

## Office of Clinical Pharmacology Review

<b>NDA Number</b>	<b>21-252 / SDN 311, 329</b>
<b>Submission Date</b>	10/15/2015, 03/11/2016
<b>Submission Type</b>	(b) (4) Supplement (S-014), (b) (4)
<b>Brand Name</b>	Canasa
<b>Generic Name</b>	Mesalamine
<b>Reviewer</b>	Shen Li, Ph.D.
<b>Team Leader</b>	Sue-Chih Lee, Ph.D.
<b>OCP Division</b>	Division of Clinical Pharmacology 3
<b>OND Division</b>	Division of Gastroenterology and Inborn Errors Products
<b>Applicant</b>	Forest Laboratories, LLC
<b>Formulation and Strength</b>	Rectal Suppository 500 mg
<b>Proposed Regimen</b>	Not applicable since the Applicant is not proposing any indication in pediatric patients.  <i>Approved Dosage in Adults:</i> <i>1000 mg rectal suppository once daily</i>
<b>Proposed Indication</b>	The Applicant is not proposing any indication in pediatric patients.  <i>Approved Indications in Adults:</i> <i>Treatment of mild to moderately active ulcerative proctitis</i>

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# 1 Executive Summary

Canasa (mesalamine) 500 mg rectal suppository was approved for adults in 2001, indicated for the treatment of mild to moderately active ulcerative proctitis. The supplemental NDA for the 1000 mg rectal suppository was approved in 2004. The approved dosage in adults is 1000 mg rectal suppository once daily. The following Pediatric Research Equity Act (PREA) Post-Marketing Requirement was included in the NDA approval letter:

- PMR 633-2: Deferred pediatric study under PREA for the treatment of active ulcerative proctitis in pediatric patients ages 12 to 17 years.

The Applicant submitted a pediatric sNDA 21-252 (S-014) for Canasa 500 mg rectal suppositories on 09/28/2010 to fulfill PMR633-2. (b) (4)

(b) (4)

(b) (4)

(b) (4). Though pharmacokinetic (PK) assessment was not included in PMR 633-2, it was noted that from a safety standpoint, PK data are needed to demonstrate that at the proposed dose, systemic exposures in pediatric populations would not exceed those observed in adults. On 11/18/2015, a Type C meeting was held between the Agency and the Applicant to clarify the discussion of the pediatric PMR 633-2. At this meeting, the FDA requested additional efficacy analyses from the existing data from Study ASPD01-CUS01. The Applicant did not have PK data for Canasa in pediatric patients and intended to submit the predicted systemic exposures following administration of the planned dose of 500 mg Canasa suppositories based on simulation. (b) (4)

In this (b) (4) pediatric sNDA (S-014), the Applicant submitted additional efficacy analyses from the subset of pediatric patients who had histologically-confirmed UP in Study ASPD01-CUS01 and the predicted pediatric exposure following administration of Canasa suppositories in order to fulfill PMR 633-2. (b) (4)

## 1.1 Recommendations

(b) (4)

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(b) (4).

## 1.2 Post-Marketing Commitments

None.

