CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

CHEMISTRY REVIEW(S)

NDA 21-830

Asacol(mesalamine) Delayed Release Tablets 800 mg

Procter and Gamble Pharmaceutical

Maria Ysern, MSc.

Office of New Drug Quality Assessment
Division II
Branch III

CMC REVIEW OF NDA 21-830
For the Division of Gastroenterology Products (HFD-180)

Table of Contents

CMC Review Data Sheet

1. NDA 21-830

2. REVIEW # 2

3. REVIEW DATE: 26-MAR-2008

4. REVIEWER: Maria Ysern.

5. PREVIOUS DOCUMENTS: CMC Review #1.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BZ)	22-OCT-07
Amendment (BC)	04-MAR-08
Amendment (BL)	04-MAR-08

7. NAME & ADDRESS OF APPLICANT:

Name:	Procter & Gamble, Inc.
Address:	Health Care Research Center 8700 Mason-Montgomery Rd. Mason, OH 45040
Representative:	Mark S. Leusch Associate Director U.S. Regulatory Affairs
Telephone:	513-622-2620

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asacol® 800 Delayed release tablets
b) Non-Proprietary Name: Mesalamine
c) Code Name/# (ONDQA only): n/a
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 3
- Submission Priority: Re-submission/Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-inflammatory. Treatment of moderately active ulcerative colitis.

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 800 mg

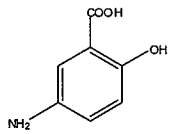
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√___Not a SPOTS product

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



5-Amino-2-hydroxybenzoic acid
MW; 153.1
Molecular formula; $C_7 H_7 NO_3$

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17. RELATED/SUPPORTING DOCUMENTS: See Review #1.

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	"Acceptable" recommendation	19-Mar-2008	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS			
EA	Adequate FONSI recommended	Feb 10, 2005	Dr. Zielinski
Microbiology	N/A		

Executive Summary Section

The CMC Review #2 for NDA 21-830

The Executive Summary:

NDA 21-830 was reviewed May 05, 2005, and based on the information provided, an approval recommendation was made from the standpoint of CMC.
However, it was not approved at this time because of clinical issues.
A BZ amendment was received on October 22, 2007. Re-inspection of the manufacturing facilities had to be initiated since the sites were inspected more than two years ago. Update to the label was also reviewed and found adequate.
The manufacturing sites were re-inspected and received an Acceptable recommendation on 19-Mar-2008.

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. Therefore, from a CMC perspective, this NDA is recommended for "Approval".

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

N/A

II. Summary of CMC Assessments

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

(1) Drug Substance:

Approved NDA 19-651 contains chemistry, manufacturing and control information for the drug substance. The mesalamine drug substance (5-amino-2-hydroxybenzoic acid) used in the manufacture of the 800 mg tablet is the same as that approved for use on the manufacture of the currently marketed Asacol 400 mg tablets. The drug substance will be sourced from the currently approved supplier, [redacted] b(4)
and all approved manufacturing processes and controls remain unchanged.

(2) Drug Product:

The drug product is a mesalamine delayed release tablet intended for the first line of treatment for ulcerative colitis associated with inflammation of the mucosa that can be extended throughout the colon.
The mesalamine delayed release tablets have a pH sensitive polymer coating (Eudragit®) which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon and a protective

film coating, an enteric coating that contains methacrylic acid copolymer, NF type B, Methacrylic acid copolymer, NF, Type A (Eudragit l , , that provides added mechanical strength to the coating and release earlier than pH 7. b(4)

The drug product is a red brown, capsule shaped, enteric coating tablet imprinted with "Asacol 800" in black ink. The core tablet contains 800 mg of mesalamine, lactose monohydrate,NF; sodium starch glycolate, NF Talc, USP; Povidone USP; magnesium stearate, NF and colloidal silicon dioxide , NF; dibutyl phthalate, NF; ferric oxide, NF yellow. Polyethylene glycol , NF b(4)

The tablets are packaged in HDPE bottles with desiccant and cotton and a child resistant cap with foil induction seal.

The product will be manufactured and tested by Procter & Gamble Pharmaceuticals, Germany GmbH. Final drug product testing may be performed by P&GP b(4) Germany . Procter and Gamble Pharmaceuticals is responsible for final release control of the drug product.

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

The usual dosage in adults is two Asacol 800 mg tablets to be taken 3 times a day for a total daily dose of 4.8 g mesalamine for duration of 6 weeks.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life. The Office of Compliance has issued an "Acceptable" overall recommendation for all the facilities involved. Labels have required information.

