CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-000

CHEMISTRY REVIEW(S)

NDA 22-000

LIALDA (mesalamine) Delayed Release Tablets, 1.2 g

Shire Development Inc.

George Lunn, Ph.D.

Division of Gastroenterology Products

Table of Contents

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ON ORIGINAL

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Chemistry Review Data Sheet

1. NDA 22-000

2. REVIEW #: 1

3. REVIEW DATE: 6-NOV-2006

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	21-DEC-2005
Amendment	27-APR-2006
Amendment	18-JUL-2006
Amendment	21-JUL-2006
Amendment	11-AUG-2006
Amendment	07-SEP-2006
Amendment	06-OCT-2006
Amendment	27-OCT-2006
Amendment	13-DEC-2006

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Shire Development Inc.
Address:	725 Chesterbrook Blvd. Wayne, PA 19087
Representative:	Nurit Rojstaczer, Ph.D. Manager, Regulatory Affairs
Telephone:	(484) 595 8308

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lialda
b) Non-Proprietary Name (USAN): Mesalamine delayed release tablets
c) Code Name/# (ONDC only): SPD476
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

NA

10. PHARMACOL. CATEGORY:

Anti-ulcerative colitis

11. DOSAGE FORM:

Delayed and extended release tablet

12. STRENGTH/POTENCY:

1.2 g

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

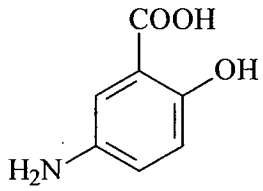
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Mesalamine
5-Aminosalicylic acid
5-Amino-2-hydroxybenzoic acid



Molecular formula: $C_7H_7NO_3$
Molecular weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	10/17/06	Reviewed by G. Lunn
	II			1	Adequate	10/17/06	Reviewed by G. Lunn
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	

[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
None		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	24-AUG-2006	S. Adams
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Not required		
OPDRA	NA		
EA	Categorical exclusion claimed. Claim	6-NOV-2006	G. Lunn

	accepted.		
Microbiology	NA		

APPEARS THIS WAY
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ON ORIGINAL

The Chemistry Review for NDA 22-000

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved and an overall recommendation of Acceptable has been made by the Office of Compliance.

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

None

II. Summary of Chemistry Assessments

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

The drug substance is mesalamine (5-aminosalicylic acid). It will be manufactured by [redacted] esting will be carried out by [redacted] An Establishment Evaluation Request was submitted and an Overall Recommendation of Acceptable has been made.

The drug substance is manufactured according to DMF [redacted] and DMF [redacted] Letters of Authorization to refer to these DMFs are provided. These DMFs have been reviewed and found to be acceptable.

The drug substance meets USP and EP specifications. Satisfactory batch analyses are provided for [redacted] lots from [redacted] 3 lots from [redacted] and 3 lots from [redacted] that have been [redacted] Up to [redacted], of satisfactory stability data are supplied for batches from each supplier.

The drug product is a formulation that the sponsor claims exhibits delayed [redacted] release characteristics. Each tablet contains 1.2 g mesalamine. After extensive discussion the term "delayed release" was agreed.

Mesalamine is [redacted]. The core tablet is coated with a gastro-resistant polymer film. The polymer film breaks down at pH 7 in the ileum (delayed release). [redacted]

The drug product consists of red-brown, ellipsoidal, film-coated tablets on one side with S476 and packed in bottles Inactive ingredients are sodium carboxymethylcellulose sodium carboxymethylcellulose carnauba wax, stearic acid, colloidal hydrated silica, sodium starch glycolate (type A), talc, magnesium stearate, and methacrylic acid copolymer, Type A, methacrylic acid copolymer, Type B, triethylcitrate, titanium dioxide, red ferric oxide, polyethylene glycol 6000, All inactive ingredients are USP/NF grade. No excipients of human or animal origin are used and the magnesium stearate and stearic acid are of vegetable origin. The active ingredient, mesalamine, is 86% of the drug product by weight.

An extensive discussion of the formulation development process is provided.

