

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-855

CHEMISTRY REVIEW(S)

NDA 21-855

**Loperamide Hydrochloride Soft Gelatin Capsules
1 mg & 2 mg**

Banner Pharmacaps, Inc.

Ramesh Raghavachari, Ph.D.

**DNDC II, Office of New Drug Chemistry
for
Division of Gastrointestinal and Coagulation Drug Products
HFD-180**



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Chemistry Review Data Sheet

1. NDA # 21-855
2. REVIEW # 2
3. REVIEW DATE: July 20, 2005
4. REVIEWER: Ramesh Raghavachari

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	October 1, 2004
C	November 5, 2004
BL	December 15, 2004
BC	December 16, 2004
BL	January 06, 2005
BL	April 20, 2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC	July 1, 2005
BC	July 12, 2005



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Banner Pharmacaps, Inc.
Address: 4125 Premier Drive, High Point, NC 27265
Representative: Shelly K. Meachum, Director, Regulatory Affairs
Telephone: 336-812-8700 ext. 3312

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Loperamide Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505 (b) (2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54

10. PHARMACOL. CATEGORY: Anti- Diarrheal

11. DOSAGE FORM: Soft Gelatin Capsules

12. STRENGTH/POTENCY: 1 mg & 2 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

	IV		4	Adequate	09/29/2003	Raghavachari Don Klein
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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
NDA	17-694	Imodium 2 mg Capsule
ANDA	72-741	Loperamide.HCl 2 mg Capsule
ANDA	72-993	Loperamide.HCl 2 mg Capsule
ANDA	73-192	Loperamide.HCl 2 mg Capsule
ANDA	73-122	Loperamide.HCl 2 mg Capsule

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	Feb. 25, 2005	Office of Compliance
Pharm/Tox	Not Applicable		
Biopharm	Completed		Tien Mien Chen
LNC	Not Applicable		
Methods Validation	Not Applicable		Based on current ONDC criteria
DMETS	Completed	Mar. 10, 2005	Reynold Tan -OTC
EA	See review notes		
Microbiology	Not Applicable		

Chemistry Review Data Sheet

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-855

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the CMC point of view, this NDA 21-855 is recommended for approval. The interim specifications approved for the 1 mg soft gelatin capsules are for a period of one year. The applicant has made a post marketing commitment as follows:

- After one year of approval of the application, the applicant will submit a prior approval supplement to establish the final dissolution specification for the 1 mg strength based on additional data from newly manufactured drug product batches.

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

Not applicable.

II. Summary of Chemistry Assessments

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

The drug substance Loperamide.HCl is an approved entity in NDA 17-694 approved dated December 28, 1976. This active pharmaceutical ingredient has been marketed commercially for over twenty five years. The drug substance in this NDA will be manufactured by [REDACTED] and has been cross referenced to an adequate DMF # [REDACTED]

The drug product is in the form of soft gelatin capsules and is a new dosage form; hence this is a 505(b)(2) type application. The gel mass for soft gelatin capsule is cross referenced to DMF by the applicant Banner Pharmacaps, Inc. The excipients filled in the soft gelatin capsules are compendial excepting for glyceryl caprylate which is a well known approved food emulsifying agent. The drug product comes in two different strengths, 1 mg and 2 mg soft gelatin capsules packaged in a six count blister pack. The six count blister pack is further packaged in a carton with one (6 soft gelatin capsules) and twelve (72 soft gelatin capsules) per carton for each of the strengths. The organization of this submission does not follow the CTDQ format.

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

The Loperamide Soft Gelatin Capsules will be dispensed Over-The-Counter and is indicated for patients with symptoms of Diarrhea and Traveler's Diarrhea. This is an

CHEMISTRY REVIEW

Executive Summary Section

oral dosage form. The drug product is packaged in six pack blisters using a [REDACTED]. The drug product is recommended for storage at 20 °C – 25 °C. The data provided supports 18 month expiration dating period.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has addressed all the deficiencies communicated by the Agency dated June 16, 2005 in their amendment dated July 01, 2005 and July 12, 2005.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS by Ramesh Raghavachari, Ph.D. Review Chemist, HFD-180

B. Endorsement Block

Signed electronically in DFS by Liang Zhou, Ph.D. Chemistry Team Leader, HFD-180.

Ramesh Raghavachari/Date:

Liang Zhou/Date:

Giuseppe Randazzo/Date:

C. CC Block

NDA 21-855
HFD-180/Chemistry Reviewer/rtraghavachari
HFD-180/Chemistry Team Leader/lzhou
HFD-180/Project Manager/grandazzo
HFD-180/Div File/NDA 21-855

1 Page(s) Withheld

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/s/

Ramesh Raghavachari
7/20/05 03:37:42 PM
CHEMIST

Liang Zhou
7/20/05 03:42:30 PM
CHEMIST

NDA 21-855

**Loperamide Hydrochloride Soft Gelatin Capsules
1 mg & 2 mg**

Banner Pharmacaps, Inc.

Ramesh Raghavachari, Ph.D.

