

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-589

CHEMISTRY REVIEW(S)



NDA 21-589

Kemstro™* (baclofen orally disintegrating tablets)

* Tentative tradename

Schwarz Pharma, Inc.

Martha R. Heimann, Ph.D.
Division of Neuropharmacological Drug Products



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Chemistry Review Data Sheet

1. **NDA 21-589**
2. **REVIEW #: 1**
3. **REVIEW DATE:** 10/29/2003
4. **REVIEWER:** Martha R. Heimann, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Item</u>	<u>Document Date</u>
Information Request Letter (CMC)	23-SEP-2003
Labeling comments to sponsor (via e-mail)	22-OCT-2003
CMC comments on recommended product expiry (via e-mail)	27-OCT-2003

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	31-DEC-2002
N (BZ) Stability update	03-JUN-2003
N (BZ) packaging amendment, Minor (editorial) revisions to specifications, Second bioequivalence study	18-AUG-2003
N (BC) Partial Response to 23-SEP-2003 CMC IR	15-OCT-2003
N (BZ) Completed response to 23-SEP-2003 CMC IR	16-OCT-2003
N (BL) Container label revised per 22-OCT-2003 e-mail request	24-OCT-2003
N (BC) Response to 27-OCT-2003 comments on product expiry	28-OCT-2003
Sponsor accepted OCPB dissolution recommendation (via e-mail)	29-OCT-2003

7. **NAME and ADDRESS OF APPLICANT:**

Name: Schwarz Pharma, Inc.
Address: 6140 W. Executive Drive
Mequon, WI 53092
Representative: Donna K. Multhauf, Director of Regulatory Affairs/QA
Telephone: (262) 238-5171



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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kemstro is proposed
- b) Non-Proprietary Name (USAN): baclofen
- c) Code Name/#: N/A
- d) Chem. Type/Submission Priority:
Chem. Type: 3



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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	REVIEWED BY/ COMMENTS
—	III		/	2	Adequate	27-SEP-2000	R. Lostritto
—	III			2	Adequate	20-JUN-2002	D. Klein
—	III			2	Adequate	03-AUG-2001	P. Peri
—	III			2	Adequate	15-SEP-2000	D. Klein
—	III			1	Adequate	06-OCT-2003	M. Heimann
—	II			2	Adequate	31-MAY-2002	S. Brown
—	IV			2	Adequate	26-JUL-2000	S. McLamore

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,882	Open label trial to assess subject preference compared to conventional baclofen tablets
NDA	17-851	Innovator drug cited under 505(b)(2) (Novartis, withdrawn—approved)
ANDA	73-093	Designated Reference Listed Drug (Watson Laboratories)



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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	--	--
EES	Acceptable	25-AUG-2003	J. D'Ambrogio
Pharm/Tox	N/A	--	--
Biopharmaceutics	Approvable, recommended change to dissolution specification	02-OCT-2003	C. Noory
Methods Validation	N/A	--	--
DMETS	unacceptable	28-APR-2003	N. Roselle
	unacceptable	21-AUG-2003	T. Harper-Velasquaz
	Kemstro acceptable as tradename	28-OCT-2003	A. Mahmud
EA	Categorical Exclusion		M. Heimann
Microbiology	N/A	--	--



The Chemistry Review for NDA 21-589

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended.

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

I recommend acceptance of the sponsor's commitment to

II. Summary of Chemistry Assessments

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

Baclofen was originally approved in 1977, under NDA 17-851, as conventional immediate-release oral tablets (Lioresal® Tablets, 10 mg and 20 mg). Production and distribution of Lioresal Tablets was voluntarily discontinued by the NDA holder, Novartis Pharmaceutical Corporation, in January 2001. Baclofen oral tablets are currently marketed by three generic firms, Ivax Pharmaceuticals, USL Pharma, and Watson Laboratories. Baclofen 20 mg tablets manufactured by Watson under ANDA 73-093 are designated as the reference listed drug (RLD) for bioequivalence studies.

The proposed products, Kemstro™ Tablets, contain 10 mg or 20 mg baclofen in an orange flavored, orally disintegrating, tablet (ODT) formulation. The baclofen ODT formulation is manufactured for the sponsor by the CIMA Labs facility in Eden Prairie, Minnesota, using CIMA's _____ . Unlike most of the ODT formulations approved recently, which are based on either a lyophilized gelatin/mannitol matrix or a sodium bicarbonate/citric acid effervescent system, _____ relies primarily on _____

_____ Disintegration of the baclofen ODT formulation *in vitro* is slow relative to other approved ODT products. Complete disintegration in the mouth requires 30 seconds to 4 minutes, with an average disintegration time of 90 seconds.

In addition to crospovidone, the baclofen ODT formulation contains mannitol, povidone, microcrystalline cellulose, aspartame, magnesium stearate, orange flavor, and colloidal silicon dioxide. All tablet excipients except aspartame (sweetener) and orange flavor are commonly used in conventional immediate release oral tablets. Aspartame is used as a sweetening in several ODT products. The tablets are manufactured _____



Executive Summary Section

The proposed commercial products are identical to the formulations used in bioequivalence studies presented in the application. No efficacy studies were performed with this product.

Kemstro Tablets will be marketed in 100-count bottles with non-child resistant closures and induction seal liners.

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

The product is intended for treatment of spasticity resulting from multiple sclerosis. The orally disintegrating tablet is proposed as a convenience dosage form for patients who have difficulty in swallowing tablets. The maximum recommended dose of Kemstro is 80 mg, administered as four 20 mg doses.

Based on stability data provided in the application, a tentative expiration dating period of 18 months is established for both strengths packaged in bottles, when stored at controlled room temperature (20 - 25°C).



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the sponsor has provided adequate documentation, either in the original application or in response to information requests made during the review, of the control of ingredients and control of the finished product. Adequate validation data to support the proposed regulatory methods was provided. The sponsor has agreed to adopt the dissolution criteria requested by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewer.

All establishment inspections have been completed and the CDER Office of Compliance issued an overall acceptable recommendation for the application on August 25, 2003.

The following comment should be included in the action letter:

*Based on stability data provided in the application, a tentative expiration dating period of 18 months is established for both strengths packaged in bottles,
, when stored at controlled room temperature (20 - 25°C).*

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

246 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling