CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40216

APPROVAL LETTER

ANDA 40-215 (10%)
40-216 (30%)

MAY 25 1999

Akorn, Inc.
Attention: Syed J. Akhtar
72-6 Veronica Avenue
Somerset, NJ 08873

Dear Sir:

This is in reference to your abbreviated new drug applications dated October 11, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sulfacetamide Sodium Ophthalmic Solution USP.

Reference is also made to your amendments dated November 9, 1998; February 26, March 8, April 19, April 26, and May 19, 1999.

We have completed the review of these abbreviated applications and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Sulfacetamide Sodium Ophthalmic Solution USP, 10% and 30%, are bioequivalent and, therefore, therapeutically equivalent to the listed drug (Sodium Sulamyd® Ophthalmic Solution, 10% and 30%, respectively, of Schering Corp.).

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require approved supplemental applications before the change may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 5/25/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-215, 40-216
Division Files
FIELD COPY
HFD-610/R.West
HFD-92
HFD-210/B.Poole
HFD-330/
HFD-205/

Endorsements:
HFD-629/N.Nashed/4-28-99 NNS 5/13/99 NNS 5/20/99
HFD-629/P.Schwartz/5-6-99 PS 5/13/99, 5/20/99
HFD-617/J.Buccine, PM/5-12-99 JB 5/14/99 JB 5/20/99
HFD-640/F.Marsik/ 5/14/99
HFD-613/L.Golson/
HFD-613/J.Grace/ 5/14/99

X:\NEW\FIRMSAM\AKORN\LTRS&REV\40215.AP

F/T by: bc/5-12-99

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40216

DRAFT FINAL PRINTED LABELING

SULFACETAMIDE SODIUM

Ophthalmic Solution USP, 30%, Ophthalmic Solution USP, 10%,

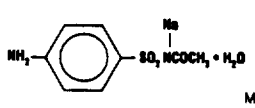
Sterile

Rx only

Rev. 9/98

001200

DESCRIPTION: Sulfacetamide sodium ophthalmic (solution) USP, is a sterile, topical, anti-bacterial agent for ophthalmic use. The active ingredient is represented by the following structural formula:



Molecular Formula:
$C_8H_9N_2NaO_3S \cdot H_2O$

Molecular Weight = 254.24

Chemical name: N-Sulfanilylacetamide monosodium salt monohydrate

Ophthalmic Solution 30%, Each mL contains:

Active: Sulfacetamide Sodium 300 mg; **Preservatives:** Methylparaben 0.5 mg and propylparaben 0.1 mg; **Inactives:** Sodium thiosulfate 1.5 mg and monobasic sodium phosphate as buffer.

Ophthalmic Solution 10%, Each mL contains:

Active: Sulfacetamide Sodium 100 mg; **Preservatives:** Methylparaben 0.5 mg and propylparaben 0.1 mg; **Inactives:** Hydroxypropyl methylcellulose 5 mg, sodium thiosulfate 3.1 mg and monobasic sodium phosphate as buffer.

CLINICAL PHARMACOLOGY

Microbiology: The sulfonamides are bacteriostatic agents and the spectrum of activity is similar for all. Sulfonamides inhibit bacterial synthesis of dihydrofolic acid by preventing the condensation of the pteridine with aminobenzoic acid through competitive inhibition of the enzyme dihydropteroate synthetase. Resistant strains have altered dihydropteroate synthetase with reduced affinity for sulfonamides or produce increased quantities of aminobenzoic acid.

Topically applied sulfonamides are considered active against susceptible strains of the following common bacterial eye pathogens: *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus* (viridans group), *Haemophilus influenzae, Klebsiella* species, and *Enterobacter* species.

Topically applied sulfonamides do not provide adequate coverage against *Neisseria* species, *Serratia marcescens* and *Pseudomonas aeruginosa*. A significant percentage of staphylococcal isolates are completely resistant to sulfa drugs.

INDICATIONS AND USAGE

For the treatment of conjunctivitis and other superficial ocular infections due to susceptible microorganisms, and as an adjunctive in systemic sulfonamide therapy of trachoma:

Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans group), *Haemophilus influenzae, Klebsiella* species, *and Enterobacter* species.

Topically applied sulfonamides do not provide adequate coverage against *Neisseria* species, *Serratia marcescens* and *Pseudomonas aeruginosa*. A significant percentage of staphylococcal isolates are completely resistant to sulfa drugs.

CONTRAINDICATIONS

Hypersensitivity to sulfonamides or to any ingredient of the preparation.

WARNINGS

FOR TOPICAL EYE USE ONLY - NOT FOR INJECTION.