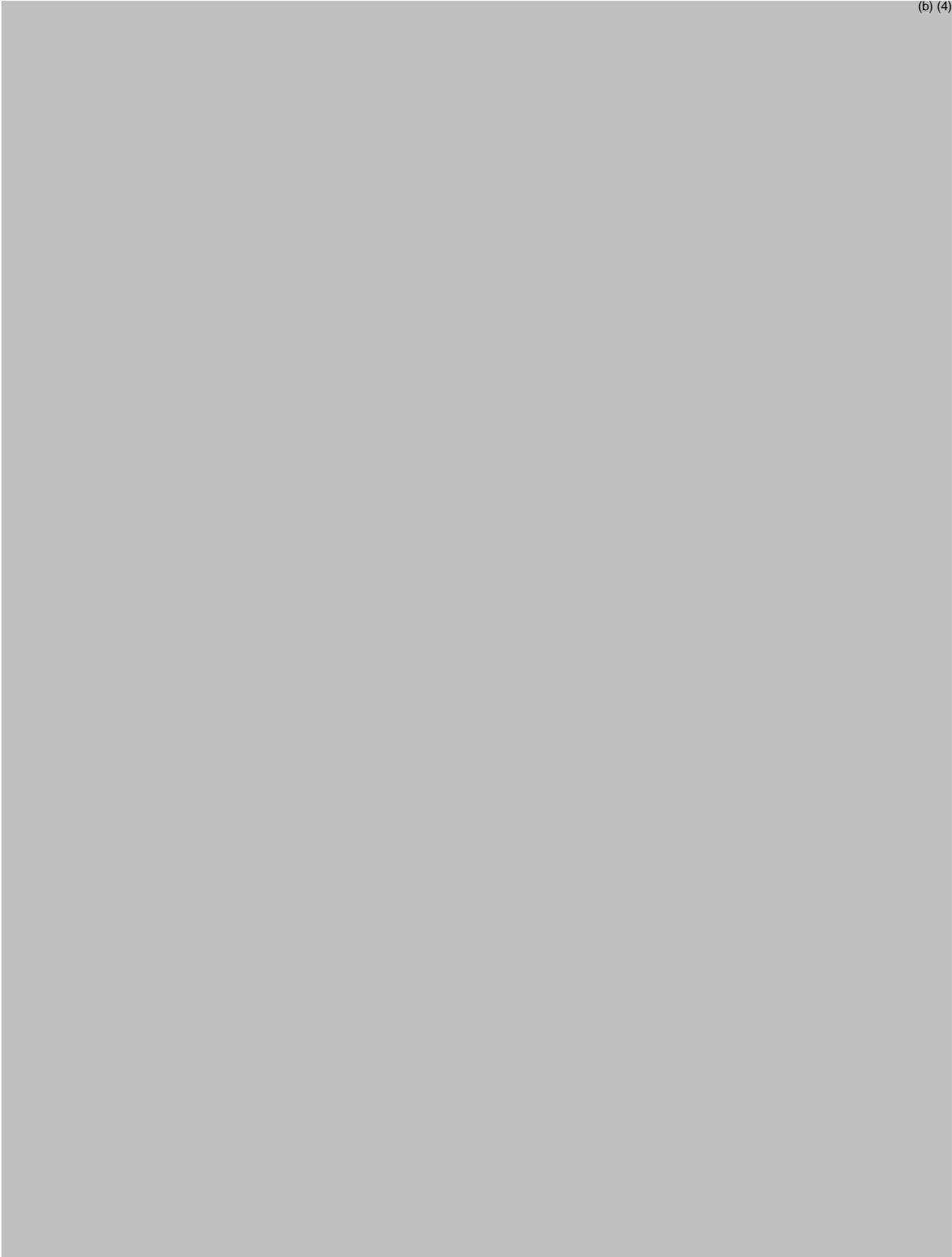
## 1.3 Summary of Clinical Pharmacology Findings

No PK data following Canasa rectal suppository dosing have been collected in pediatric patients. (b) (4), the Applicant submitted the predicted systemic exposures of 5-ASA and its metabolite, N-Ac-5-ASA, following administration of the planned dose of 500 mg Canasa suppositories in a pediatric population, which was simulated using oral and rectal PK data from literature in healthy adults, adult patients with inflammatory bowel disease (IBD) and children with IBD and certain assumptions.

The predicted mesalamine (5-ASA) exposure by the Applicant following administration of the planned dose of 500 mg Canasa suppositories in a pediatric population are summarized in Table 1:



(b) (4)



. The need for the sponsor to submit further pediatric PK data was discussed with DCP3 Management on 11/02/2015. On 07/13/2016, this submission

was also discussed at the Pediatric Review Committee (PeRC) meeting. PeRC acknowledged that the feasibility of conducting an additional pediatric study for Canasa was unlikely at this time due to enrollment difficulty and its minimal use. Therefore, it has been determined that additional pediatric PK data for Canasa will not be required.

## 2 Question-Based Review

### 2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Canasa (mesalamine) is an aminosalicylate indicated for the treatment of mild to moderately active ulcerative proctitis. The approved dosage in adults is 1000 mg rectal suppository once daily. The following Pediatric Research Equity Act (PREA) Post-Marketing Requirement was included in the NDA approval letter:

- PMR 633-2: Deferred pediatric study under PREA for the treatment of active ulcerative proctitis in pediatric patients ages 12 to 17 years.

The Applicant submitted a pediatric supplement NDA (S-014) for Canasa 500 mg rectal suppositories on 09/28/2010 intended to fulfill PMR633-2. (b) (4)

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(b) (4)

Additionally, FDA recommended that the PK component of the efficacy study should still be conducted.

A Type C meeting was held on 11/18/2015 to clarify the discussion of the pediatric PMR 633-2. At this meeting, the FDA requested additional efficacy analyses from the existing data from Study ASPD01-CUS01. The Applicant did not have PK data for Canasa in pediatric patients and intended to submit the predicted systemic exposures following administration of the planned dose of 500 mg Canasa suppositories based on simulation.

