

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-786

CHEMISTRY REVIEW(S)

**DIVISION OF SPECIAL PATHOGEN
AND TRANSPLANT PRODUCTS**

Review of Chemistry, Manufacturing and Controls

NDA #: 50-786

DATE REVIEWED: 28-SEP-2006

CHEMISTRY REVIEW #: 4

REVIEWER: Gene W. Holbert, Ph.D.

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	28-SEP-2001
Amendment (BZ)	18-APR-2002
Amendment (BC)	10-MAY-2002
Amendment (BZ)	08-JUL-2002
CMC Review #1	26-JUL-2002
Not Approvable Letter	12-AUG-2002
Amendment (BC)	29-JUL-2002
Amendment (BZ)	26-SEP-2002
Amendment (BZ)	30-OCT-2002
Amendment (AZ)	31-MAR-2003
Amendment (BL)	06-JUN-2003
Amendment (BZ)	08-AUG-2003
Amendment (BZ)	26-SEP-2003
CMC Review #2	26-JUL-2002
Not Approvable Letter	03-OCT2003
Amendment (AZ)	28-MAR-2006
Amendment (BL)	13-APR-2006
Amendment (BC)	26-JUN-2006
Amendment (BC)	14-AUG-2006

NAME & ADDRESS OF SPONSOR:

Name: Axcan Scandipharm, Inc.
Address: 22 Inverness Parkway Suite 310
Birmingham, AL 35242
U.S. Agent: CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060
Representative: Irma Monaco
Manager, Regulatory Affairs (CMC)
Telephone: (866) 722-6734
Fax: (905) 689-1465

DRUG PRODUCT NAME:

Proprietary: Pylera

Nonproprietary: biscalcitrate (proposed)/metronidazole/tetracycline hydrochloride

Code Name/#:

Chem. Type/Ther. Class: 1S

PHARMACOLOGICAL CATEGORY: Antibacterial/Antiulcerative

INDICATION: *H. pylori* infection

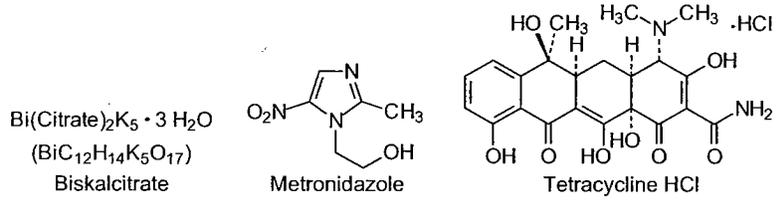
DOSAGE FORM/STRENGTH: Capsules/140 mg biscalcitrate/125 mg metronidazole/125 mg tetracycline hydrochloride

ROUTE OF ADMINISTRATION:

Rx/OTC: Rx OTC

SPECIAL PRODUCTS: Yes No

CHEMICAL NAME/STRUCTURAL FORMULA:



Component	Molecular Formula	Molecular Weight	CAS Number
Biscalcitrate	$\text{BiC}_{12}\text{H}_{14}\text{K}_5\text{O}_{17}$	834.7	Not available
Metronidazole	$\text{C}_6\text{H}_9\text{N}_3\text{O}_3$	171.2	443-48-1
Tetracycline Hydrochloride	$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8 \cdot \text{HCl}$	480.80	64-75-5

SUPPORTING DOCUMENTS: The application references the following DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
[Redacted]	[Redacted]	[Redacted]	[Redacted]	3	Adequate	20-AUG-2001	[Redacted]
				1	Adequate	08-FEB-2002	
				3	Adequate for [Redacted]	21-AUG-2001	
[Redacted]	[Redacted]	[Redacted]	[Redacted]	4	Adequate for [Redacted]		
				3	Adequate	04-FEB-2000	
				3	Adequate	23-SEP-1997	
				1	Adequate	05-AUG-2002	
				3, 4	Adequate	05-SEP-2001	

¹ Action codes for DMF Table:

1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

2 – █████ DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

RELATED DOCUMENTS:

COMMENTS: The Form 483 issues dated 22-SEP-2006 concerning the █████ / have been satisfactorily resolved and the Office of Compliance issued an overall Acceptable recommendation on 28-SEP-2006. This application may now be approved from a CMC perspective.