FATALITIES HAVE OCCURRED, ALTHOUGH RARELY, DUE TO SEVERE REACTIONS TO SULFONAMIDES INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS. Sensitizations may recur when a sulfonamide is readministered, irrespective of the route of administration. Sensitivity reactions have been reported in individuals with no prior history of sulfonamide hypersensitivity. At the first sign of hypersensitivity, skin rash or other serious reaction, discontinue use of this preparation.

PRECAUTIONS

General: Prolonged use of topical anti-bacterial agents may give rise to overgrowth of nonsusceptible organisms including fungi. Bacterial resistance to sulfonamides may also develop.

Ophthalmic ointments may retard corneal wound healing.

The effectiveness of sulfonamides may be reduced by the para-aminobenzoic acid present in purulent exudates.

Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration, and cross-sensitivity between different sulfonamides may occur.

At the first sign of hypersensitivity, increase in purulent discharge, or aggravation of inflammation or pain, the patient should discontinue use of the medication and consult a physician (see WARNINGS).

Information for Patients: To avoid contamination, do not touch tip of container to eye, eyelid or any surface.

Drug Interactions: Sulfacetamide preparations are incompatible with silver preparations.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No studies have been conducted in animals or in humans to evaluate the possibility of these effects with ocularly administered sulfacetamides. Rats appear to be especially susceptible to the giotrogenic effects of sulfonamides, and long-term oral administration of sulfonamides has resulted in thyroid malignancies in these animals.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with sulfonamide ophthalmic preparations. Kernicterus may occur in the newborn as a result of treatment of a pregnant woman at term with orally administered sulfonamides. There are no adequate and well-controlled studies of sulfonamide ophthalmic preparations in pregnant women and it is not known whether topically applied sulfonamides can cause fetal harm when administered to a pregnant woman. This product should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered sulfonamides are capable of producing kernicterus in infants of lactating women. Because of the potential for the development of kernicterus in neonates, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of two months have not been established.

ADVERSE REACTIONS

Bacterial and fungal corneal ulcers have developed during treatment with sulfonamide ophthalmic preparations.

The most frequently reported reactions are local irritation, stinging and burning. Less commonly reported reactions include non-specific conjunctivitis, conjunctival hyperemia, secondary infections and allergic reactions.

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias (see WARNINGS).

DOSAGE AND ADMINISTRATION

For conjunctivitis and other superficial ocular infections:

Solution: Instill one or two drops into the conjunctival sac(s) of the affected eye(s) every two to three hours initially. Dosages may be tapered by increasing the time interval between doses as the condition responds. The usual duration of treatment is seven to ten days.

For Trachoma:

Solution: Instill two drops into the conjunctival sac(s) of the affected eye(s) every two hours. Topical administration must be accompanied by systemic administration.

HOW SUPPLIED

Sulfacetamide Sodium Ophthalmic Solution 30%, 15 ml dropper bottle (NDC 17478-242-12), box of one. **Store between 2° and 30°C (36° and 86°F).**

