

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-301**

**CHEMISTRY REVIEW(S)**



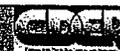
**NDA 22-301**

**Apriso (mesalamine)  
Extended-Release Capsules, 0.375 g**

**Salix Pharmaceuticals, Inc.**

**Gene W. Holbert, Ph.D.**

**Division of Gastroenterology Products**



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# Chemistry Review Data Sheet

1. NDA 22-301
2. REVIEW #: 1
3. REVIEW DATE: 29-AUG-2008
4. REVIEWER: Gene W. Holbert Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

21-DEC-2007

Amendment (BZ)

25-JUL-2008

Amendment (BC)

25-AUG-2008

Amendment (BC)

01-OCT-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Salix Pharmaceuticals, Inc.  
Address: 1700 Perimeter Park Drive  
Morrisville, NC 27560

Representative: William P. Forbes, Pharm. D.  
Telephone: (919) 862-1818

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Apriso  
Non-Proprietary Name (USAN/INN/BAN): Mesalamine  
Chemical Abstracts Name: Benzoic acid, 5-amino-2-hydroxy-  
Other Names: 5-Aminosalicylic acid (5-ASA)  
CAS Registry No: 89-57-6  
Code Name/ #: NA  
Chem. Type/Submission Priority:

- Chem. Type: 3 Submission Priority: S



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)
10. PHARMACOL. CATEGORY: Anti-inflammatory (gastrointestinal)
11. DOSAGE FORM: Capsule, extended release Code: 610

The formulation exhibits both delayed and extended release properties. On the advice of the labeling and nomenclature committee, the dosage form name "capsules, extended release" will be used.

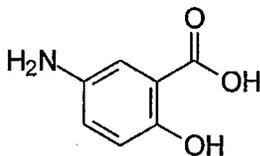
12. STRENGTH/POTENCY: 0.375 g
13. ROUTE OF ADMINISTRATION: Oral Code: 001
14. Rx/OTC DISPENSED:  Rx  OTC

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:



Molecular Formula:  $C_7H_7NO_3$     Molecular Weight: 153.14

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | Type | Holder | Item Referenced | Code <sup>1</sup> | Status <sup>2</sup> | Date Review Completed        | Comments                 |
|-------|------|--------|-----------------|-------------------|---------------------|------------------------------|--------------------------|
|       | II   | /      | /               | 1                 | Adequate            | 25-JAN-2007<br>G. Holbert    | LOA Date:<br>27-JUN-2003 |
|       | IV   |        |                 | 3, 4              | Adequate            | 30-DEC-2002<br>G. Lunn       | LOA Date:<br>12-OCT-2007 |
|       | IV   |        |                 | 3                 | Adequate            | 8-FEB-2005<br>B. Wu          | LOA Date:<br>29-AUG-2005 |
|       | IV   |        |                 | 1                 | Adequate            | 17-Mar-2008<br>G. Holbert    | LOA Date:<br>06-SEP-2007 |
|       | IV   |        |                 | 3                 | Adequate            | 22-FEB-2005<br>M. Ysern      | LOA Date:<br>29-AUG-2005 |
|       | IV   |        |                 | 3                 | Adequate            | 7-JAN-1998<br>D. Gill        | LOA Date:<br>29-AUG-2005 |
|       | IV   |        |                 | 3                 | Adequate            | 18-APR-2007<br>G. Holbert    | LOA Date:<br>29-AUG-2005 |
|       | III  |        |                 | 1                 | Adequate            | 15-SEP-2000<br>D. Klein      | LOA Date:<br>11-SEP-2007 |
|       | III  |        |                 | 1                 | Adequate            | 22-APR-2002<br>R. Frankewich | LOA Date:<br>31-JUL-2007 |
|       | III  |        |                 | 1                 | Adequate            | 07-DEC-2006<br>G. Holbert    | LOA Date:<br>31-JUL-2007 |
|       | III  |        |                 | 1                 | Adequate            | 06-DEC-04<br>R. Madurawe     | LOA Date:<br>07-AUG-2007 |
|       | III  |        |                 | 1                 | Adequate            | 27-JUL-2004<br>S. Pope       | LOA Date:<br>12-SEP-2007 |
|       | III  |        |                 | 1                 | Adequate            | 27-MAY-2003<br>D. Christner  | LOA Date:<br>31-JUL-2007 |
|       | III  |        |                 | 1                 | Adequate            | 07-DEC-2006<br>G. Holbert    | LOA Date:<br>31-JUL-2007 |

b(4)

<sup>1</sup> 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”)

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### B. Other Documents:

| <u>DOCUMENT</u> | <u>APPLICATION NUMBER</u> | <u>DESCRIPTION</u>                 |
|-----------------|---------------------------|------------------------------------|
| IND             | 62,113                    | Mesalamine granules                |
| NDA             | 19-651                    | Asacol® (mesalamine tablets)       |
| NDA             | 21-252                    | Canasa® (mesalamine suppositories) |

#### 18.STATUS:

| <b>CONSULTS/CMC<br/>RELATED REVIEWS</b> | <b>RECOMMENDATION</b> | <b>DATE</b> | <b>REVIEWER</b> |
|---|-----------------------|-------------|-----------------|
| Biometrics                              | N/A                   |             |                 |
| EES                                     | Acceptable            | 04-AUG-2008 | S. Ferguson     |
| Pharm/Tox                               | N/A                   |             |                 |
| Biopharm                                | N/A                   |             |                 |
| Methods Validation                      | Not required.         |             |                 |
| DMEPA                                   | Acceptable            | 08-OCT-2008 | M. Griffis      |
| EA                                      | Categorical exclusion | 08-APR-2008 | G. Holbert      |
| Microbiology                            | N/A                   |             |                 |



# The Chemistry Review for NDA 22-301

## The Executive Summary

### 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. All facilities involved are in compliance with cGMP, and labels have adequate information as required. 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

None.

### II. Summary of Chemistry Assessments

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

Apriso (mesalamine) Capsules are light blue capsules printed with the letters G and M on either side of a black band. Each capsule contains 0.375 g of Mesalamine USP. Inactive ingredients include microcrystalline cellulose, colloidal silicon dioxide, hypromellose, poly(ethyl acrylate/methyl methacrylate) — nonoxynol 100 dispersion — simethicone emulsion, magnesium stearate,  talc, triethyl citrate, titanium dioxide, aspartame, anhydrous citric acid, povidone — vanilla flavoring agent and edible black ink. With the exception of the flavoring, film coating, and printing ink, all excipients are compendial. The flavoring, film coating and ink are composed of ingredients that are compendial and/or GRAS. The product exhibits both delayed and extended release properties.

b(4)

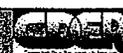
Apriso Capsules are manufactured by Catalent Pharma (formerly Cardinal Health), Winchester KY.

b(4)

b(4)



## CHEMISTRY REVIEW



### Executive Summary Section

The application contains 36 months of long term stability data on three registration batches manufactured by Catalent and packaged into 30 cc (4-count) and \_\_\_\_\_ bottles. b(4)

There were no significant changes in any of the lots stored at the long term, intermediate or accelerated condition, supporting the applicant's proposed 36 month expiration dating period for any packaging configuration between 4-count and \_\_\_\_\_ bottles when stored at 20-25°C (68-77°F) and protected from freezing. b(4)

The active drug substance is mesalamine. Mesalamine is an almost white, light grey or light pink powder used as a gastrointestinal anti-inflammatory agent. Several mesalamine formulations are approved for marketing in the US.

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

The recommended dose for maintenance of remission of ulcerative colitis in adults is 1.5 g (4 Apriso 0.375 g capsules) once daily.

#### **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 the required information.

### **III. Administrative**

#### **A. Reviewer's Signature**

*Signed electronically in DFS.*

#### **B. Endorsement Block**

Gene W. Holbert, Ph.D. 28-OCT-2008  
Marie Kowblansky, Ph.D. 28-OCT-2008

61 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/  
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Gene Holbert  
10/28/2008 11:49:31 AM  
CHEMIST

Marie Kowblansky  
10/28/2008 01:51:35 PM  
CHEMIST

Initial Quality Assessment  
Branch 3  
Pre-Marketing Assessment Division 2

**OND Division:** Division of Gastroenterology Products  
**NDA:** 22-301  
**Applicant:** Salix Pharmaceuticals  
**Stamp Date:** 12/31/2007  
**Received by PAL:** 1/8/2008  
**Review Date:** 2/13/2008  
**PDUFA Date:** 10/31/2008  
**Filing Meeting:** 2/13/2008  
**Proposed Trademark:** \_\_\_\_\_  
**Established Name:** mesalamine  
**Dosage Form:** capsule  
**Route of Administration:** oral  
**Indication:** ulcerative colitis

b(4)

**P.A.L.:** Marie Kowblansky, PhD

|                                   |                                     |                                     |
|-----------------------------------|-------------------------------------|-------------------------------------|
|                                   | YES                                 | NO                                  |
| <b>ONDQA Fileability:</b>         | <input checked="" type="checkbox"/> |                                     |
| <b>Comments for 74-Day Letter</b> |                                     | <input checked="" type="checkbox"/> |

### A. Summary

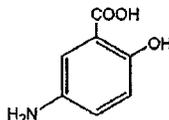
\_\_\_\_\_ (mesalamine) Capsules is intended for maintenance of remission of ulcerative colitis in patients 18 years of age and older. The proposed product is a hard gelatin capsules containing 0.375 mg of mesalamine in a delayed and extended release formulation, with instructions to administer four capsules (1.5 g) once daily. \_\_\_\_\_ This product, which was studied under IND 62,113, is being filed by Salix as a 505(b)(2) application. Since this is a new formulation of a currently approved drug, this application is classified as a Type 3 in the Chemical Classification Code.

