CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21252/014
Priority or Standard	Standard
Submit Date(s)	March 11, 2016
PDUFA Goal Date	September 11, 2016
Division / Office	DGIEP/ODE 3
Reviewer Name(s)	Marjorie F. Dannis, M.D.
Established Name	Mesalamine
(Proposed) Trade Name	Canasa
Therapeutic Class	5-aminosalicylic acid (5-amino-2-hydroxybenzoic acid)
Applicant	Forest Laboratories
Formulation(s)	Suppository
Dosing Regimen	1000 mg daily
Indication(s)	Treatment of mild to moderately active ulcerative proctitis
Intended Population(s)	(b) (4)

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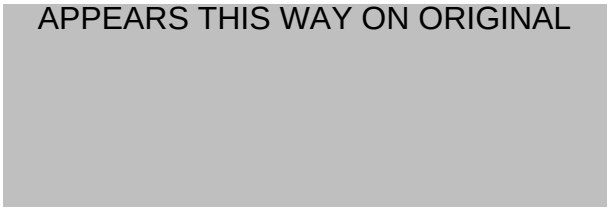
Appendix A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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

(b) (4)

PeRC recommended that the Sponsor be released from the PMR. (b) (4) Thus, this reviewer agrees that it is reasonable to release this Sponsor from this PMR.
In summary, (b) (4) this supplement should be approved and the PMR considered released.

1.2 Risk Benefit Assessment

(b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A

[1] as determined from pediatric use evaluations(of Canasa) by the Sponsor and confirmed by the Division of Epidemiology II (see Appendix A)
[2] PeRC meeting on July 13, 2016

1.4 Recommendations for Postmarket Requirements and Commitments

No further postmarket requirements and/or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Mesalamine (also known as mesalazine or 5-aminosalicylic acid (5-ASA)) is the active moiety of the pro-drug sulfasalazine (SAS) which has been used in the treatment of ulcerative colitis for over 55 years. Mesalamine 500 mg suppositories have been approved for over 15 years in Canada (marketed as Salofalk, also available as 250 mg) as well as in several other countries. Canasa has been approved in the US since 2001. Mesalamine suppository treatment is considered first-line therapy by clinicians for the treatment of ulcerative proctitis (UP) in adults.

2.2 Currently Available Treatments for Proposed Indications

Topical medication with rectally administered 5-aminosalicylic acid (5-ASA) and corticosteroid suppositories or enemas are considered effective treatment for most UP patients. At this time, there are no drugs available for pediatric patients with mild to moderately active UP. However, there are oral mesalamine preparations approved for the treatment of mildly to moderately active UC in pediatric patients. [3]

2.3 Availability of Proposed Active Ingredient in the United States

Oral and rectal mesalamine formulations are approved and marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The *Warnings and Precautions* section of the current Canasa label identifies renal impairment, mesalamine-induced acute intolerance syndrome, hypersensitivity reactions and hepatic failure as important safety issues to monitor for during treatment with Canasa.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

For regulatory activities prior to the (b) (4) see the clinical review by Dr. Il-Lun Chen (DARRTS 3/09/2011).

[3] Corticosteroid suppositories and enemas are not approved products but are used in clinical practice.

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2.6 Other Relevant Background Information

There is no other relevant background information, except as discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of this submission was good. The application was electronic, non-ECTD format with an adequate layout.

3.2 Compliance with Good Clinical Practices

No new clinical trials were conducted for this application.
See previous clinical review by Dr. Il-Lun Chen (DARRTS 3/09/2011)

3.3 Financial Disclosures

No new clinical trials were conducted for this application.
See previous clinical review by Dr. Il-Lun Chen (DARRTS 3/09/2011)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No additional CMC data was submitted for review (b) (4).

However, on November 5, 2004, the FDA approved the Sponsor's sNDA to add a new 1000 mg strength suppository for the treatment of active UP in adults (500 mg BID was shown to be similar efficacy to 1000 mg)
On June 17, 2005, the Sponsor notified the FDA that it had decided to discontinue the sale of Canasa 500 mg suppositories and **solely market the 1000 mg suppository**.
On June 8, 2006, the FDA approved the revised Canasa labeling that removed information regarding the 500 mg BID dosing regimen from the package insert.

4.2 Clinical Microbiology

No clinical microbiology studies were submitted for review (b) (4)

4.3 Preclinical Pharmacology/Toxicology

No nonclinical/toxicology studies were submitted (b) (4)

4.4 Clinical Pharmacology

The Clinical Pharmacology Reviewer concluded:

(b) (4)

For complete details, please see Clinical Pharmacology Review by Shen Li, Ph.D (DAARTS dated 7/18/16)

4.4.1 Mechanism of Action

As per the Canasa label

4.4.2 Pharmacodynamics

As per the Canasa label

4.4.3 Pharmacokinetics

As per the Canasa label

5 Sources of Clinical Data

No new clinical trials were submitted to support the efficacy (or safety) of the proposed product. (b) (4)

5.1 Tables of Studies/Clinical Trials

N/A

5.2 Review Strategy

(b) (4) Pertinent safety information from the PSURs will be discussed in Section 8 Post-market experience. For safety evaluation for Study ASPD01-CUS01, see the Clinical Review by Dr. Il-Lun Chen (DARRTS 3/09/2011).

5.3 Discussion of Individual Studies/Clinical Trials

N/A

6 Review of Efficacy

Efficacy Summary

No new clinical trials were submitted; (b) (4)

6.1 Indication

(b) (4) the Sponsor is not seeking a pediatric indication.

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

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(b) (4)

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

N/A

[10] In addition, the limitation of very limited evaluable patients (histologically confirmed) still existed.

7.1.2 Categorization of Adverse Events

N/A

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

N/A

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

N/A

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

7.3 Major Safety Results

N/A

7.3.1 Deaths

N/A

7.3.2 Nonfatal Serious Adverse Events

N/A

7.3.3 Dropouts and/or Discontinuations

N/A

7.3.4 Significant Adverse Events

N/A

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

N/A

7.4.1 Common Adverse Events

N/A

7.4.2 Laboratory Findings

N/A

7.4.3 Vital Signs

N/A

7.4.4 Electrocardiograms (ECGs)

N/A

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

N/A

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

The Sponsor submitted a Periodic Safety Update Report (PSUR) which covered the timeframe from January 05, 2015 to January 04, 2016 (this also included safety data from 2013) Most AEs were either already included in the current label or could be considered to be secondary to the underlying disease (UP/UC)[11]. No new safety signals were identified upon review of the post market data and these data do not suggest that anything other than continued routine post-market surveillance is necessary at this point. See Table 5 below.

Table 5: General Overview: Summary tabulation of Adverse Events Reported >1 in Any of the 3 PSURs Presented by SOC and PT

[11] interstitial lung disease and pneumonitis are both included in current label ("interstitial pneumonitis") and could also be due to underlying disease

System Organ Class Preferred Term	*Number of Events (Reporting Proportion)**		
	PSUR 7 (previous) 05 Jan 2013 – 04 Jan 2014	***PSUR 8 (previous) 05 Jan 2014 – 04 Jan 2015***	***PSUR 9 (current) 05 Jan 2015 – 04 Jan 2016***
Blood and lymphatic system disorders			
Agranulocytosis	0 (0%)	2 (6%)	0 (0%)
Cardiac disorders			
Pericarditis [a]	0 (0%)	0 (0%)	2 (7%)
Gastrointestinal disorders			
Constipation [a]	2 (5%)	0 (0%)	0 (0%)
Flatulence [a]	2 (5%)	0 (0%)	0 (0%)
Mucous stools [a]	2 (5%)	0 (0%)	0 (0%)
Anal fistula	2 (5%)	0 (0%)	0 (0%)
Diarrhoea [a]	0 (0%)	2 (6%)	2 (7%)
General disorders and administration site conditions			
Condition aggravated [a]	6 (16%)	2 (6%)	0 (0%)
Drug ineffective [a]	5 (13%)	0 (0%)	2 (7%)
Pyrexia [a]	0 (0%)	5 (14%)	0 (0%)
Chest pain	0 (0%)	2 (6%)	0 (0%)
Injury, poisoning and procedural complications			
Expired drug administered	2 (5%)	0 (0%)	0 (0%)
Incorrect product storage	0 (0%)	0 (0%)	2 (7%)
Musculoskeletal and connective tissue disorders			
Muscle spasms	0 (0%)	2 (6%)	0 (0%)
Psychiatric disorders			
Confusional state	0 (0%)	2 (6%)	0 (0%)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0%)	2 (6%)	0 (0%)
Interstitial lung disease	0 (0%)	0 (0%)	3 (10%)
Pneumonitis	0 (0%)	0 (0%)	3 (10%)
Skin and subcutaneous tissue disorders			
Alopecia [a]	0 (0%)	2 (6%)	0 (0%)
Surgical and medical procedures			
Off label use [a]	0 (0%)	3 (8%)	0 (0%)

* Number of events reported during period / Number of cases reported during period

[a] Listed or consistent with listed events per Mesalamine CDS dated 21 May 2013

Adapted from Sponsor's PSUR Table 9.1.1–3. Pgs 20-21

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9 Appendices

9.1 Literature Review/References

See footnotes

9.2 Labeling Recommendations

Labeling negotiations are ongoing. However, the data provided (or lack thereof) in this submission will be the basis for changes to the pediatric section of the label. (Section 8.4), despite there being no pediatric indication (b) (4). See the final approved label.

9.3 Advisory Committee Meeting

N/A

Appendix A

(b) (4)

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/s/

MARJORIE F DANNIS
07/26/2016

ANIL K RAJPAL
07/26/2016
I concur with Dr. Dannis.