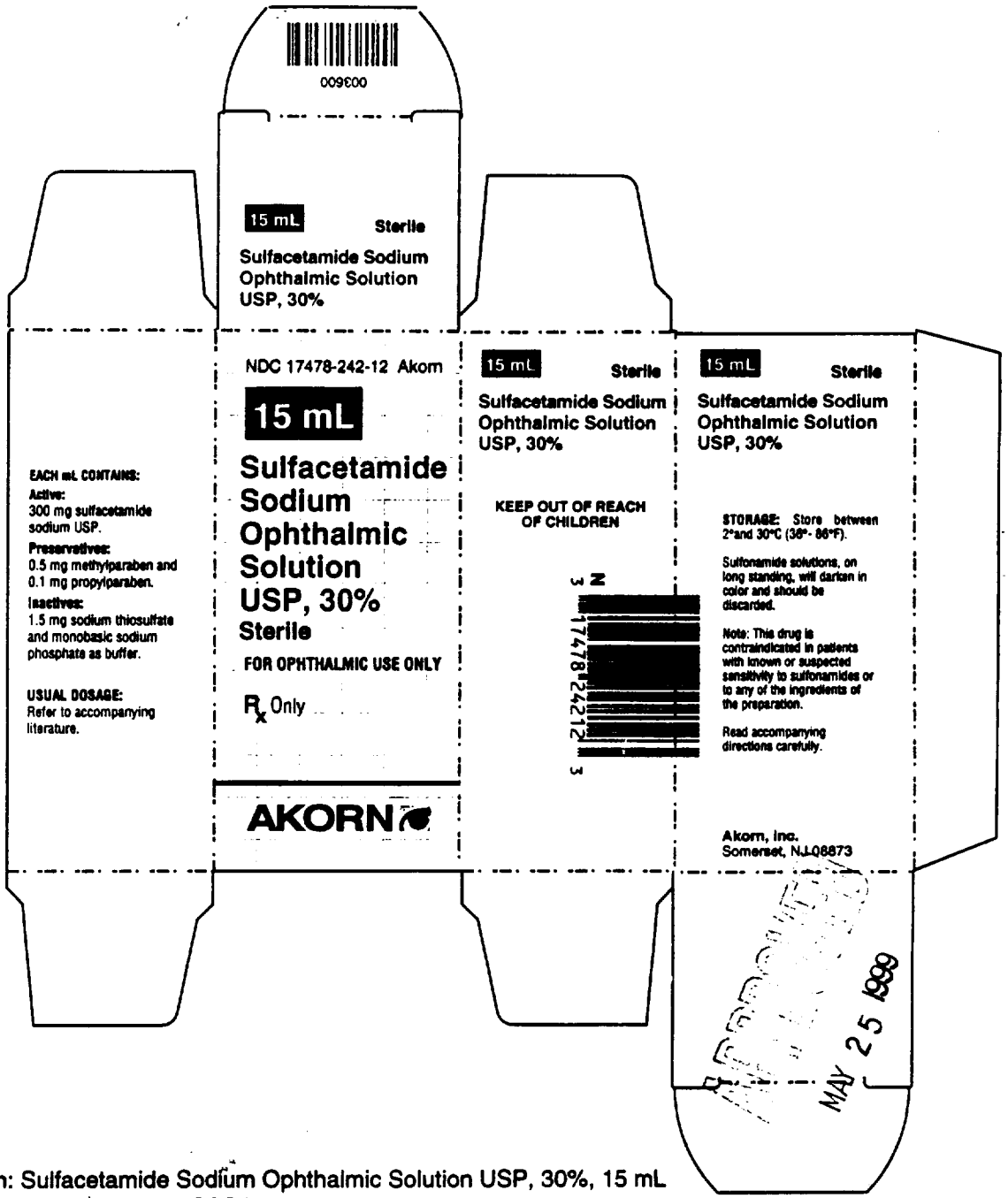
Sulfacetamide Sodium Ophthalmic Solution 10%, 15 ml dropper bottle (NDC 17478-221-12), box of one. **Store between 2° and 30°C (36° and 86°F).**

Store away from heat.

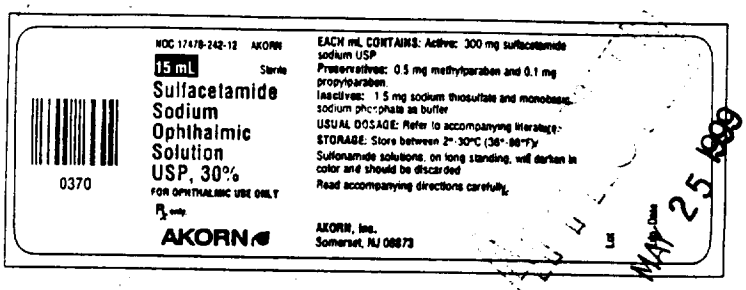
On long standing, sulfonamide solutions will darken in color and should be discarded.

Manufactured By:
AKORN, INC.
Somerset, NJ 08873

9/98

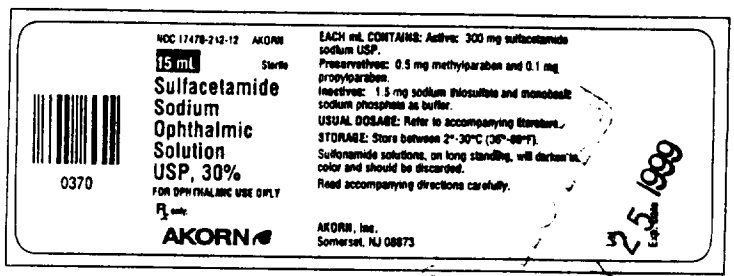


Item: Sulfacetamide Sodium Ophthalmic Solution USP, 30%, 15 mL
Stock: 16 point White SBS board
Size: 10/15 mL ctn. (1-13/32" x 1-9/32" x 3-3/16")
Colors: Pantone 463 and black
Code on flap - Code 128 - # 003600
NDC # 17478-242-12
UPC code: 3 17478-2 42-12