CONCLUSIONS & RECOMMENDATIONS: Approval of this application is recommended.

[signed electronically in DFS]
Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590: N. Schmuff

cc:

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

/s/

Gene Holbert
9/28/2006 12:46:53 PM
CHEMIST

Elaine Morefield
9/28/2006 01:10:46 PM
CHEMIST



CHEMISTRY REVIEW



Chemistry Review Data Sheet

NDA 50-786

PYLERA™
(Biskalcitrate 140 mg,
Metronidazole 125 mg
Tetracycline Hydrochloride 125 mg)
CAPSULES

Axcan Scandipharm Inc.

Division of Special Pathogen and Transplant Products

Gene W. Holbert, Ph.D.
Office of New Drug Quality Assessment
Branch III
Division of Premarketing Assessment 2



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Chemistry Review Data Sheet

1. NDA 50-786
2. REVIEW #: 3
3. REVIEW DATE: September 27, 2006
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	28-SEP-2001
Amendment (BZ)	18-APR-2002
Amendment (BC)	10-MAY-2002
Amendment (BZ)	08-JUL-2002
CMC Review #1	26-JUL-2002
Not Approvable Letter	12-AUG-2002
Amendment (BC)	29-JUL-2002
Amendment (BZ)	26-SEP-2002
Amendment (BZ)	30-OCT-2002
Amendment (AZ)	31-MAR-2003
Amendment (BL)	06-JUN-2003
Amendment (BZ)	08-AUG-2003
Amendment (BZ)	26-SEP-2003
CMC Review #2	26-JUL-2002
Not Approvable Letter	03-OCT2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (AZ)	28-MAR-2006
Amendment (BL)	13-APR-2006
Amendment (BC)	26-JUN-2006
Amendment (BC)	14-AUG-2006



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Axcan Scandipharm, Inc.
Address: 22 Inverness Parkway Suite 310
Birmingham, AL 35242
U.S. Agent: CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060
Representative: Irma Monaco
Manager, Regulatory Affairs (CMC)
Telephone: (866) 722-6734
Fax: (905) 689-1465

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PYLERA™ (proposed, formerly HELIZIDE™)
b) Non-Proprietary Name (USAN): Biscalcitrates (proposed)/Metronidazole/Tetracycline Hydrochloride
c) Code Name/#: _____ #00-11-706-00; Axcan #1001277
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Antibacterial/Antiulcerative

11. DOSAGE FORM: Capsules CODE: 600

12. STRENGTH/POTENCY: 140 mg biscalcitrates /125 mg metronidazole/125 mg tetracycline hydrochloride

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

14. Rx/OTC DISPENSED: Rx OTC

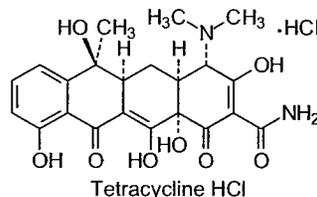
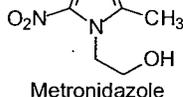
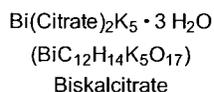
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Component	Molecular Formula	Molecular Weight	CAS Number
Biscalcitrates	BiC ₁₂ H ₁₄ K ₅ O ₁₇	834.7	Not available
Metronidazole	C ₆ H ₉ N ₃ O ₃	171.2	443-48-1
Tetracycline Hydrochloride	C ₂₂ H ₂₄ N ₂ O ₈ · HCl	480.80	64-75-5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See CMC Reviews #1 and 2.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	20-AUG-2001	
				1	Adequate	08-FEB-2002	
				3	Adequate for	21-AUG-2001	
				4	Adequate for		
				3	Adequate	04-FEB-2000	
				3	Adequate	23-SEP-1997	
				1	Adequate	05-AUG-2002	
				3, 4	Adequate	05-SEP-2001	

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2 –  DMF

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4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold	11-AUG-2006	S. Adams
Pharm/Tox.			
Biopharm.			
DDMAC	None: 44 comments	21-JUL-2006	Sheila Ryan, Pharm.D.
Methods Validation			
DMETS	Acceptable	11-AUG-2006	Laura Poncock
EA			
Microbiology			

The Chemistry Review for NDA 50-786

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Non-approval of this application is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This NDA proposes the use of Pylera™ capsules in combination with omeprazole for eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease.

