

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

LABELING REVIEW(S)

(3-1)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-751

Date of Submission: May 30, 2003

Applicant's Name: Agis Industries (1983) Ltd.

Established Name: Mesalamine Rectal Suspension USP, 4 g/60 mL

Labeling Deficiencies:

1. CONTAINER (60 mL unit-dose)
 - a. We encourage you to increase the prominence of "potassium metabisulfite".
 - b. Revise the storage temperature statement to "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".
 - c. Increase the prominence of "For Rectal Use Only".
2. CARTON (7 x 60 mL unit-dose bottles)

See CONTAINER comments
3. INSERT
 - a. We encourage you to add the full text of the patient instructions at the end of the labeling.
 - b. Although the reference listed drug does not refer to the patient instructions in the PRECAUTIONS section, we encourage you to add a statement to that section that refers to the patient instructions.
- b. HOW SUPPLIED

See CONTAINER comment (b).
4. PATIENT INSTRUCTIONS

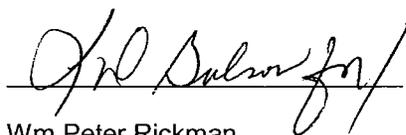
Please explain how the patient instructions will accompany the drug product.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm Peter Rickman", written over a horizontal line.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note:		x	

Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X See FTR 10		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING : ROWASA ® NDA 19-618/S-013, approved October 1, 2001
2. INACTIVE INGREDIENTS (pages 42 and 2836)

Ingredient	Function	%w/w	AND A Batch
Mesalamine, USP*	Active	6.800	
Edetate Disodium, USP			
Carbomer 934P, NF			
Xanthan Gum, NF			

Potassium Acetate, USP					
Sodium Benzoate, NF					
Potassium Metabisulfite, NF					
Purified Water, USP					

preservative agent

3. PATENTS/EXCLUSIVITIES

Patent Data

represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Certification
019618	001	#4657900	APR 14,2004	PIII	None
019618	001	#RE33239	MAY 12,2004	PIII	None

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There is no unexpired exclusivity for this product	

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight, light-resistant containers.
- NDA: Store at controlled room temperature 20° to 25° C (68° to 77°F).
- ANDA: Store at controlled room temperature 20° to 25° C (68° to 77°F). (Chemistry comment -Accelerated (40 °C/75% RH) stability data are provided for packaged lot #ML002 and #ML003 tested at initial, 1, 2 and 3 months. Thermal cycling data has also been provided. The data are adequate and within the specified limits. The antimicrobial effectiveness testing on pages 4577-4594 show that the product passes the USP criteria for antimicrobial effectiveness at all concentrations of sodium benzoate 0% to 100%.)

5. DISPENSING STATEMENT COMPARISON

- NDA: Dispense in original foil-wrapped package.
- ANDA: Dispense in original foil-wrapped package.

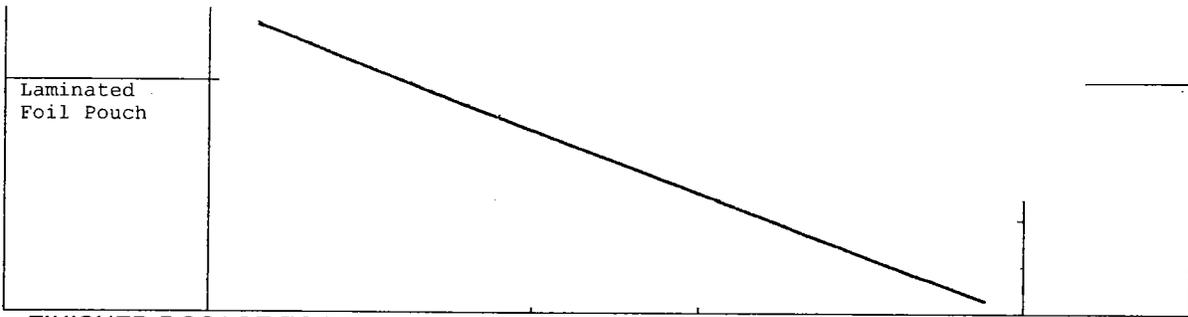
6. PACKAGE CONFIGURATION

- NDA: 7 X 60 mL Unit-Dose Bottles
- ANDA: 7 X 60 mL Unit-Dose Bottles

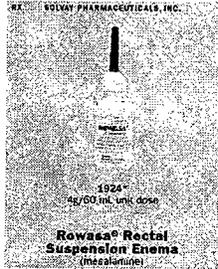
7. CONTAINER/CLOSURE

Summary of packaging systems (page 3361):