Item: Sulfacetamide Sodium Ophthalmic Solution USP, 30%
Label Size: 1-3/16" x 3-5/8", 15 mL
Stock:
Adhesive:
Colors: PMS 463 and Black
Varnish: Leave 3/8" area on right unvarnished for hot stamping
Code: Interweaved 2 of 5, # 0370, NDC #17478-242-12
Printer to order code to meet his requirements and the following specs
Ratio (Thick bar to thin bar) 3:1
Height of code 3/16"
Narrow bar = 8 mil.
Quiet Zone around code: 1/16"
HRC Height = .055" (for number under code)

Area on left side of label which will be wrapped under: 5/8"
Area on right hand side of label for hot stamping Lot number and Expiration date: 3/8"



Item: Sulfacetamide Sodium Ophthalmic Solution USP, 30%
Label Size: 1-3/16" x 3-5/8", 15 mL
Stock:
Adhesive:
Colors: PMS 463 and Black
Varnish: Leave 3/8" area on right unvarnished for hot stamping
Code: Interweaved 2 of 5, # 0370, NDC #17478-242-12
Printer to order code to meet his requirements and the following specs
Ratio (Thick bar to thin bar) 3:1
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Quiet Zone around code: 1/16"
HRC Height = .055" (for number under code)

Area on left side of label which will be wrapped under: 5/8"
Area on right hand side of label for hot stamping Lot number and Expiration date: 3/8"

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40216

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY 75-216

ANDA: 40-216

FIRM: Akorn, Inc.

DRUG: Sulfacetamide sodium

DOSAGE: Ophthalmic Solution

STRENGTH: 300 mg/mL (30%)

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable.

BIO STUDY/BIOEQUIVALENCE STATUS: Bio waiver was granted 12/10/97

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40°C, 24 months room temperature data at 25-30°C, and cycle study for 32 days. The expiration date is 12 month.

LABELING REVIEW STATUS: Labeling is satisfactory 11/18/98

STERILIZATION: Microbiologist review is satisfactory 11/19/98

BATCH SIZES: The firm has provided a copy of the executed batch record lot # PD96006 (100 liter) for 30%. Also, provided a copy of the master formula and manufacturing instructions for the maximum batch size liters. The firm will be using the same drug substance manufacturer, same equipment and same procedure.

COMMENTS: The Application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D. /S/ 5/20/99 DATE: 5/6/99

SUPERVISOR: Paul Schwartz, Ph.D. DATE: 5/6/99

\\CDV008\WP51F99\FIRMSAM\AKORN\LTRS&REV\40-216.SUM.DOC /S/ 5/20/99

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-216 (30%)

3. NAME AND ADDRESS OF APPLICANT

Akorn, Inc.
72-6 Veronic Ave
Somerset, NJ 08873

4. LEGAL BASIS FOR SUBMISSION

In the firm opinion and to the best of their knowledge there are no patents that claim the use of the listed drug, and the reference listed drug is not entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Sulfacetamide sodium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 10/11/96
Amendment 5/7/97
Amendment 6/12/97
Amendment 2/25/98
Amendment 11/9/98
Amendment 4/19/99
Amendment 4/26/99
Amendment 5/19/99

10. PHARMACOLOGICAL CATEGORY

Treatment of conjunctivitis, and corneal ulcer

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

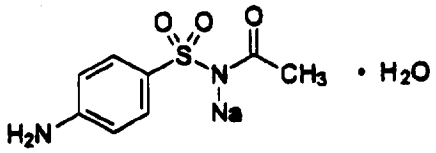
Solution (Ophthalmic)

14. POTENCY

300 mg/mL (30%)

15. CHEMICAL NAME AND STRUCTURE

Sulfacetamide Sodium. Acetamide, *N*-[(4-aminophenyl)sulfonyl]- monosodium salt, monohydrate. $C_8H_9N_2NaO_3S$. 254.24. 6209-17-2. Antibacterial. USP 23, page 1450.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

Nashed E. Nashed, Ph.D.

DATE COMPLETED:

5/19/99

Supervisor: Paul Schwartz, Ph.D.

\\CDV008\WP51F99\FIRMSAM\AKORN\LTRS&REV\40-216.3.DOC

cc: ANDA 40-216
Division File
Field Copy

Endorsements:

HFD-627/NNashed/ NN 5/20/99
HFD-627/PSchwartz/ PS 5/20/99
F/t by: gp/5/19/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40216

MICROBIOLOGY REVIEW

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #1

November 29, 1996

A. 1. ANDA: **40-216**

APPLICANT: Advanced Remedies, Inc.
Attention: Hari Menon
72-6 Veronica Avenue
Somerset, New Jersey 08873

2. PRODUCT NAMES: **Sulfacetamide Sodium Ophthalmic Solution, USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: **30% (300 mg/mL)**
Sterile ophthalmic solution for topical administration; 15 mL fill in a 15 mL bottle

