

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

CHEMISTRY REVIEW(S)



ANDA #76-751

Mesalamine Rectal Suspension, USP

Agis Industries (1983) Ltd.

**Shahnaz Read
Office of Generic Drugs, Division of Chemistry II**

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Chemistry Review Data Sheet

1. ANDA # 76-751
2. REVIEW #: 1
3. REVIEW DATE: December 8, 2003
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS:

Previous Documents
Original Submission
Acknowledgement Letter

Document Date
May 30, 2003
August 25, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original Submission

Document Date
May 30, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Agis Industries (1983) Ltd.
Address:	Industrial Zone Yeruham, Israel 80500
Authorized U.S. Agent	Clay-Park Labs, Inc. 1701 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Mesalamine Rectal Suspension, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Rowasa Rectal Suspension Enema the subject of NDA 19-618 manufactured by Solvay Pharmaceuticals containing mesalamine. There is no unexpired marketing exclusivity for Rowasa Rectal Suspension Enema under section 505(j)(4)(D) of the Act. There are two unexpired patents listed:

- U.S. Patent # 4657900, expiration date April 14, 2004
- U.S. Patent # RE33239, expiration date May 12, 2004

Agis has submitted a Paragraph III Certification Statement for these patents.

10. PHARMACOLOGICAL CATEGORY:

Treatment of mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 4 g/60 mL Unit Dose

13. ROUTE OF ADMINISTRATION: Rectal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note 17]:

SPOTS product – Form Completed

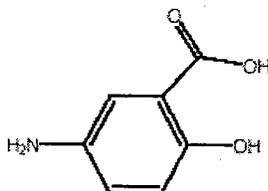
Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Mesalamine
 5-Aminosalicylic acid
 5-amino-2-hydroxybenzoic acid

Chemical Structure:



Molecular Formula: $C_7H_7NO_3$
 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Deficient	December 5, 2003	DMF holder has been notified
	III			4	NA		

¹ 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")

² Adequate, Inadequate, or NA (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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Rowasa Rectal Suspension Enema	NDA 19-618	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	Nov 4, 2003	S. Adams
Methods Validation	NA		
Labeling	Deficient	Dec 12, 2003	K. Lee
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA # 76-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

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

The active pharmaceutical ingredient, Mesalamine is believed to be the therapeutically active component of Sulfasalazine used in treatment of mild to moderate ulcerative colitis. The mechanism of action of Masalamine is unknown and appears to be topical rather than systemic. All the tests described for the drug substance are compendial tests.

The drug product is Mesalamine Rectal Suspension (Enema), packaged in unit-dose containers (4 g/60 mL). The manufacturing process involves _____

_____. The product is packaged as unit dose containers containing 4 g of Mesalamine in 60 mL suspension.

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

The product is intended for rectal instillation once a day, preferably at bedtime and retained in the body for eight hours. Detailed instructions are provided in the patient instructions which are included along with the insert.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues related to drug substance and stability specifications, and bulk testing.



III. Administrative

A. Reviewer's Signature

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/12/8/03
HFD-645/BTArnwine/1/15/04
HFD-617/NLee/1/15/04

C. CC Block

ANDA 76-751
DIV FILE
Field Copy

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #1



Chemistry Assessment Section

2. Please acknowledge that Mesalamine Rectal Suspension is an official monograph in the United States Pharmacopeia (USP). The approval to use an analytical procedure that may differ from that in the USP does not release your firm from any obligation to comply with the method and procedure in the USP specified for that product. Therefore, in the event of a dispute, only the results obtained by the official method and procedures in the USP will be considered conclusive.

Sincerely yours,

Brenda J. Gennine / for
1/22/04

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



Chemistry Assessment Section

cc: ANDA 76-751
ANANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/12/8/03 *Read 1/16/04*
HFD-645/BTArnwine/1/15/04 *(BT) Arnwine 1/20/04*
HFD-617/NLee/1/15/04 *ML 1/22/04*

F/T by: EW 1/16/04
\\cds013\ogds11\FIRMSAM\AGIS\LTRS&REV\76751R1

TYPE OF LETTER: Not Approvable (Minor)

**APPEARS THIS WAY
ON ORIGINAL**

ANDA #76-751

Mesalamine Rectal Suspension, USP

Agis Industries (1983) Ltd.

**Shahnaz Read
Office of Generic Drugs, Division of Chemistry II**

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C. CC Block.....	8
Chemistry Assessment	9



Chemistry Review Data Sheet

1. ANDA # 76-751
2. REVIEW #: 2
3. REVIEW DATE: March 1, 2004
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS:

Previous Documents

Original Submission
Acknowledgement Letter

Document Date

May 30, 2003
August 25, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Minor Amendment

Document Date

February 19, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Agis Industries (1983) Ltd.
Address:	Industrial Zone Yeruham, Israel 80500
Authorized U.S. Agent	Clay-Park Labs, Inc. 1701 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
- b) Non-Proprietary Name (USAN): Mesalamine Rectal Suspension, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Rowasa Rectal Suspension Enema the subject of NDA 19-618 manufactured by Solvay Pharmaceuticals containing mesalamine. There is no unexpired marketing exclusivity for Rowasa Rectal Suspension Enema under section 505(j)(4)(D) of the Act. There are two unexpired patents listed:

- U.S. Patent # 4657900, expiration date April 14, 2004
- U.S. Patent # RE33239, expiration date May 12, 2004

Agis has submitted a Paragraph III Certification Statement for these patents.