Packaging in bottles, testing, and release will take place at a. Packaging in bottles testing, and release will take place at QC analytical release testing and release to market will take place at Shire, Owings Mills, MD. An Establishment Evaluation Request was submitted and an Overall Recommendation of Acceptable has been made. An inspection was carried out for the drug product manufacturer.

A flow diagram and a narrative of the manufacturing process are provided.

Reasonable specifications are provided including dissolution testing at pH 1, pH 6.4, and pH 7.2. The analytical methods are well described. Batch analysis data are supplied for batches packaged in various ways.

The commercial product is packaged in bottles with child-resistant closures and induction seals. Samples of the labeling are supplied.

Extensive stability data are supplied for batches packaged in a variety of configurations and stored at 5°C, 25°C/60% RH, 30°C/60% RH, 30°C/65% RH, 30°C/70% RH, and 40°C/75% RH. With the exception of the dissolution values there are only a few out of specification results. Impurities remain at very low levels.

Eventually it was agreed to characterize the product as "Delayed Release". This is clearly an accurate term. The delayed release action of this product does not change on storage at room temperature. The expiration dating period will be 36 months with storage at controlled room temperature.

The sponsor claims a categorical exclusion from the requirements to file an Environmental Assessment. This claim is acceptable.

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

Mesalamine delayed-release tablets are indicated for the induction of remission (in patients with active, mild to moderate ulcerative colitis. The tablets contain 1.2 g mesalamine. The recommended dose is two to four tablets taken orally once daily. The tablets are supplied in bottles with a child-resistant closure and an induction seal and containing 120 tablets. he storage recommendation is "Store at room temperature 15°C to 25°C (59°F to 77°F); excursions permitted to 30°C (86°F). See USP Controlled Room Temperature." The expiration dating period is 36 months.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for mesalamine drug substance are contained in DMFs from These DMFs have been reviewed and found to be adequate. The composition, manufacturing process, and specifications for the tablets are appropriate. The expiration dating period of 36 months when stored at Controlled Room Temperature is supported by adequate data when the product is designated as "delayed-release". The container-closure system and labeling are appropriate. All manufacturing sites have been found to be acceptable. This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Moo Jhong Rhee, Ph.D. {Signed Electronically in DFS}
Branch Chief

C. CC Block

Marie Kowblansky, Ph.D.
Pharmaceutical Assessment Lead

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____ Draft Labeling

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/s/

George Lunn
1/3/2007 11:35:44 AM
CHEMIST

Final review - EA changed

Moo-Jhong Rhee
1/3/2007 02:23:26 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division:	Division of Gastroenterology Products
NDA:	22-000
Applicant:	Shire
Stamp Date:	12/21/05
Received by PAL:	1/9/06
PDUFA Date:	10/21/06
Trademark:	Mesavance
Established Name:	mesalamine
Dosage Form:	Delayed —→ release tablet (1.2 g)
Route of Administration:	oral
Indication:	Ulcerative colitis
PAL:	Marie Kowblansky, PhD

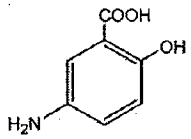
	YES	NO
ONDQA Fileability:	√	
Comments for 74-Day Letter		√

Summary and Critical Issues:

INTRODUCTION

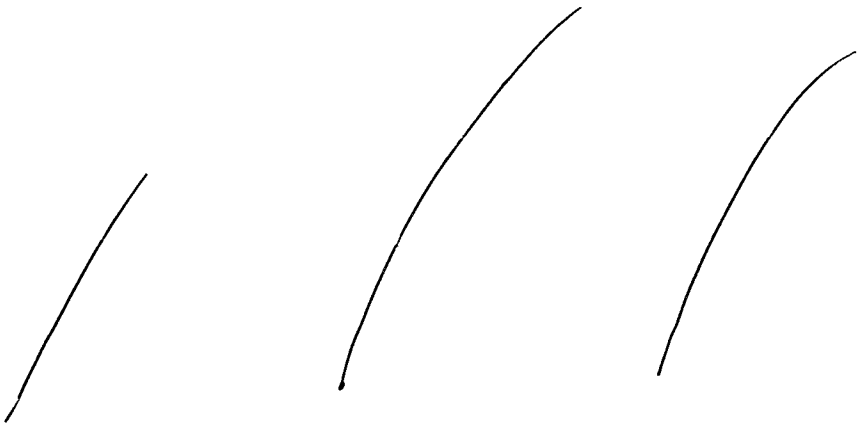
Mesavance is a new formulation of mesalamine with — delayed — release properties. It is intended for chronic use in patients with ulcerative colitis, with administration of two to four 1.2 g tablets once daily. Since mesalamine is a locally acting drug, it is important that the tablet not dissolve until after it leaves the stomach and the early part of the intestine; the maximum amount of drug must reach the colon (where most patients have pathology). The delayed release properties of the tablet prevent drug release in the acidic conditions of the upper intestinal tract; at pH 7 and above (pH of the colon) the enteric coating breaks down ——— — , of mesalamine from the tablet core.