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: Treatment of superficial ocular infections such as conjunctivitis & corneal ulcer and other; also used as an adjunct to systemic sulfonamide therapy of trachoma

6. PHARMACOLOGICAL CATEGORY: Anti-infective

B. 1. DATE OF INITIAL SUBMISSION:

October 11, 1996 (Received on 10/25/96)
- Subject of this Review

2. DATE OF AMENDMENT: N/A; no amendments containing sterility assurance information were submitted by the time of this review

3. RELATED DOCUMENTS:

DMF:

DMF

3. RELATED DOCUMENTS (continued):

DMF

DMF

4. ASSIGNED FOR REVIEW: November 27, 1996

C. REMARKS: The information provided in the application was insufficient to determine if the applicant is taking the necessary steps to ensure the sterility of the subject drug product (Sulfacetamide Sodium Ophthalmic Solution, USP 10%). For example, the microbial integrity of the subject drug product container/closure system was not demonstrated. Also, the microbial retentivity of the sterilizing filter to be used for the subject drug product was not validated.

D. CONCLUSIONS: The submissions are therefore not recommended for approval on the basis of sterility assurance.

Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel
drafted by: KHMuhvich, 11/29/96

cc:

Original ANDA 40-216
Field Copy

OFFICE OF GENERIC DRUGS

Microbiologist's Review #2

November 19, 1998

A. 1. ANDA: **40-216**

APPLICANT: Advanced Remedies, Inc.
Attention: Hari Menon
72-6 Veronica Avenue
Somerset, New Jersey 08873

2. PRODUCT NAMES: **Sulfacetamide Sodium Ophthalmic Solution, USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: **30% (300 mg/mL)** Sterile ophthalmic solution for topical administration; 15 mL fill in a 15 mL dropper bottle.

4. METHOD(S) OF STERILIZATION:

5. PRINCIPAL INDICATIONS: Treatment of superficial ocular infections such as conjunctivitis & corneal ulcer and other; also used as an adjunct to systemic sulfonamide therapy of trachoma

6. PHARMACOLOGICAL CATEGORY: Anti-infective

B. 1. DATE OF INITIAL SUBMISSION: October 11, 1996 (Received on 10/25/96)

2. DATE OF AMENDMENT: **February 25, 1998 (received Feb. 26, 1998)- Subject of this Review.**

3. RELATED DOCUMENTS:

DMF

DMF

DMF

DMF

4. ASSIGNED FOR REVIEW: November 18, 1998.

C. REMARKS: Original review and questions were done in 1996.

D. CONCLUSIONS: The submission is **recommended for approval** on the basis of sterility assurance.

/S/ 11/19/98
James L. McVey

initialed by M.Fanning /S/ 11/24/99

cc:
Original ANDA
Duplicate Copy
Field Copy
drafted by: JLMcVey 40216ap2.m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40216

BIOEQUIVALENCY REVIEW(S)

(3)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 40-216 **SPONSOR:** Advanced Remedies, Inc.
DRUG & DOSAGE FORM: Sulfacetamide Sodium Ophthalmic Solution, USP
STRENGTH: 30%
TYPE OF STUDY: **SD** **SDF** **MULT** **OTHER** Waiver Request
STUDY SITE: NA **CLINICAL:** NA **ANALYTICAL:** NA

STUDY SUMMARY:

The product is coded AT in the Therapeutic Equivalence List. The inactive ingredients in the drug product are qualitatively identical in the test and reference products. The inactive ingredients are quantitatively identical in the test and reference products, except for the amounts of phosphate buffer and sodium thiosulfate preservative. The amounts of phosphate buffer and preservative are within the potency range for ophthalmic solutions listed in the January 1996 issue of the IIG. The waiver of the *in-vivo* bioequivalence study requirements for the 30% Ophthalmic Solution (test product) is granted under 21 CFR 320.24 (b)(6).

DISSOLUTION: Not applicable

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I
INITIAL: /S/ **DATE:** 12/1/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I
INITIAL: /S/ **DATE:** 12/1/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: /S/ **DATE:** 12/3/98

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ **DATE:** _____

Sulfacetamide Sodium
Ophthalmic Solution, 30%
ANDA #40-216
Reviewer: James Chaney

Advanced Remedies, Inc.
Somerset, New Jersey
Submission date:
May 7, 1997

Review of A Waiver Request

Introduction

Sulfacetamide Sodium Ophthalmic Solution, USP 30% is a sterile aqueous solution indicated for the treatment of conjunctivitis, corneal ulcer, and other superficial ocular infections due to susceptible microorganisms, and as adjunctive treatment in systemic sulfonamide therapy of trachoma. The reference listed product is Sodium SULAMYD® Ophthalmic Solution, USP 30% (Schering Corporation).