Component Description	Component Manufacturer	Materials of Construction	DMF #
60 mL Round bottle	/	/	/
Screw Cap Applicator Tip			
Tray			



8. FINISHED DOSAGE FORM



- NDA:
- ANDA: 60 mL round bottles with screw cap applicator tip wrapped in a laminated foil pouch.

9. The Manufacturer of this drug product is:

Agis Industries (1983) Ltd.
Industrial Zone
Yeruham 80500
Israel

10. This drug product contains potassium metabisulfate. The sulfite warning statement is included in the WARNINGS section per 21 CFR 201. 22.

Date of Review: 12/10/03

Date of Submission: May 30, 2003

Primary Reviewer: Koung Lee *KL*

Date: *02/24/03*

Team Leader: Lillie Golson *L Golson*

Date: *12/24/03*

cc:

ANDA: 76-751
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\Agis\LTRS&REV\76751.NA1.Labeling
Review

APPROVAL SUMMARY
(Only in effect after May 12, 2004)
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH

ANDA Number: 76-751

Date of Submission: May 30, 2003

Applicant's Name: Agis Industries (1983) Ltd.

Established Name: Mesalamine Rectal Suspension USP, 4 g/60 mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES

	Date Submitted	Code	Recommendation
Container (4gram/60 mL)	2/19./04	LCPL09846-4X N0204	Acceptable for Approval
Carton (7X60 mL Unit-Dose Bottles)	2/19./04		Acceptable for Approval
INSERT	2/19./04	I144-4X N0403	Acceptable for Approval
PATIENT INSTRUCTIONS	2/19./04	I098-4X N0403	Acceptable for Approval

- Revisions needed post-approval: Yes

Revise the title of the package insert to read "Mesalamine Rectal Suspension, USP (Enema) 4 grams/unit (60 mL)

BASIS OF APPROVAL:

- Was this approval based upon a petition? None
- What is the RLD on the 356(h) form: Rowasa
- NDA Number: 19-618
- NDA Drug Name: Rowasa
- NDA Firm: Solvay Pharmaceuticals, Inc.
- Date of Approval of NDA Insert and supplement #: October 1, 2001; S-013
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by Side
- Basis of Approval for the Carton Labeling: Side by Side

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x

Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
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Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
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Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X See FTR 10		

Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
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Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
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FOR THE RECORD:

- MODEL LABELING : ROWASA ® NDA 19-618/S-013, approved October 1, 2001
- INACTIVE INGREDIENTS (pages 42 and 2836) Consistent

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Edetate Disodium, USP			
Carbomer 934P, NF			
Xanthan Gum, NF			
Potassium Acetate, USP			
Sodium Benzoate, NF	preservative agent		
Potassium Metabisulfite, NF			
Purified Water, USP			

3. PATENTS/EXCLUSIVITIES

Patent Data

represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Certification
019618	001	#4657900	APR 14, 2004		PILL None

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
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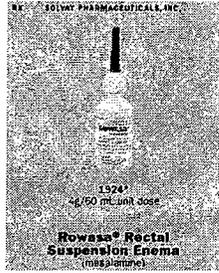
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Summary of packaging systems (page 3361):

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Tray			
Laminated Foil Pouch			

8. FINISHED DOSAGE FORM



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Agis Industries (1983) Ltd.
Industrial Zone
Yeruham 80500
Israel
10. This drug product contains potassium metabisulfate. The sulfite warning statement is included in the WARNINGS section per 21 CFR 201. 22.

Date of Review: February 26, 2004

Date of Submission: February 19, 2004

Primary Reviewer: Koung Lee

Date: 3/4/04

Team Leader: Lillie Golson

Date: 3/4/04

cc:

ANDA: 76-751
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\Agis\LTRS&REV\76751.AP.Labeling
Review