b(4)

### Drug Substance

The active drug substance, which will be manufactured by \_\_\_\_\_ is mesalamine USP

b(4)



Only limited chemistry, manufacturing, and controls information regarding this drug substance is provided in the submission; reference is made to \_\_\_\_\_ for complete CMC information. The proposed specification fully conforms to the USP monograph for mesalamine, with additional requirements for particle size [ ] and microbial limits.

b(4)

**Drug Product**

The product, which has both delayed and extended release properties, will be prepared in a single strength, 0.375 mg mesalamine per capsule. The capsules will be filled with release-controlling granules of the following composition.

| Component   | Quality Standard | Function          | mg/capsule |
|---|------------------|-------------------|------------|
| Mesalamine  | USP              | Active ingredient | 375        |
| Colloidal silicon dioxide   | NF               |                   |            |
| Magnesium stearate  | NF               |                   |            |
| Microcrystalline cellulose  | NF               |                   |            |
| Simethicone emulsion,   | USP              |                   |            |
| Poly(ethylacrylate-methylmethacrylate) nonoxynol 100 dispersion         |                  |                   |            |
| Hypromellose  | USP              |                   |            |
|   | USP              |                   |            |
|   | USP              |                   |            |
| Magnesium stearate  | NF               |                   |            |
| Talc  | USP              |                   |            |
| Titanium dioxide  | USP              |                   |            |
| Triethyl citrate  | NF               |                   |            |
|   | USP              |                   |            |
|   | USP              |                   |            |
| Hypromellose (65SH50)   | USP              |                   |            |
| Talc  | USP              |                   |            |
|   | USP              |                   |            |
| Aspartame   | NF               |                   |            |
| Citric acid, anhydrous  | USP              |                   |            |
| Povidone  | USP              |                   |            |
| Talc  | USP              |                   |            |
| Titanium dioxide  | USP              |                   |            |
| Vanilla flavoring   |                  |                   |            |
| Hypromellose  | USP              |                   |            |
|   | USP              |                   |            |
| Light blue, opaque "00" hard gelatin capsule shell with identifier mark |                  |                   |            |
| <b>Print Ink</b>  |                  |                   |            |
| Ink   |                  |                   |            |

b(4)

All excipients in the formulation are compendial, with the exception of the vanilla flavoring and poly(ethylacrylate-methylmethacrylate) — nonoxynol 100 dispersion — DMFs are referenced for these two excipients.

The granule formulation is composed of: [

b(4)

[ The applicant explains that the current granule formulation was developed by Dr. Falk Pharma, which markets the product in Europe as a sachet product where the granules are meant to be swallowed whole, without a capsule. When Salix acquired the product, they did not want to change it. [

The product will be manufactured by Catalent Pharma Solutions and will be of the same composition as the batches used in the Phase 3 clinical studies. The manufacturing process [

b(4)

[

b(4)

[

b(4)

-----  
The proposed specification appears reasonable, conforming to ICH guidelines with respect to impurity limits, and the acceptance criteria for Stage 2 of the dissolution test (conducted in pH 6.8 buffer) are typical for an extended release product. It should be noted, however, that in several sections of the submission the acceptance criterion for unidentified impurities is listed as NMT — as listed above, but the batch analysis data list NMT — as the acceptance criterion.

b(4)

The applicant provides 24 months of 25°C stability data and 6 months of accelerated stability data for product packaged in 30 cc HDPE bottles (4 capsules) and \_\_\_\_\_ HDPE bottles \_\_\_\_\_ with induction seals. The applicant considers the submitted stability studies as a bracketing approach, requesting a \_\_\_\_\_ expiry for 4 to \_\_\_\_\_ capsules packaged in any size HDPE bottle ranging from 30 to 300 cc.

b(4)

Salix appropriately claims categorical exclusion from the requirement for submitting an environmental assessment on the basis that the estimated concentration of mesalamine at the point of entry into the aquatic environment will be below 1 part per billion (the estimated concentration is \_\_\_\_\_).

b(4)

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

### **B. Critical issues for review**

Based on this initial assessment, the following issues will need particular attention during the full review of this NDA:

-- For the two non-compendial excipients, poly(ethylacrylate-methylmethacrylate) \_\_\_\_\_ nonoxynol 100 dispersion \_\_\_\_\_ and vanilla flavoring, confirmation should be obtained from the Clinical Toxicology reviewer that these are safe at the proposed levels.

b(4)

-- The drug product specification specifies a [   
 [ ] Yet, the batch analysis data show two of the batches containing [ ]

b(4)