The firm has requested a waiver of the *in vivo* bioavailability/bioequivalence requirements for its sulfacetamide sodium 30% ophthalmic solution. The firm has submitted the composition of the formulation which is shown in the following table:

(COMPOSITION NOT TO BE RELEASED THROUGH FOI)

Composition of Test Sulfacetamide Sodium Ophthalmic Solution, USP 30% (Advanced Remedies, Inc.) and Reference Sodium SULAMYD® Ophthalmic Solution, USP 30% (Schering Corporation)

Ingredient	Quantity (mg/mL)	
	Test	Reference
Sulfacetamide Sodium, USP	300	300
Sodium Thiosulfate Pentahydrate, USP	1.50	--
Sodium Thiosulfate	--	1.5
Methylparaben, NF	0.50	0.5
Propylparaben, NF	0.10	0.1
Monobasic Sodium Phosphate, Monohydrate	4.85	--
Monobasic Sodium Phosphate	--	Adjust pH
Purified Water, USP	QS	QS

Comments

1. FDA regulations at 21 CFR 314.94 (a) (9) (iv) state in pertinent part: "..a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug...However,

an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information... demonstrating the differences do not affect the safety of the proposed drug product..."

2. The inactive ingredients in the drug product are qualitatively identical in the test and reference products. The inactive ingredients are quantitatively identical in the test and reference products, except for the phosphate buffer and sodium thiosulfate preservative.

3. analyzed the referenced drug product to determine the amount of sodium monobasic phosphate monohydrate present in the formulation of the referenced Sulamyd®. Based on this analysis, 4.85 mg/mL of monobasic sodium phosphate monohydrate was included in the test product. This amount of monobasic sodium phosphate monohydrate is equivalent to 4.22 mg/mL of monobasic sodium phosphate which is within the potency range for ophthalmic solutions listed in the January 1996 issue of the Inactive Ingredients Guide.

4. The amount of sodium thiosulfate pentahydrate preservative, used in the test formulation is equivalent to 0.83 mg/mL of sodium thiosulfate which is within the potency range for ophthalmic solutions listed in the January 1996 issue of the Inactive Ingredients Guide.

Recommendation

The Division of Bioequivalence agrees that the information submitted by . demonstrates that its Sulfacetamide Sodium Ophthalmic Solution, 30% falls under the criteria set forth in 21 CFR 320.24 (b)(6) of the Bioavailability/ Bioequivalence Regulations. The waiver of the *in-vivo* bioequivalence study requirements for the 30% Ophthalmic Solution (test product) is granted. From the bioequivalence point of view the Division of Bioequivalence deems the test ophthalmic product to be bioequivalent to Sodium SULAMYD® Ophthalmic Solution, USP 30% manufactured by Schering Corporation.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 12/10/97

Concur: /S/ Date 12/10/97
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/121097
X:\new\firmsam\advanrem\ltrs&rev\40216w.597

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-216 APPLICANT: Advanced Remedies, Inc.

DRUG PRODUCT: Sulfacetamide Sodium Ophthalmic Solution, 30%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40216

CORRESPONDENCE

ADVANCED REMEDIES, INC.
72-6 VERONICA AVENUE
SOMERSET, NJ 08873
(908) 846-8066 • FAX (908) 846-7952

May 7, 1997

NDA ORIG AMENDMENT

N/A

via Airborne Express

Roger L. Williams, M.D., Director
Office of Generic Drugs; CDER, FDA
Metro Park North II
5600 Standish Place
Rockville, MD 20855-2773

Re: Sulfacetamide Sodium Ophthalmic Solution USP, 30%
ANDA #40-216

Dear Dr. Williams:

Reference is made to your correspondence dated December 3, 1996 regarding the above application.

As an amendment, we are submitting our responses to the deficiencies that were made in your communication.

If you need any further information, please feel free to contact me.

Very truly yours,

Hari Menon
President

HM/sta
Enclosure

cc: U.S. Food & Drug Administration
Attn: Ms. Regina Brown

MAY 19 1997

ADVANCED REMEDIES, INC.
72-6 VERONICA AVENUE
SOMERSET, NJ 08873
(908) 846-8066 • FAX (908) 846-7952

11/21/96
Cancel

October 11, 1996

via Airbone Express
Roger L. Williams, M.D., Director
Office of Generic Drugs; CDER, FDA
Metro Park North II
5600 Standish Place
Rockville, Maryland 20855-2773

Re: Abbreviated New Drug Application for Sulfacetamide Sodium Ophthalmic Solution USP, 30% Sterile

Dear Dr. William:

Pursuant to 21 CFR, Section 314.50, Advanced Remedies, Inc., is hereby submitting its Abbreviated New Drug Application for the drug product, Sulfacetamide Sodium Ophthalmic Solution USP, 30% Sterile, for your review. The data demonstrating that the process is capable of providing "Sterility Assurance" is included in Section XI 1a of this application.