III. Administrative

A. Reviewer's Signature: In DFS

Maria Ysern, MSc., Review Chemist Division II, branch III

B. Endorsement Block:

Moo-Jhong Rhee, Branch Chief, Branch III, ONDQA
Marie Kowblansky, PAL, Division II
Clinical Project Manager, Kristen Everett

C. CC Block: entered electronically in DFS

11 Page(s) Withheld

6 Trade Secret / Confidential b(4)

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Maria Ysern
4/14/2008 11:20:19 AM
CHEMIST

Moo-Jhong Rhee
4/17/2008 01:03:30 PM
CHEMIST
Chief, Branch III

NDA 21-830

Asacol (mesalamine) Delayed Release Tablets, 800 mg

Procter & Gamble Pharmaceuticals

Maria E. Ysern
Division of Gastrointestinal and Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-830

2. REVIEW # 1

3. REVIEW DATE: May 05, 2005

4. REVIEWER: Maria E. Ysern:

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-830	October 22, 2004
NDA 21-830 BC Amendment	December 09, 2004
NDA 21-830 BZ Amendment	January 14, 2005
NDA 21-830 BC Amendment	February 17, 2005
NDA 21-830 BL Amendment	February 24, 2005
NDA 21-830 BL Amendment	April 27, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Procter & Gamble Pharmaceuticals, Inc.
Address:	Health Care Research Center
Representative:	Mark S. Leusch Associate Director, U.S. Regulatory Affairs.

Telephone: (513) 622-2620
Fax: (513) 622-5363

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Asacol® (mesalamine)Delayed Release Tablets
   b) Non-Proprietary Name (USAN): Mesalamine
   c) Code Name/# (ONDC only):
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: Type 3.
      - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-inflammatory. Treatment of moderately active ulcerative colitis.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 800 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

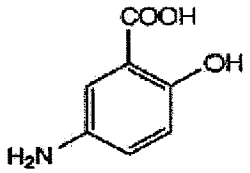
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

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

    5-Amino-2-hydroxybenzoic acid

Chemistry Review Data Sheet



Molecular Weight: 153.1
Molecular Formula: $C_7H_7NO_3$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	3			3	Adequate	April 13, 2000	
	3			3	Adequate	April 26, 2002	
	3			3	Adequate	Aug 5, 2002	
	3			3	Adequate	Feb 28, 2005	b(4)
	3			3	Adequate	March 11, 2005, 2005	
	3			3	Adequate	Jun13, 2004	
	3			3	Adequate	Aug 30, 1994	
	3			3	Adequate	Jul 22, 1999	
	3			3	Adequate to support this NDA	Feb 24, 2005	
	3			3	Adequate	April 29, 2002	

	3	3	Adequate	Aug 6, 1999	
	3	4			b(4)

[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	19-651	Original application. It has the Drug substance information for NDA 21-830

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	pending		
Pharm/Tox			
Biopharm	pending		
LNC			
Methods Validation	Pending		
OPDRA			
EA	Adequate/ FONSI recommended	Feb 10, 2205	Dr. Zielinski
Microbiology	N/A		

Chemistry Review Data Sheet

OGD: N/A

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:

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Executive Summary Section

The Chemistry Review for NDA 21-830

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the information provided this NDA can be approved .
An overall acceptable recommendation was received from the plant inspections.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance:

Approved NDA 19-651 contains the Drug Substance chemistry, manufacturing and control information. The mesalamine drug substance (5-amino-2-hydroxybenzoic acid) used in the manufacture of the 800 mg tablet is the same as that approved for use on the manufacture of the currently marketed Asacol 400 mg tablets. The drug substance will be sourced from the currently approved supplier, and all approved manufacturing processes and controls remain unchanged. b(4)

Drug Product:

The Drug Product is a mesalamine delayed release tablet intended for the first line of treatment for ulcerative colitis associated with inflammation of the mucosa that can be extended throughout the colon.

The mesalamine delayed release tablets use a pH sensitive polymer coating (Eudragit S®) which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon and a protective film coating, an enteric coating which contains Methacrylic acid copolymer, NF, type B, Methacrylic acid copolymer, NF, Type A (Eudragit l , that provides added mechanical strength to the coating and releases earlier than pH 7. b(4)

The product is a red-brown, capsule shaped, enteric coating tablet printed in black ink with appropriate identification. The core tablet contains 800 mg of mesalamine, Lactose monohydrate, NF; sodium starch glycolate, NF b(4)
Talc, USP; Povidone USP; magnesium stearate, NF and colloidal silicon dioxide, NF.
Talc, USP, dibuthyl phthalate, NF, Ferric oxide, NF yellow;
Polyethylene glycol NF

The tablets are packaged in [redacted] HDPE bottle with desiccant and cotton (sample, [redacted] HDPE bottle with desiccant and cotton with [redacted] child resistant cap with foil induction seal. b(4)

The drug product will be manufactured and tested by Procter& Gamble Pharmaceuticals, Germany GmbH (P&GP Germany). Final tablet printing and primary package will be performed by [redacted]. Final drug product testing may be performed by [redacted] P&GP Germany [redacted]. Procter and Gamble Pharmaceuticals is responsible for final release control of Mesalamine delayed-release tablets, 800 mg. b(4)

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

The usual dosage in adults is two Asacol 800 mg tablets to be taken 3 times a day for a total daily dose of 4.8 g of mesalamine as six tablets for a duration of 6 weeks.

C. Basis for Approvability or Not-Approval Recommendation

The information provided is sufficient to support the approval of this NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Maria Ysern/
Chemistry Team Leader: Liang Zhou /Date
Project Manager Name/Betsy Scroggs /Date

C. CC Block

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6 Trade Secret / Confidential b(4)

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Maria Ysern
8/12/05 12:29:01 PM
CHEMIST
Inspection evaluation received.

Liang Zhou
8/12/05 01:15:34 PM
CHEMIST
See reviewer's signature Comment