(b) (4)

(b) (4)

This supplement (b) (4) included the predicted pediatric exposure following administration of Canasa suppositories and the re-analysis using the subset of pediatric patients who had histologically-confirmed UP from the following previously submitted study:

- Study ASPD01-CUS01: Clinical Efficacy and Safety of Mesalamine Suppositories (Canasa/Salofalk) in the Treatment of Pediatric Ulcerative Proctitis: A Multicenter, Open label, Parallel Group Study.

No new clinical trials in pediatric patients have been conducted and no pediatric PK data following rectal suppository dosing have been collected.

#### 2.1.2 What is the formulation of the drug product used in pediatric studies?

Canasa 500 mg rectal suppository was approved for adults on 01/05/2001, and the supplemental NDA for the 1000 mg rectal suppository was approved on 11/05/2004. The Applicant notified the FDA on 06/17/2005 that they had decided to discontinue the sale of Canasa 500 mg Suppository strength and submitted a labeling supplement NDA on 12/13/2005. This supplemental NDA for the removal of the 500 mg suppository from the labeling for Canasa suppositories was approved on 06/08/2006. The formulation of Canasa rectal suppository 500 mg used in Study ASPD01-CUS01 is the same formulation as approved for use in adults on 01/05/2001.

#### 2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The mechanism of action of mesalamine is not fully understood, but appears to be topical rather than systemic. Although the pathology of inflammatory bowel disease is uncertain, both prostaglandins and leukotrienes have been implicated as mediators of mucosal injury and inflammation.

Canasa rectal suppositories are approved in adults for the treatment of mild to moderately active ulcerative proctitis. The Applicant is not proposing any indication in pediatric patients.

#### 2.1.4 What are the proposed dosage(s) and route(s) of administration?

Approved dosage for adults is 1000 mg rectal suppository administered once daily. Since the Applicant is not proposing any indication in pediatric patients, no dosage has been proposed for pediatric patients.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This supplement NDA resubmission included one previously submitted study ASPD01-CUS01, entitled “Clinical Efficacy and Safety of Mesalamine Suppositories [Canasa, Salofalk] in the Treatment of Pediatric Ulcerative Proctitis: A Multicenter, Open label, Parallel Group Study”. A total of 49 patients with ulcerative proctitis, aged 5-17 years, were enrolled in this trial, with 25 male (51%) and 24 female (49%) patients. Among them, 14 patients had histologically-confirmed ulcerative proctitis. All patients received Canasa 500 mg rectal suppository once daily for the first 3 weeks of the 6-week treatment period. (b) (4)

[REDACTED]

[REDACTED]. No PK data were collected in this pediatric study.

Since the Applicant is not proposing any indication in pediatric patients, no dosage has been proposed for pediatric patients.

### 2.2.2 What is the clinical endpoint for efficacy?

In the open-label trial (Study ASPD01-CUS01), efficacy was evaluated using the DAI score change from baseline to Week 6 using a last observation carried forward approach. The DAI consisted of scores for 6 clinical criteria that are represented in a semi-quantitative rating scale including 5 subscales (except for the extracolonic features): Stool Frequency (Day), Stool Frequency (Night), Urgency of Defecation, Blood in Stool, and General Well-Being.

### 2.2.3 Is mesalamine in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The PK samples for mesalamine measurement were not collected in pediatric patients following administration of Canasa rectal suppositories. (b) (4) the Applicant submitted the predicted pediatric systemic exposure.

#### 2.2.4 Exposure-Response Evaluation

Not applicable to this submission.



(b) (4)

***Reviewer's comment:***

***The review of acceptability for the safety and efficacy analyses in this submission is deferred to the clinical reviewers.***

#### 2.2.5 Pharmacokinetic Characteristics

##### 2.2.5.1 What are the PK parameters in pediatric patients?

No PK data following Canasa rectal suppository dosing have been collected in pediatric patients. In the resubmission, the Applicant submitted the predicted systemic exposures of 5-ASA and its metabolite, N-Ac-5-ASA, following administration of the planned dose of 500 mg Canasa suppositories in a pediatric population. The predicted exposures for 5-ASA and N-Ac-5-ASA are summarized in Table 1 and Table 2, respectively.



(b) (4)

### **2.3 Analytical Section**

Not applicable. No PK data were collected following Canasa 500 mg rectal suppository dosing in pediatric patients.

### **3 Labeling Recommendation**

The Office of Clinical Pharmacology has no additional recommendations on the labeling since no new PK data in pediatric patients were submitted in this resubmission.

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SHEN LI  
07/18/2016

SUE CHIH H LEE  
07/18/2016