DRUG SUBSTANCE



Mesalamine (also known as mesalazine) is the active drug substance in currently approved products and is the subject of both USP and EP monographs. Two suppliers of mesalamine are identified in the submission, ——— ~ DMFs from each of the manufacturers (DMF — and DMF — respectively) have been referenced and both will need to be reviewed in their entirety. Distinctly different routes of synthesis are used by the two manufacturers, resulting in different impurity profiles. These differences are illustrated in the table below, where the

mesalamine impurity limits specified by each supplier are compared with the limits defined in the USP and EP monographs.



The manufacturer of the drug product will test the drug substance for conformance to USP requirements, EP requirements, and "OTHER" requirements, as defined in the above table. ("OTHER" impurities will be determined by test methods.) Batch analysis data for mesalamine from both suppliers show all impurities to be present at levels well below the above limits. Samples on stability testing at 25°C and 40°C, show mesalamine to be a particularly stable compound, with no increase in the amounts of impurities throughout the entire testing period (up to at 25°C and at 40°C).

Although are used in the manufacture of mesalamine at is used as at A limit for should be added to the mesalamine specification.

Critical physical properties of the drug substance that will significantly impact the of the tablets have been identified:

During the full evaluation of this NDA, particular attention should be given to evaluating the drug substance specifications and manufacturing controls that are in place to ensure that the above physical properties are adequately controlled.

DRUG PRODUCT

Mesavance tablets is a new formulation of mesalamine designed to deliver mesalamine to the colon with limited systemic absorption. This targeted delivery is accomplished by delayed release properties into the tablet. The tablet formulation is given as

Ingredient	Amount (mg)	Function	Reference to Standards
Drug substance(s) Mesalazine	1200.0	Active ingredient	EP and USP/NF
Excipient(s)			
Sodium Carboxymethylcellulose			EP + USP/NF
			EP + USP/NF
Carnauba Wax			EP + USP/NF
Stearic Acid			EP + USP/NF
Silica, Colloidal Hydrated			EP + USP/NF
Sodium Starch Glycolate (Type A)			EP + USP/NF
Talc			EP + USP/NF
Magnesium Stearate			EP + USP/NF
			EP + USP/NF
			EP + USP/NF
Methacrylic Acid Copolymer, Type A[2]			EP + USP/NF
Methacrylic Acid Copolymer, Type B[2]			EP + USP/NF
Triethylcitrate[2]			EP + USP/NF
Titanium Dioxide[2]			EP + USP/NF
Red Ferric Oxide (Ferric Oxide)[2]			USP/NF
Polyethylene glycol 6000[2]			EP and USP
			EP and USP
			EP and USP
Total	1385.0		

where the 1.2 grams of mesalamine is incorporated into the tablet core along with lipophilic components and hydrophilic

3 Page(s) Withheld

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Comments for 74-Day Letter: Although a number of the issues discussed in this initial evaluation will likely be included in an information request to the applicant, there are no comments that need to be included in the 74-day letter.

Marie Kowblansky, PhD	2/8/2006
Pharmaceutical Assessment Lead	Date
Moo-Jhong Rhee, PhD	2/8/2006
Branch Chief	Date

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/s/

Marie Kowblansky
2/8/2006 02:38:17 PM
CHEMIST

Moo-Jhong Rhee
2/13/2006 02:08:41 PM
CHEMIST
Chief, Branch III