Pylera™ capsules are composed of bismaltrate (140 mg), metronidazole (125 mg) and tetracycline hydrochloride (125 mg).

Bismuth salts have astringent, antacid and mildly germicidal properties and historically have been used for treatment of diarrhea, nausea, indigestion and inflammatory diseases of the stomach and colon (e.g., Pepto Bismol).

Metronidazole has antibacterial activity against obligate anaerobes. Tetracycline hydrochloride is effective against a wide variety of organisms, including gram-positive and gram-negative bacteria. Both drugs are widely marketed in the United States.

Bismaltrate, a new molecular entity, is a soluble complex bismuth salt of citric acid. As such, bismaltrate

_____ The schematized empirical molecular formula is $\text{Bi}(\text{citrate})_2\text{K}_5 \cdot 3 \text{H}_2\text{O}$ or $\text{BiC}_{12}\text{H}_{14}\text{K}_5\text{O}_{17}$ with a corresponding molecular weight of 834.71.

Executive Summary Section

[REDACTED]

Biskalcitrate is stored in [REDACTED]; at the long-term condition of $25 \pm 2^\circ\text{C}$ and at the accelerated condition of $40^\circ\text{C}/75\% \text{RH}$. Samples stored at the long term condition were tested every [REDACTED] to a total of [REDACTED]. All samples under both storage conditions were well within the proposed acceptance criteria.

Metronidazole, USP and tetracycline hydrochloride, USP are commercial drug substances manufactured according to DMFs [REDACTED], respectively. Axcan has proposed specifications for these items which exceed the USP requirements.

Pylera™ capsules are formulated as hard gelatin capsules (size 0 elongated) containing 140 mg biskalcitrate, 125 mg metronidazole and a smaller (size 3) capsule containing 125 mg tetracycline hydrochloride.

[REDACTED]

The product is packaged in [REDACTED] bottles with [REDACTED] caps. The bottles also contain a [REDACTED].

[REDACTED]

[REDACTED]

Stability samples were stored at both $25^\circ\text{C}/60\% \text{RH}$ and $40^\circ\text{C}/75\% \text{RH}$. Samples stored at the long term condition were tested at 0, 3, 6, 9, 12, 18 and 24 months. Stability data (12 months long term and 6 months accelerated) for [REDACTED] batches of drug product manufactured with Biskalcitrate from [REDACTED] was submitted. Samples were within specification. Likewise, no evidence of decomposition was noted in samples stored at 40°C . The sponsor has proposed that the product be stored at controlled room temperature ($59\text{-}86^\circ\text{F}/15\text{-}30^\circ\text{C}$).

This resubmission provides for a new manufacturer of biskalcitrate drug substance, [REDACTED]. The applicant has submitted data to demonstrate that biskalcitrate from [REDACTED] is equivalent to that obtained from the previous manufacturer.



Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Pylera™ Capsules, in combination with omeprazole are indicated for eradication of *H. pylori* in patients with *H. pylori* infections or duodenal ulcer disease. Eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

Pylera™ should be given as 3 capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice daily, for 10 days.

Pylera™ is supplied as a capsule with a red body and cap, with Axcan Pharma logo printed on the body, HP, diagram of the stomach and BMT printed on the cap. The product is supplied in bottles of 120 capsules.