-- In all listings of the drug product specification the acceptance criterion for unidentified impurities is given as NMT \_\_\_\_\_ However, in the batch analysis data the unidentified impurities acceptance criterion is listed as NMT \_\_\_\_\_ This should be clarified and evaluated in terms of the 2 mg ICH identification threshold for a daily dose of 1.5 grams per day. The \_\_\_\_\_ exceeds the ICH recommendation.

b(4)

-- The applicant has used a bracketing approach to stability data providing stability data for a 30 cc and \_\_\_\_\_ container, [ ]

b(4)

### **C. Comments for 74-Day Letter – None**

### **D. Recommendation: From the CMC perspective, this application should be filed**

Marie Kowblansky, PhD  
Pharmaceutical Assessment Lead

2/14/2008  
Date

Moo-Jhong Rhee, PhD  
Branch Chief

2/14/2008  
Date

NDA 22-301

Manufacturing Sites

Drug Substance

| Commercial Manufacturing and Testing Sites   | Site Function   | Contact Person  |
|--|---|---|
| /  | Drug substance manufacturing<br>Particle size regulatory release testing<br>Stability testing | /   |
| Catalent Pharma Solutions<br>(formerly Cardinal Health)<br>1100 Enterprise Drive<br>Winchester, KY 40391<br><br>Site registration number: 1528607<br>Labeler code number: 011014 | Testing for regulatory release (all attributes except particle size)                          | Contact Name: Beth Rhodes<br>Title: Director, Quality Systems<br>Telephone: 859-745-8126<br>Email: beth.rhodes@catalent.com |

b(4)

Drug Product

| Commercial Manufacturing and Testing Sites   | Site Function   | Contact Person   |
|--|---|--|
| Catalent Pharma Solutions<br>(formerly Cardinal Health)<br>1100 Enterprise Drive<br>Winchester, KY 40391<br><br>Site registration number: 1528607<br>Labeler code number: 011014 | Drug product manufacturing<br>Testing for regulatory release<br>Stability testing | Contact Name: Beth Rhodes<br>Title: Director, Quality Systems<br>Telephone: 859-745-8126<br>Email: beth.rhodes@catalent.com      |
| Catalent Pharma Solutions<br>(formerly Cardinal Health)<br>3001 Red Lion Road<br>Philadelphia, PA 19114<br><br>Site registration number: 2530802<br>Labeler code number: 011014  | Packaging   | Contact Name: John Ronn<br>Title: Sr. Regulatory Affairs Specialist<br>Telephone (215) 613-3580<br>Email: john.ronn@catalent.com |
| /  | Packaging   | /  |
| /  | Stability testing   | /  |

b(4)

## Filing Checklists (NDA 22-301)

### A. Administrative Checklists;

| YES | NO |   | Comments |
|-----|----|---|----------|
| √   |    | On its face, is the section organized adequately?   |          |
| √   |    | Is the section indexed and paginated adequately?  |          |
| √   |    | On its face, is the section legible?  |          |
| √   |    | Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs? |          |
| √   |    | Has an environmental assessment report or categorical exclusion been provided?  |          |

### B. Technical Checklists;

#### 1. Drug Substance

|   |  |   |  |
|---|--|---|--|
| √ |  | Does the section contain synthetic scheme with in-process parameters? |  |
| √ |  | Does the section contain structural elucidation data?                 |  |
| √ |  | Does the section contain specifications?                              |  |
| √ |  | Does the section contain information on impurities?                   |  |
| √ |  | Does the section contain validation data for analytical methods?      |  |
| √ |  | Does the section contain container and closure information?           |  |
| √ |  | Does the section contain stability data?                              |  |

#### 2. Drug Product

|   |  |  |  |
|---|--|--|--|
| √ |  | Does the section contain manufacturing process with in-process controls? |  |
| √ |  | Does the section contain quality controls of excipients?                 |  |
| √ |  | Does the section contain information on composition?                     |  |
| √ |  | Does the section contain specifications?                                 |  |
| √ |  | Does the section contain information on degradation products?            |  |
| √ |  | Does the section contain validation data for analytical methods?         |  |
| √ |  | Does the section contain information on container and closure systems?   |  |
| √ |  | Does the section contain stability data with a proposed expiration date? |  |
| √ |  | Does the section contain information on labels of container and cartons? |  |
| √ |  | Does the section contain tradename and established name?                 |  |

### C. Review Issues

|   |   |   |  |
|---|---|---|--|
| √ |   | Has all information requested during the IND phases, and at the pre-NDA meetings been included? |  |
|   | √ | Is a team review recommended?   |  |
| √ |   | Are DMFs adequately referenced?   |  |

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Marie Kowblansky  
2/21/2008 04:50:03 PM  
CHEMIST

Moo-Jhong Rhee  
2/21/2008 04:51:45 PM  
CHEMIST  
Chief, Branch III