**DNDC II, Office of New Drug Chemistry
for
Division of Gastrointestinal and Coagulation Drug Products
HFD-180**

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Chemistry Review Data Sheet

1. NDA # 21-855
2. REVIEW #: 1
3. REVIEW DATE: June 13, 2005
4. REVIEWER: Ramesh Raghavachari

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original submission

October 1, 2004

C

November 5, 2004

BL

December 15, 2004

BC

December 16, 2004

BL

January 06, 2005

BL

April 20, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:

Banner Pharmacaps, Inc.

Address:

4125 Premier Drive, High Point, NC 27265



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Shelly K. Meachum, Director, Regulatory Affairs

Telephone: 336-812-8700 ext. 3312

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Loperamide Hydrochloride
- c) Code Name/# (ONDC only): N/A
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 - Chem. Type: 3
 - Submission Priority: S

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11. DOSAGE FORM: Soft Gelatin Capsules

12. STRENGTH/POTENCY: 1 mg & 2 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: OTC

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

SPOTS product – Form Completed

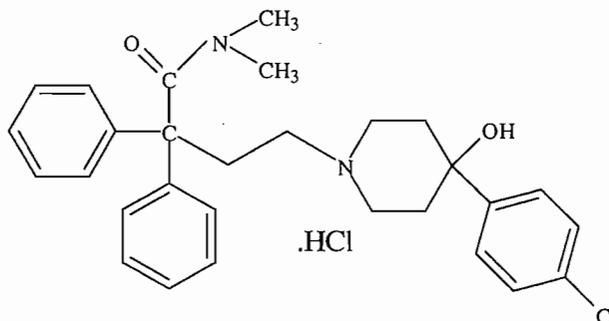
Not a SPOTS product

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

4-(4-Chlorophenyl)-4-hydroxy-N,N-dimethyl- α,α -diphenyl-1-piperidinebutanamide hydrochloride



Molecular Formula: $C_{29}H_{33}ClN_2O_2 \cdot HCl$

Molecular Weight: 513.51

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/		Adequate	11/29/2004	Ramesh Raghavachari
	III				Adequate	11/18/2004	Martha R. Heimann
14194	IV	Banner Pharmacaps, Inc.	Gel Mass		Adequate	12/14/2004	Ramesh Raghavachari
/	III	/	/		Adequate	05/02/2002	Elsbeth Chikhale

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

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ANDA	73-122	Loperamide.HCl 2 mg Capsule

18. STATUS:

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CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	Feb. 25, 2005	Office of Compliance
Pharm/Tox	Not Applicable		
Biopharm	Pending		
LNC	Not Applicable		
Methods Validation	Not Applicable		Based on current ONDC criteria
DMETS	Completed	Mar. 10, 2005	Reynold Tan -OTC
EA	See review notes		
Microbiology	Not Applicable		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-855

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the CMC point of view, this NDA 21-855 is approvable pending the sponsor addresses the list of deficiencies on page # 36 of this review.

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

Not applicable.

II. Summary of Chemistry Assessments

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

The drug substance Loperamide.HCl is an approved entity in NDA 17-694 approved dated December 28, 1976. This active pharmaceutical ingredient has been marketed commercially for over twenty five years. The drug substance in this NDA will be manufactured by [REDACTED] and has been cross referenced to an adequate DMF # [REDACTED].

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

The Loperamide Soft Gelatin Capsules will be dispensed Over-The-Counter and is indicated for patients with symptoms of Diarrhea and Traveler's Diarrhea. This is an oral dosage form. The drug product is packaged in six pack blisters using a [REDACTED]. The drug product is recommended for storage at 20 °C – 25 °C.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance has been used in many other approved drug products since 1976. This drug product is a new oral soft gelatin capsules dosage form. The application is approvable pending the applicant adequately addresses the deficiencies (on page #36 of this review). Three freshly manufactured batches were used for the bio-studies and primary stability study in this submission. No scientific rationale was provided for the inconsistent dissolution test results on the stability batches under accelerated conditions. The cross linking of gelatin may have impact of drug release *in vivo* which could lead to dose dumping and bio-availability issue. In addition, this is a 505(b)(2) application, the approval of this NDA depends upon bio-studies. Limited stability data and the validity of the bio-studies may be questionable, from the CMC point of view, the quality of the drug product may not support the safety and efficacy for this dosage form.

III. Administrative**A. Reviewer's Signature**

Signed electronically in DFS by Ramesh Raghavachari, Ph.D. Review Chemist, HFD-180

B. Endorsement Block

Signed electronically in DFS by Liang Zhou, Ph.D. Chemistry Team Leader, HFD-180.

Ramesh Raghavachari/Date:

Liang Zhou/Date:

Giuseppe Randazzo/Date:

C. CC Block

NDA 21-855
HFD-180/Chemistry Reviewer/rtraghavachari
HFD-180/Chemistry Team Leader/lzhou
HFD-180/Project Manager/grandazzo
HFD-180/Div File/NDA 21-855

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Liang Zhou
6/13/05 04:05:07 PM
CHEMIST
DR letter needs to be sent.