C. Basis for Approvability or Not-Approval Recommendation

The Non-Approval recommendation is based on the following. There are serious cGMP concerns surrounding one of the facilities in this application. The firm in question, _____ the manufacturer of biscalcitrates was inspected by the FDA on June 6, 2006. A Form 483 was issued following the inspection. For a listing of some of the major deficiencies from the May 2002 inspection, see CMC review #1. Some of the major items of concern from the June 2006 inspection are:

This inspection found the following deficiencies:

The firm's use, qualification, calibration and maintenance of critical equipment;

No SOPs for calibration or maintenance for manufacturing equipment;

Conditions or practices exist where possible avenues of contamination of pharmaceutical products could occur;

Not all elements of validation have been satisfied;

Critical manufacturing processing points are not adequately controlled;
inadequate change control documentation;

No Annual Product Reviews;

Inadequate review and approval of equipment calibration.



III. Administrative

A. Reviewer's Signature

Signed electronically in DMF.

B. Endorsement Block

Gene W. Holbert, Ph.D./Date:
Norman R. Schmuff, Ph.D./Date
Rebecca D. Saville, Pharm.D./Date

C. CC Block

79 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

Gene Holbert
9/27/2006 04:40:04 PM
CHEMIST

Norman Schmuff
9/27/2006 04:48:55 PM
CHEMIST

NDA 50-786

HELIZIDE CAPSULES
**(biskalcitrate potassium/metronidazole/
tetracycline hydrochloride)**

Axcan Scandipharm, Inc.

Gene W. Holbert, Ph.D.

**Division of Special Pathogen and
Immunologic Drug Products**

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Chemistry Review Data Sheet

1. NDA 50-786
2. REVIEW #: 2
3. REVIEW DATE: 01-OCT-2003
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	28-SEP-2001
Amendment (BZ)	18-APR-2002
Amendment (BC)	10-MAY-2002
Amendment (BZ)	08-JUL-2002
CMC Review # 1	26-JUL-2002
Not Approvable Letter	12-AUG-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	29-JUL-2002
Amendment (BZ)	26-SEP-2002
Amendment (BZ)	30-OCT-2002
Amendment (AZ)	31-MAR-2003
Amendment (BL)	06-JUN-2003
Amendment (BZ)	08-AUG-2003
Amendment (BZ)	26-SEP-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Axcan Scandipharm, Inc.
Address: 22 Inverness Parkway, Suite 310
Birmingham AL 35242
Representative: Becky Prokipcak, Ph.D.
U.S. Regulatory Affairs
Telephone: (800) 615-4393

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: HELIZIDE (proposed)
 b) Non-Proprietary Name (USAN): biskalcitrate potassium (proposed)/metronidazole/
 tetracycline hydrochloride
 c) Code Name/# (ONDC only): None
 d) Chem. Type/Submission Priority (ONDC only): Chem. Type: 1
 Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Antiulcerative

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 140 mg biskalcitrate potassium/125 mg
metronidazole/125 mg tetracycline hydrochloride

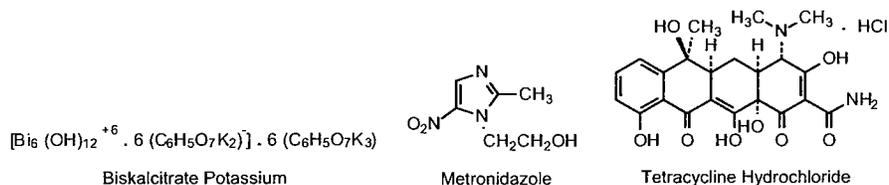
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Component	Molecular Formula	Molecular Weight	CAS Number
Biskalcitrate Potassium	_____	_____	Not available
Metronidazole	$\text{C}_6\text{H}_9\text{N}_3\text{O}_3$	171.2	443-48-1
Tetracycline Hydrochloride	$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8 \cdot \text{HCl}$	480.80	64-75-5



CHEMISTRY REVIEW



Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See CMC Review # 1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	20-AUG-2001	
				1	Adequate	08-FEB-2002	
				1	Deficient	19-MAY-2003	
				3	Adequate	21-AUG-2001	
				4	Adequate		
				3	Adequate	04-FEB-2000	
				3	Adequate	23-SEP-1997	
				1	Adequate	05-AUG-2002	
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Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

