling of the product Helidac with respect to the proposed labeling for Helizide. The sponsor should implement any possible changes that will differentiate the products, and prevent medication errors.
3. DMETS also recommends the above labeling revisions to encourage the safest possible use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

**This is a representation of an electronic record that was signed electronically and
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/s/

Scott Dallas
8/20/02 03:15:31 PM
PHARMACIST

Carol Holquist
8/20/02 03:42:21 PM
PHARMACIST

Jerry Phillips
8/20/02 04:01:19 PM
DIRECTOR



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Previous Admin Letter 8/12/02

NDA 50-786

Axcan Scandipharm Inc.
c/o CanReg, Inc.
Attention: Becky Prokipcak
Manager US Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Prokipcak:

Please refer to your new drug application (NDA) dated September 28, 2001, user fee payment received on October 23, 2001, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for metronidazole, biscalcitrates potassium, and tetracycline hydrochloride capsules.

This application is subject to the exemption provisions in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated:

October 12, 2001

December 19, 2001

January 28, 2002

April 18, 2002

May 10, 2002

July 8, 2002

We also acknowledge receipt of your two submissions dated July 29, 2002. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. In a letter dated April 19, 2002, deficiencies to DMF [redacted] were conveyed to the DMF holder, [redacted] through their U.S. agent. Some of these deficiencies are approvability issues. At this time, no response has been received.
2. Deficiencies in the drug substance section of the NDA were conveyed to the applicant on June 18, 2002. Some of these deficiencies are approvability issues.
3. The data submitted in support of your proposed dissolution method are inadequate for evaluation. You must submit dissolution profiles obtained with [redacted]

During a recent inspection for your NDA of _____ a number of deficiencies were noted and conveyed to you or your supplier by the investigator. Under 21 CFR 314.125(b)(13), these deficiencies must be satisfactorily resolved before approval.

In addition, it will be necessary to revise the package insert. We anticipate labeling discussions will take place prior to approval.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. 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.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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

If you have any questions, please contact Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
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/

Mark Goldberger
8/12/02 01:50:46 PM
NDA 50-786



NDA 21-362

Axcan Scandipharm Inc.
Attention: Becky Prokipcak
Manager US Regulatory Affairs, CanReg Inc.
22 Inverness Parkway, Suite 310
Birmingham, AL 35242

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: Helicide
Date of Application: September 28, 2001
Date of Receipt: October 2, 2001
Our Reference Number: NDA 21-362

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Leo Chan, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
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/

Ellen Frank
10/11/01 03:37:12 PM
NDA 21-362