We are also submitting a Review Copy of the application, contained in red jackets, comprising two (2) volumes and a Bioequivalency/Bioavailability section contained in an orange jacket.

We are also submitting an Archival Copy of the application, contained in blue jackets, comprising two (2) volumes. In addition, we are submitting the field copy which is a true copy of the technical section contained in the Archival and Review copies of this ANDA application to the District office.

Your expeditious review of our application is greatly appreciated. If you require any further information, please contact the undersigned.

Thanking you in advance.

Sincerely,

Hari Menon
President

HM/sta
Enclosures
cc: U.S. Food & Drug Administration
Attn: Mr. Frank O'Sullivan

ADVANCED REMEDIES, INC.
72-6 VERONICA AVENUE
SOMERSET, NJ 08873
(908) 846-8066 • FAX (908) 846-7952

June 12, 1997

via Airborne Express

Roger L. Williams, M.D., Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Sulfacetamide Sodium Ophthalmic Solution, 10%
ANDA 40-215

Dear Dr. Williams:

Reference is made to the June 3, 1997 telephone conversation with Mr. Jim Wilson of your organization, regarding the above captioned matter.

Enclosed please find the revised information pertaining to the functions of outside firms including contract laboratories. We have included the specific functions that were performed by contract laboratories related to this application.

As you can see, we have acquired the services of these laboratories to perform limited testing. The purpose of including these laboratories in our application is to utilize services of outside laboratories in the event the need should arise.

If you have any further questions, please feel free to contact the undersigned.

Thank you for your continued cooperation.

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JUN 13 1997
GENERIC DRUGS

Very truly yours,

Hari Menon
President

HM/sta
Enclosures

cc: U.S. Food & Drug Administration
Attn: Ms. Regina Brown (w/encls.)

ADVANCED REMEDIES, INC.
72-6 VERONICA AVENUE
SOMERSET, NJ 08873
(908) 846-8066 • FAX (908) 846-7952

ORIG AMENDMENT
NJAM

February 25, 1998

via Airborne Express

Roger L. Williams, M.D., Director
Office of Generic Drugs; CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Sulfacetamide Sodium Ophthalmic Solution USP, 30%
ANDA 40-216
MAJOR AMENDMENT

Dear Dr. Williams:

Reference is made to your correspondence dated September 22, 1997 regarding the above mentioned application.

Enclosed please find our responses to the deficiencies outlined in your communication stated above. Please note that we have observed a significant loss in the potency of the preservatives during shelf life stability studies. Therefore, we would like to add a % overage of preservatives in our product formulations. The revised master batch record is enclosed with response #1. We have also revised the drug substance testing monograph to include impurities and is enclosed as well.

We also acknowledge the comments that were made in your deficiency letter under Section C, that our firm should be in compliance with CGMP's at the time of approval, bioequivalence waiver status and the regulatory status of USP analytical method. We understand that the USP analytical method will prevail in the event of dispute.

I trust our responses will be to your satisfaction. If you need any further information, please feel free to contact me.

Thank you for your continued cooperation.

Sincerely,

Hari Menon
President

HM/sta
Enclosures
cc: Food & Drug Administration
Attn: Ms. Regina Brown (w/encls.)

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November 9, 1998

via Airborne Express

Roger L. Williams, M.D., Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Sulfacetamide Sodium Opthalmic Solutions USP
ANDA 40-215 (10%)
ANDA 40-216 (30%)
Minor Amendment

TPL
NDA ORIG AMENDMENT
fm

Dear Dr. Williams:

Reference is made to your communication dated September 9, 1998 regarding the above mentioned applications.

As per your request, we have revised our specifications for the Stability samples to tighten the limits for the specified impurities and delete the overages of preservatives and active drug substance from our product formulations.

Due to the deletion of % overage of the active drug substance from our product formulations, we are now considering lowering our proposed expiration date to 18 months instead of 24 months to provide added assurance. The expiration date may be extended to 24 months at a later date when we have enough data to support a 24 month expiration date.

I trust our responses will be to your satisfaction.

Thank you for your continued cooperation.