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5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	—	Single-Triple Capsules
NDA	20-868	Flagyl®
NDA	50-719	HELIDAC®



CHEMISTRY REVIEW



Executive Summary Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold	01-OCT-2003	
Pharm/Tox			
Biopharm		30-SEP-2003	Seong H. Jang
LNC			
Methods Validation			
DMETS	Helizide name acceptable	15-AUG-2002	Scott Dallas
EA			
Microbiology			

*Appears This Way
On Original*



The Chemistry Review for NDA 50-786

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A Non-Approval action based on the results of the cGNP inspection is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This NDA proposes the use of Helizide capsules in combination with omeprazole for eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease.

Helizide capsules are composed of biscalcitrates, metronidazole and tetracycline hydrochloride.

Bismuth salts have astringent, antacid and mildly germicidal properties and historically have been used for treatment of diarrhea, nausea, indigestion and inflammatory diseases of the stomach and colon (e.g., Pepto Bismol).

Metronidazole has antibacterial activity against obligate anaerobes. Tetracycline hydrochloride is effective against a wide variety of organisms, including gram-positive and gram-negative bacteria. Both are widely marketed in the United States.

Biscalcitrates, a new molecular entity, is a [REDACTED]

As such, biscalcitrates is: [REDACTED]

The proposed molecular formula is [REDACTED] with corresponding molecular weights of [REDACTED] respectively). These formulae differ by [REDACTED] molecules of [REDACTED]

Executive Summary Section

Biskalcitrate is stored in doubled polyethylene bags at the long-term condition of $25 \pm 2^\circ\text{C}$ and at the accelerated condition of $40^\circ\text{C}/75\% \text{RH}$. Samples stored at the long term condition were tested every 6 months to a total of 60 months. All samples under both storage conditions were well within the proposed acceptance criteria.

Metronidazole, USP and tetracycline hydrochloride, USP are commercial drug substances manufactured according to DMFs _____ respectively. Axcan has proposed specifications for these items which exceed the USP requirements.

Helizide capsules are formulated as hard gelatin capsules (size 0 elongated) containing 140 mg biskalcitrate, 125 mg metronidazole and a smaller (size 3) capsule containing 125 mg tetracycline hydrochloride.

The product is packaged in _____ bottles with _____. The bottles also contain a _____.

The resubmitted application contains specifications for the complete capsule as well as each of the individual active ingredients. Acceptance criteria for biskalcitrate potassium include identification and assay for bismuth by atomic adsorption spectroscopy, citric acid assay (HPLC), dissolution, content uniformity and citric acid degradation products. Controls for tetracycline include identification (UV and HPLC), assay, dissolution, weight variation and impurities. Acceptance criteria for metronidazole include identification (HPLC and UV), assay, dissolution, content uniformity and impurities.

Stability samples were stored at both $25^\circ\text{C}/60\% \text{RH}$ and $40^\circ\text{C}/75\% \text{RH}$. Samples stored at the long term condition were tested at _____. Data at _____ months using newly developed and validated analytical methods was also provided. Samples were within specification. Likewise, no evidence of decomposition was noted in samples stored at 40°C . The sponsor has proposed that the product be stored at controlled room temperature / _____.

B. Description of How the Drug Product is Intended to be Used

Helizide® Capsules, in combination with omeprazole are indicated for eradication of *H. pylori* in patients with *H. pylori* infections or duodenal ulcer disease. Eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.



CHEMISTRY REVIEW



Executive Summary Section

Helizide® should be given as 3 capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice daily, for 10 days.

Helizide® is supplied as a capsule with a red body and cap, with Axcan Pharma logo printed on the body, HP, diagram of the stomach and BMT printed on the cap. The product is supplied in bottles of 120 capsules.

C. Basis for Approvability or Not-Approval Recommendation

The Non-Approval recommendation is based on the following. There are serious cGMP concerns surrounding one of the facilities in this application. The firm in question, _____, the manufacturer of biscalcitrates under _____ DMF _____ was inspected by the FDA on May 3-7, 2002, and reinspected on September 8-11, 2003. A Form 483 was issued following both inspections. For a listing of some of the major deficiencies from the May 2002 inspection, see CMC review #1. Some of the major items of concern from the September 2003 inspection are:

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Executive Summary Section

It should be noted that some of these or similar items were identified during the May 2002 inspection and it appears that no corrective action was taken.

