CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204412Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	20-4412
Supporting document/s:	001
Applicant's letter date:	July 31, 2012
CDER stamp date:	August 1, 2012
Product:	Mesalamine Delayed-Release Capsules
Indication:	Treatment of mildly to moderately active ulcerative colitis and for maintenance of remission of ulcerative colitis
Applicant:	Warner Chilcott Company, LLC Rockaway, NJ
Review Division:	Division of Gastroenterology and Inborn Errors Products
Reviewer:	Sruthi Tallapragada King, PhD
Supervisor/Team Leader:	Sushanta K. Chakder, PhD
Division Director:	Donna J. Griebel, MD
Project Manager:	Anissa Davis, RN, BSN, CPHM

Disclaimer

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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Ulcerative colitis (UC) is characterized by chronic inflammation of all or parts of the colon, with diffuse mucosal inflammation of the rectum in 95% of patients. UC patients experience recurrent bloody diarrhea, abdominal pain and rectal urgency. Extraintestinal symptoms of UC include episcleritis, scleritis, uveitis, peripheral arthropathies of small and large joints, erythema nodosum, pyoderma gangrenosum, axial arthropathies, sacrolitis, ankylosing spondylitis, and primary sclerosing cholangitis. Furthermore, because of the chronic inflammation, UC patients also have an increased risk of colorectal cancer. In current clinical practice, patients are treated with anti-inflammatory medications chronically to suppress intestinal inflammation or undergo colectomy to remove the diseased organ. There are no known cures for UC. Available therapies are currently administered to induce or maintain remission and prevent relapse of symptoms.

Mesalamine (Asacol® 400 mg tablets) is approved for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission UC. Asacol® The currently approved product contains the plasticizer dibutyl phthalate in the enteric coating. Due to safety concerns associated with dibutyl phthalate, the sponsor developed a phthalate-free formulation of the previously approved product Asacol® 400 mg tablets.

1.2 Brief Discussion of Nonclinical Findings

In this submission, the applicant is seeking marketing approval for a capsule formulation of mesalamine, which was previously approved as Asacol® 400 mg tablets. The new formulation contains the plasticizer dibutyl sebacate (DBS), which has been substituted in the enteric coating for dibutyl phthalate (DBP) due to safety concerns associated with DBP. No new nonclinical studies were conducted in support of this NDA. Dibutyl sebacate is listed in the FDA Inactive Ingredient Database and has been previously used at higher amounts in FDA-approved oral formulations.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, this product is approvable for the indication proposed.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Sponsor's Version:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well controlled studies of mesalamine delayed-release use in pregnant women. Limited published human data on mesalamine show no increase in the overall rate of congenital malformations. Some data show an increased rate of preterm birth, stillbirth, and low birth weight; however, these adverse pregnancy outcomes are also associated with active inflammatory bowel disease. Animal reproduction studies of mesalamine found no evidence of fetal harm.

Mesalamine crosses the placenta. In prospective and retrospective studies of over 600 women exposed to mesalamine during pregnancy, the observed rate of congenital malformations was not increased above the background rate in the general population. Some data show an increased rate of preterm birth, stillbirth, and low birth weight, but it is unclear whether this was due to underlying maternal disease, drug exposure, or both, as active inflammatory bowel disease is also associated with adverse pregnancy outcomes.

Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of impaired fertility or harm to the fetus. These mesalamine doses were about (b) (4) times (rat) and (b) (4) times (rabbit) the recommended human dose, based on body surface area.

Recommended Version:
Pregnancy Category B: There are no adequate and well controlled studies of mesalamine delayed-release capsules use in pregnant women. Limited published human data on mesalamine show no increase in the overall rate of congenital malformations. Animal reproduction studies with mesalamine found no evidence of fetal harm.

Mesalamine crosses the placenta. In prospective and retrospective studies of over 600 women exposed to mesalamine during pregnancy, the observed rate of congenital malformations was not increased above the background rate in the general population. Some data show an increased rate of preterm birth, stillbirth, and low birth weight, but it is unclear whether this was due to underlying maternal disease, drug exposure, or both, as active inflammatory bowel disease is also associated with adverse pregnancy outcomes.

Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of impaired fertility or harm to the fetus. These mesalamine doses were about 1.6 times (rat) and 3.2 times (rabbit) the recommended human dose, based on body surface area.

Sponsor's Version:

10 OVERDOSAGE

(b) (4)

Recommended Version:

10 OVERDOSAGE

Two cases of pediatric overdosage have been reported. A 3-year-old male who ingested 2 grams of mesalamine was treated with ipecac and activated charcoal; no adverse reactions occurred. Another 3-year-old male, approximately 16 kg, ingested an unknown amount of a maximum of 24 grams of mesalamine crushed in solution; he was treated with orange juice and activated charcoal, and experienced no adverse reactions.

Sponsor's Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Recommended Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Mesalamine was not carcinogenic at dietary doses of up to 480 mg/kg/day in rats and 2000 mg/kg/day in mice, which are about 2.9 and 6.1 times the maximum recommended maintenance dose of mesalamine delayed-release of 1.6 g/day or 26.7 mg/kg/day, based on 60 kg body weight), respectively, based on body surface area.

Mutagenesis
Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, and negative for induction of micronuclei in mouse bone marrow polychromatic erythrocytes.

Impairment of Fertility
Mesalamine, at oral doses up to 480 mg/kg/day (about 1.6 times the recommended human treatment dose on a body surface area basis), was found to have no effect on fertility or reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity. (In the following, comparisons of animal dosing to recommended human dosing are based on body surface area and a 2.4 g/day dose for a 60 kg person.)

Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg (approximately 3 to 4 times the recommended human dose based on body surface area). Doses of 170 and 360 mg/kg/day (about 0.7 and 1.5 times the recommended human dose based on body surface area) given to rats for six months produced papillary necrosis, papillary edema, tubular degeneration, tubular mineralization, and urothelial hyperplasia.

In mice, oral doses of 4000 mg/kg/day mesalamine (approximately 8 times the recommended human dose based on body surface area) for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis.

In dogs, single doses of 6000 mg (approximately 81 times the recommended human dose based on body surface area) of delayed-release mesalamine tablets resulted in renal papillary necrosis but were not fatal. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day (1.1 times the recommended human dose based on body surface area).

2 Drug Information

2.1 Drug

CAS Registry Number: 89-57-6

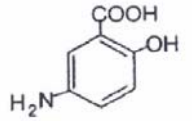
Generic Name: Mesalamine

Code Name: WC3045, Capsule

Chemical Name: 5-amino-2-2-hydroxybenzoic acid; 5-aminosalicylic acid

Molecular Formula/Molecular Weight: $C_7H_7NO_3$/157.14

Structure or Biochemical Description



Pharmacologic Class: aminosalicylate

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 26,093 (5-Aminosalicylic acid, delayed action enteric coated tablets, Warner Chilcott Pharmaceuticals, Inc.), NDA 19-651 (Asacol®)

2.3 Drug Formulation

The drug product is formulated as a delayed-release, enteric coated capsule. The composition of each WC3045, Capsule is listed in the applicant's Table 1 below:

Table 1: Composition of WC3045, Capsule

Component	Quality Standard	Function	Quantity (mg/cap)	Quantity % w/w
(b) (4)				
Mesalamine	USP	Active ingredient	400.0	(b) (4)
Lactose monohydrate	NF			(b) (4)
Sodium starch glycolate	NF			
Talc	USP			
Povidone	USP			
Magnesium Stearate	NF			
Colloidal silicon dioxide	NF			
(b) (4)	USP			
		Subtotal		(b) (4)
(b) (4)				
Methacrylic acid copolymer, type B (Eudragit S (b) (4)	-			(b) (4)
Talc	USP			
Dibutyl sebacate	NF			
Ferric oxide, red	NF			
Ferric oxide, yellow	NF			
(b) (4)	NF			
	USP			
		Subtotal		(b) (4)
(b) (4)				
Polyethylene glycol (b) (4)	USP			(b) (4)
(b) (4)	USP			
		Subtotal		(b) (4)
(b) (4)				
Hydroxypropyl methylcellulose (HPMC) Capsule, Size (b) (4)	-	(b) (4)		(b) (4)
		Subtotal		
Total Theoretical Capsule Weight			(b) (4)	100.0