10. PHARMACOLOGICAL CATEGORY:

Treatment of mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 4 g/60 mL Unit Dose

13. ROUTE OF ADMINISTRATION: Rectal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note17]:

SPOTS product – Form Completed

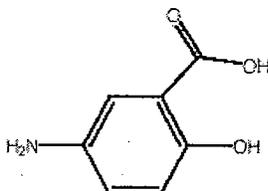
Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Mesalamine
 5-Aminosalicylic acid
 5-amino-2-hydroxybenzoic acid

Chemical Structure:



Molecular Formula: $C_7H_7NO_3$
 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Inadequate	3/1/04	
/	III	/	/	4	NA		

¹ 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")

² Adequate, Inadequate, or NA (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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Rowasa Rectal Suspension Enema	NDA 19-618	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	Nov 4, 2003	S. Adams
Methods Validation	NA		
Labeling	Acceptable(only after May 12, 2004)	3/4/04	K. Lee
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for ANDA # 76-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

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

The active pharmaceutical ingredient, Mesalamine is believed to be the therapeutically active component of Sulfasalazine used in treatment of mild to moderate ulcerative colitis. The mechanism of action of Masalamine is unknown and appears to be topical rather than systemic. All the tests described for the drug substance are compendial tests.

The drug product is Mesalamine Rectal Suspension (Enema), packaged in unit-dose containers (4 g/60 mL). The manufacturing process involves _____

_____ The product is packaged as unit dose containers containing 4 g of Mesalamine in 60 mL suspension.

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

The product is intended for rectal instillation once a day, preferably at bedtime and retained in the body for eight hours. Detailed instructions are provided in the patient instructions which are included along with the insert.

C. Basis for Approvability or Not-Approval Recommendation

A couple of minor issues remain to be resolved.



III. Administrative

A. Reviewer's Signature

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/Review Chemist
HFD-645/BTArnwine/Team Leader
HFD-617/NLee/Project Manager

C. CC Block

ANDA 76-751
DIV FILE
Field Copy

**APPEARS THIS WAY
ON ORIGINAL**

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CHEMISTRY REVIEW #2



33. ESTABLISHMENT INSPECTION

Acceptable by S. Adams, November 4, 2003

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The firm claims a categorical exclusion from the requirement of an Environmental Impact Analysis statement under 21 CFR sec §25.31(a).

**APPEARS THIS WAY
ON ORIGINAL**



36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-751

APPLICANT: Agis Industries (1983) Ltd.

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 g/60 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. _____

2. Since Mesalamine Rectal Suspension is a USP product, stability specifications for Impurities should match USP limits for the product.
3. _____

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-751
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/3/1/04

HFD-645/BTArnwine/3/24/04

HFD-617/NLee/3/24/04

Read 3/25/04

B. Arnwine 3/25/04

N 3/26/04

F/T by: EW 3/25/04

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TYPE OF LETTER: Not Approvable (Minor)

**APPEARS THIS WAY
ON ORIGINAL**

APPEARS THIS WAY
ON ORIGINAL

~~ANDA #76-751~~

Mesalamine Rectal Suspension, USP

Agis Industries (1983) Ltd.

**Shahnaz Read
Office of Generic Drugs, Division of Chemistry II**

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A. Reviewer's Signature	8
B. Endorsement Block	8
C. CC Block.....	8
Chemistry Assessment	9



Chemistry Review Data Sheet

1. ANDA # 76-751
2. REVIEW #: 3
3. REVIEW DATE: May 6, 2004, revised June 18, 2004
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	May 30, 2003
Acknowledgement Letter	August 25, 2003
Minor Amendment	February 19, 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	April 6, 2004
Telephone Amendment	May 5, 2004
Telephone Amendment	June 17, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Agis Industries (1983) Ltd.
Address:	Industrial Zone Yeruham, Israel 80500
Authorized U.S. Agent	Clay-Park Labs, Inc. 1701 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
- b) Non-Proprietary Name (USAN): Mesalamine Rectal Suspension, USP

9. LEGAL BASIS FOR SUBMISSION:

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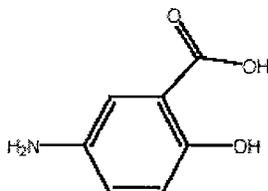
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Chemistry Review Data Sheet

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Chemical Structure:



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 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	I	Adequate	4/27/2004	
/	III	/	/	4	NA		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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2 – Type 1 DMF

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4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or NA (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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Rowasa Rectal Suspension Enema	NDA 19-618	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
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Methods Validation	NA		
Labeling	Acceptable(only after May 12, 2004)	3/4/04	K. Lee
Bioequivalence	Acceptable	3/23/2004	M. Makary
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for ANDA # 76-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approve

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

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C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved.



III. Administrative

A. Reviewer's Signature

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/Review Chemist
HFD-645/BTArnwine/Team Leader
HFD-617/NLee/Project Manager

C. CC Block

ANDA 76-751
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Field Copy

**APPEARS THIS WAY
ON ORIGINAL**

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CHEMISTRY REVIEW #3



CHEMISTRY REVIEW



Chemistry Assessment Section

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The firm claims a categorical exclusion from the requirement of an Environmental Impact Analysis statement under 21 CFR sec §25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

None.

APPEARS THIS WAY
ON ORIGINAL



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-751
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/5/6/04, revised 6/18/04 *Read 6/22/04*
HFD-645/BTArnwine/5/13/04/ 6/21/04 *(B) Arnwine 6/22/04*
HFD-617/NLee/5/10/04; 6/18/04

F/T by: EW 5/13/04

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TYPE OF LETTER: Approvable