The Office of Compliance has therefore determined that _____ the manufacturer of biscalcitrato potassium under _____ DMF _____, is in non-compliance with cGMPs and has recommended that the firm not be approved as a supplier of biscalcitrato drug substance.

Other deficiencies remain. In a letter dated May 29, 2003 deficiencies to DMF _____ were conveyed to the DMF holder, _____ through their U.S. agent. At this time, no response has been received.

Based on the extensive serious cGMP deficiencies for biscalcitrato, and on a corresponding lack of adequate CMC information on biscalcitrato, a Non-Approval action seems appropriate.

**Appears This Way
On Original**



III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Gene W. Holbert, Ph.D. 01-OCT-2003
ChemistryTeamLeaderName/Date: Norman R. Schmuff, Ph.D.
ProjectManagerName/Date: Andrei Nabakowski, Pharm.D.

C. CC Block

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Norman Schmuff
10/2/03 01:08:54 PM
CHEMIST



NDA 50-786

**HELICIDE Capsules
(biscalcitrates potassium/metronidazole/
tetracycline hydrochloride)**

Axcan Scandipharm, Inc.

**Gene W. Holbert, Ph.D.
Division of Special Pathogen and
Immunologic Drug Products**



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Chemistry Review Data Sheet

1. NDA 50-768
2. REVIEW #: 1
3. REVIEW DATE: 26-JUL-2002
4. REVIEWER: Gene W. Holbert, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

28-SEP-2001

Amendment

10-MAY-2002

Amendment

08-JUL-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Axcan Scandipharm, Inc.
Address: 22 Inverness Parkway Suite 310
Birmingham, AL 35242
Representative: Becky Prokipcak, Ph.D.
U.S. Regulatory Affairs
Telephone: (800) 615-4393



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: HELICIDE (proposed)
b) Non-Proprietary Name (USAN): biscalcitrates potassium (proposed)/metronidazole/
tetracycline hydrochloride
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Antiulcerative

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 140 mg biscalcitrates potassium
125 mg metronidazole
125 mg tetracycline hydrochloride

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

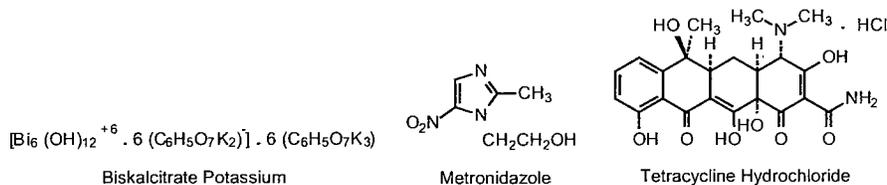
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) :

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Component	Molecular Formula	Molecular Weight	CAS Number
Biscalcitrates Potassium	—	—	N/A
Metronidazole	C ₆ H ₉ N ₃ O ₃	171.2	443-48-1
Tetracycline Hydrochloride	C ₂₂ H ₂₄ N ₂ O ₈ · HCl	480.80	64-75-5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1				3	Adequate	20-AUG-2001	
1				1	Adequate	08-FEB-2002	
1				1	Inadequate	05-FEB-2002	
				3	Adequate	21-AUG-2001	
				4			
				3	Adequate	04-FEB-2000	
				7	Inadequate		
				3, 4	Adequate	05-SEP-2001	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – — DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	 	Single-Triple Capsules
NDA	20-868	Flagyl®
NDA	50-719	HELIDAC®

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold	25-JUL-2002	
Pharm/Tox	Pending		S. Hundley
Biopharm	Approval	26-JUL-2002	J. Meyer
LNC			
Methods Validation			
OPDRA	Pending		
EA			N/A
Microbiology			N/A



The Chemistry Review for NDA 50-786

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A Not Approvable action is recommended based on the cGMP status of one of the facilities and the lack of response to DMF comments related to the drug substance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This NDA proposes the use of Helicide capsules in combination with omeprazole for eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease.