1 (b) (4)
2
3

The applicant replaced dibutyl phthalate with dibutyl sebacate in the enteric coating of the new product. Each capsule of mesalamine contains (b) (4) mg of dibutyl sebacate. Therefore, the total daily intake of dibutyl sebacate is (b) (4) mg (6 capsules of mesalamine per day).

2.4 Comments on Novel Excipients

There were no novel excipients used in the manufacture of WC3045, Capsules.

2.5 Comments on Impurities/Degradants of Concern

The following impurities and degradants were identified in the drug substance, as shown in the applicant's Tables 1 and 2 below:

Table 1: Drug Substance Impurities

Impurity	Specification Limit	Reaction Mechanism
(b) (4)		

Table 2: Drug Product Degradants

Impurity	Specification Limit	Reaction Mechanism
(b) (4)		

The applicant stated that the impurity profile in WC3045, Capsules is (b) (4) to that in the currently marketed Asacol® tablets.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is comprised of patients with mild to moderately active ulcerative colitis (UC) and those with UC in remission. The proposed dosing regimen is shown in the table below:

Indication	Dosage and Administration
Treatment of mildly to moderately active ulcerative colitis	Two 400 mg capsules to be taken orally three times a day
Maintenance of remission of ulcerative colitis	1.6 g/day to be taken in divided doses by mouth

2.7 Regulatory Background

Warner Chilcott was granted a Pre-NDA meeting and met with the Review Division on June 13, 2012 to discuss their clinical development plan for a new dibutyl phthalate-free formulation of Asacol, WC3045. Dibutyl sebacate was proposed as the plasticizer to replace dibutyl phthalate in the proposed clinical product. Warner Chilcott was informed that adequate justification of the safety of dibutyl sebacate as an excipient in the new formulation should be provided with the NDA.

3 Studies Submitted

No nonclinical studies were submitted. The applicant cross-referenced the nonclinical studies submitted under NDA 19-651 and IND 26,093.

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

NDA 19-651 (Asacol® 400 mg delayed release tablets), IND 26,093

4 Pharmacology

Asacol® is currently approved for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. The mechanism of action of mesalamine is not clear. It is an orally administered aminosalicylate with local anti-inflammatory effects in the lower intestine. Several mechanisms have been proposed for the pharmacodynamic effects of mesalamine. Mesalamine is thought to interact with damaged epithelium and is converted to the acetyl-5-aminosalicylic acid; it is then absorbed and excreted via the urine and stool. Other proposals include inhibition of IL-2 production in peripheral mononuclear cells and leading to impaired inflammatory and immune responses[1].

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetic studies were submitted in support of this application. Pharmacokinetics and toxicokinetics studies were conducted under IND 26,933 and have been reviewed previously.

6 General Toxicology

No toxicology study reports were submitted with this NDA. The applicant is relying on nonclinical safety studies conducted under IND 26,933 and submitted in support of NDA 19-651, which were previously reviewed.

[1] Ham M. and Moss AC (2012) *Expert Rev Clin Pharmacol* **5**(2), 113-123.

7 Genetic Toxicology

No genetic toxicology studies were submitted with this NDA. The sponsor referenced studies submitted under NDA 19-651, which were previously reviewed.

8 Carcinogenicity

No carcinogenicity studies were submitted with this NDA. Carcinogenicity studies were submitted under NDA 19-651 and were reviewed previously.

9 Reproductive and Developmental Toxicology

No reproductive toxicology studies were submitted with this NDA. Studies were submitted under NDA 19-651 and were reviewed previously.