Sincerely,

Hari Menon
Vice President, Scientific Affairs

HM/sb
cc: Regina Brown
U.S. Food and Drug Administration
Data\william.doc

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NOV 10 1998
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1-732-846-8066 • FAX 1-732-846-7952
Akorn Ophthalmics, 72-6 Veronica Avenue, Somerset, NJ 08873

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OPHTHALMICS

April 26, 1999

Mr. Joseph Buccine
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

RE: Sulfacetamide Sodium Ophthalmic Solution
10% (ANDA 40-215)
30% (ANDA 40-216)
Telephone Amendment dated April 26, 1999

Dear Mr. Buccine:

As per your telephone request of April 26, 1999, we are including the limit for the total impurities as NMT % in our finished product release monograph.

Should additional information and/or clarification be required, please contact me at (732) 846-8066 or Fax (732) 846-7952.

Sincerely,

Syed J. Akhtar
Director, Compliance

SJA/sb
Enclosure

cc: Regina T. Brown
Food & Drug Administration

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APR 27 1999
GENERIC DRUGS

1-732-846-8066 • FAX 1-732-846-7952
Akorn Ophthalmics, 72-6 Veronica Avenue, Somerset, NJ 08873

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April 19, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TELEPHONE AMENDMENT TO ANDA 40-216
Sulfacetamide Sodium Ophthalmic Solution USP, 30%
15 mL fill size in 15 cc container

Dear Ladies and Gentlemen:

This amendment is in response to a teleconference held on March 18, 1999 with Mr. Joseph Buccine (FDA Project Manager) and Syed Akhtar (Akorn, Inc.). The issue involved revising Akorn's Stability Monographs for the above referenced drug product to indicate the limit for the total impurities as NMT %. The limit for the impurities stated below have also been revised per your suggestions as follows:

Sulfanilamide NMT %
N-4 Acetylsulfanilamide NMT %
Bi-Acetylsulfanilamide NMT %
Bis-(4-Aminopohenyl) sulfone NMT %
Total unspecified impurities NMT %

We are providing the revised specifications in attachment A. We have also revised our finished product release specifications for the impurities level as well due to the change in the Stability Monograph so that the release limit should be tighter than the Stability limit (Attachment B).

As we understand, the Agency recommended an expiration date of 12 months for the above mentioned product based on the Stability data conducted at 25° – 30° C, due to the impurity levels of Sulfanilamide and Bi-Acetylsulfanilamide.

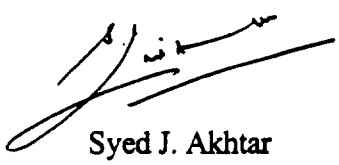
Akorn is filing an archival copy consisting of one volume (original) of this amendment and a technical review copy (duplicate) which is identical to the archival copy. An additional copy is being sent to the FDA District office.

1-732-846-8066 • FAX 1-732-846-7952
Akorn Ophthalmics, 72-6 Veronica Avenue, Somerset, NJ 08873

In accordance with 21 CFR § 314.96(b), and, by reference 314.6(c), Akorn, Inc., certifies that a true copy of this Telephone Amendment to ANDA 40-216 for Sulfacetamide Sodium Ophthalmic Solution, USP, 30% has been provided to the FDA District Office. A copy of this certification with an original signature is provided with this amendment as Attachment C.

Should additional information and/or clarification be required, please contact me at (732) 846-8066 or fax (732) 846-7952.

Sincerely,



Syed J. Akhtar
Director, Compliance

SJA/sb
Enclosures

aksulfacetamd.doc

AKORN
OPHTHALMICS

May 19, 1999

NDA ORIG AMENDMENT
N/A

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Mr. Joseph Buccine

RE: TELEPHONE AMENDMENT TO ANDA 40-216
Sulfacetamide Sodium Ophthalmic Solution USP, 30%
15 mL fill size in 15 cc container

Dear Mr. Buccine:

As per your telephone request of May 18, 1999 we are enclosing the test data for the particulate matter that was performed on Sulfacetamide Sodium Ophthalmic Solution 30% PD96006, for your review.

Please be advised that the post approval Stability Studies will be conducted on the initial three commercial batches. In addition to the three production batches, each year one production batch from each strength of the drug product will be added to our stability program. This program has been defined in our original application, please refer to Section XVII.

The expiration date may be extended beyond the proposed expiration date of 12 months at a later date based on adequate post approval real time stability data on three commercial batches, stored at controlled room temperature.

Should additional information and/or clarification be required, please contact me at (732) 846-8066.

1-732-846-8066 • FAX 1-732-846-7952
Akorn Ophthalmics, 72-6 Veronica Avenue, Somerset, NJ 08873

Thank you for your continued cooperation.

Sincerely,

Syed J. Akhtar
Director, Compliance

SJAJ/sb

cc: Regina T. Brown
Food & Drug Administration

Enclosures

Aksulfacamd2.doc