Helicide capsules are composed of biscalcitrates, metronidazole and tetracycline hydrochloride.

Bismuth salts have astringent, antacid and mildly germicidal properties and historically have been used for treatment of diarrhea, nausea, indigestion and inflammatory diseases of the stomach and colon (e.g., Pepto Bismol).

Metronidazole has antibacterial activity against obligate anaerobes. Tetracycline hydrochloride is effective against a wide variety of organisms, including gram-positive and gram-negative bacteria. Both are widely marketed in the United States.

Biscalcitrates, a new molecular entity, is a [REDACTED]

As such, biscalcitrates is [REDACTED]

The proposed molecular formula is [REDACTED]
with corresponding molecular weights of [REDACTED]
respectively). These formulas differ by [REDACTED] molecules of [REDACTED]

Executive Summary Section

Biskalcitrate is stored in _____ at the long-term condition of $25 \pm 2^\circ\text{C}$ and at the accelerated condition of $40^\circ\text{C}/75\% \text{RH}$. Samples stored at the long term condition were tested every _____ to a total of _____. All samples under both storage conditions were well within the proposed acceptance criteria.

Metronidazole, USP and tetracycline hydrochloride, USP are commercial drug substances manufactured according to DMFs _____ respectively. Axcan has proposed specifications for these items which exceed the USP requirements.

Helicide capsules are formulated as hard gelatin capsules (size 0 elongated) containing 140 mg biskalcitrate, 125 mg metronidazole and a smaller (size 3) capsule containing 125 mg tetracycline hydrochloride. The capsules also contain _____

The product is packaged in _____ bottles and _____. The bottles also contain a _____

Stability samples were stored at both $25^\circ\text{C}/60\% \text{RH}$ and $40^\circ\text{C}/75\% \text{RH}$. Samples stored at the long term condition were tested at _____. Data at _____ months using newly developed and validated analytical methods was also provided. Samples were within specification. Likewise, no evidence of decomposition was noted in samples stored at 40°C . The sponsor has proposed that the product be stored at controlled room temperature _____

B. Description of How the Drug Product is Intended to be Used

Helicide® Capsules, in combination with omeprazole are indicated for eradication of *H. pylori* in patients with *H. pylori* infections or duodenal ulcer disease. Eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

Helicide® should be given as 3 capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice daily, for 10 days.

Helicide® is supplied as a capsule with a red body and cap, with Axcan Pharma logo printed on the body, HP, diagram of the stomach and BMT printed on the cap. The product is supplied in bottles of 120 capsules.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The Not Approvable recommendation is based on the following. There are serious cGMP concerns surrounding one of the facilities in this application. The firm in question, _____ the manufacturer of biscalcitrates under _____ DMF _____, was inspected by the FDA on May 3-7, 2002, and a Form 483 was issued that listed 23 deficiencies. Some of the major items of concern are:

- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____

The Office of Compliance has therefore determined that _____ the manufacturer of biscalcitrates potassium under _____; DMF _____, is in non-compliance with cGMPs and has recommended that the firm not be approved as a supplier of biscalcitrates drug substance.

Other deficiencies remain.

- In a letter dated April 19, 2002, deficiencies to DMF _____ were conveyed to the DMF holder, _____ through their U.S. agent. Some of these issues are approvability issues. At this time, no response has been received.
- Deficiencies in the drug substance section of the NDA were conveyed to the applicant on June 18, 2002. Some of these issues are approvability issues. No reply has been received despite repeated inquiries.

Based on the extensive serious cGMP deficiencies for biscalcitrates, and on a corresponding lack of adequate CMC information on biscalcitrates, a Non-Approvable action seems appropriate.



III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Gene W. Holbert
ChemistryTeamLeaderName/Date:	Norman R. Schmuff
ProjectManagerName/Date:	Leo Chan

C. CC Block

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/s/

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