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

The applicant Warner Chilcott is seeking marketing approval for a phthalate-free formulation of Asacol® 400 mg, which is currently approved for the treatment of mildly to moderately active ulcerative colitis and maintenance of remission of ulcerative colitis. No nonclinical studies were submitted in this NDA. The applicant relied on nonclinical studies submitted for the approval of Asacol® Tablets. The change in the new formulation is the substitution of dibutyl sebacate (DBS), a plasticizer which was used in the enteric coating, for dibutyl phthalate (DBP). This new product is formulated as delayed-release capsules instead of tablets.

Each 400 mg delayed-release capsule of contains (b) (4) mg of DBS. The proposed maximum daily dose of mesalamine is 2400 mg. Therefore, the total daily dose of DBS is (b) (4) mg (6 capsules per day). DBS is listed in the FDA Inactive Ingredient Database and has been previously used at higher doses in FDA-approved oral formulations[2]. DBS was shown to be tolerated at very high doses after oral administration in Sprague-Dawley rats, with LD_{50} values $\geq$ 17,200 mg/kg/day[3,4].

[2] Inactive Ingredients for Approved Drug Products (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm)
[3] "Toxicological Profile for OTTO Fuel II and its Components" Agency for Toxic Substance and Disease Registry (ATSDR), June 1995.

Hypervolemia was observed in several organs (heart, kidneys) and walls of the small intestines and paresis in the stomach after single doses of DBS $\geq$ 10,000 and 15,000 mg/kg, respectively; however, it was unclear whether these findings were due to test-article related toxicity or due to the administration of a large oral volume or test article. Chronic toxicity studies with DBS failed to show similar histopathological findings. Dietary administration of DBS in a 2-year carcinogenicity study in male Sprague-Dawley rats at doses of up to 3,125 mg/kg/day did not affect tumor incidence[5]. Fertility in male and female rats, litter size, and survival of offspring were not affected in a separate study with DBS administered in the diet at doses of up to 3,125 mg/kg/day. DBS is listed as synthetic flavoring substances and adjuvants under 21 CFR 172.515, an indirect food additive under 21 CFR Section 175, and as a plasticizer under 21 CFR 181.27.

Nonclinical toxicology studies with mesalamine were conducted in mice, rats, and dogs and reviewed previously under NDA 19651 and IND 26,933. In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity. Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg. Doses of 170 and 360 mg/kg/day given to rats for six months produced papillary necrosis, papillary edema, tubular degeneration, tubular mineralization, and urothelial hyperplasia. In mice, oral doses of 4000 mg/kg/day for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis. In dogs, single doses of 6000 mg of delayed-release mesalamine tablets resulted in renal papillary necrosis but were not fatal. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day.

Mesalamine had no effects on fertility or reproduction in male and female rats and was not teratogenic in rats and rabbits. A Segment III peri- postnatal study was conducted in rats and showed no adverse developmental effects. Mesalamine was not mutagenic in a battery of *in vitro* and *in vivo* genotoxicity assays and was not carcinogenic in rats and mice.

In conclusion, from a nonclinical standpoint, there are no significant safety concerns for the marketing approval of the new formulation of Asacol® containing DBS. The total daily dose of DBS in the proposed extended release capsule formulation of Asacol® 400 mg is lower than levels used in oral formulation previously approved by the FDA.

12 Appendix/Attachments

None

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[4] Smith CC (1953) *AMA Arch Ind Hyg Occup Med* **7**(4):310-8.
[5] "Toxicological Profile for OTTO Fuel II and its Components" Agency for Toxic Substance and Disease Registry (ATSDR), June 1995.

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/s/

SRUTHI T KING
12/19/2012

SUSHANTA K CHAKDER
12/20/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 20-4412 **Applicant: Warner Chilcott Company, LLC** **Stamp Date: August 1, 2012**

Drug Name: Mesalamine **NDA/BLA Type: 505(b)(1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable No new nonclinical studies were submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sruthi Tallapragada King, Ph.D. — September 12, 2012
Reviewing Pharmacologist — Date

Sushanta Chakder, Ph.D. — September 12, 2012
Team Leader/Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

SRUTHI T KING
09/12/2012

SUSHANTA K CHAKDER
09/12/2012