

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206966Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 5, 2020
From: Hamid Shafiei, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products 2
Office of New Drug Products

To: To Executive Summary, IQA for Assessment # 2 of NDA 206966

Subject: Final OPQ Recommendation of Approval

At the time of the review of the resubmission of this NDA and the memorandum to the review dated May 4, 202, this application was recommended for complete response from the OPQ perspective due to the following deficiencies:

- 1) The required preapproval inspection of the drug substance testing facility [REDACTED] (b) (4) associated with COVID-19 pandemic.
- 2) The CMC issues on labels/labeling have not been satisfactorily resolved in this review cycle.

These deficiencies were communicated to the applicant in a Discipline Review Letter dated May 4, 2020. In response, the applicant decided to removed [REDACTED] (b) (4); as the proposed commercial drug substance testing site and move the testing responsibility to two alternative testing sites that were recently inspected and are currently in good-standing with the Agency regarding the current good manufacturing practices. Subsequently, to allow timely review of the proposed new testing facilities for the commercial drug substance, the Agency submitted a Major Amendment Letter dated May 12, 2020 to inform the applicant that the review clock for this application will be extended by 90 days

The proposed two new drug substance testing facilities have been reviewed by the facilities reviewer, Dr. Aditi Thakur. Dr. Thakur has found the proposed new testing facilities adequate to support the approval of this application. (see Attachment I for the review).

Also, on June 1, 2020 the applicant submitted updated PI labeling and container/carton labels. The updated PI labeling and container/carton labels have been reviewed by the drug product reviewer, Dr. Venkateswara Pavuluri. Dr. Pavuluri has found that the

updated labeling/labels have adequately addressed all CMC deficiencies that were noted during the second review cycle for this application (see Attachment II).

Therefore, from the OPQ perspective, this NDA is now recommended for **approval** with the expiration dating period of **36 months**.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch V/DNDP 2/ONDP/OPQ

Attachment I

Manufacturing Assessment Review Addendum #2

NDA 206966 Abametapir 0.74%w/w Dr. Reddy's Laboratories, SA

Reviewer's note:

NDA 206966 was reviewed and found inadequate per N206966 Manufacturing- (b) (4) on 04/17/2020 and Manufacturing Assessment Review Addendum on 05/04/2020. This Addendum #2 review is documenting the assessment for the applicant's response to the Agency's Discipline Review Letter dated May 4, 2020.

Dr. Reddy's acknowledged and recognized the delay in completing the (b) (4) (b) (4) due to the effect of the COVID-19 pandemic on conducting site inspections. Applicant proposed to replace (b) (4) with two alternative analytical laboratories to perform the (b) (4) testing for the release of drug substance. The relevant information was submitted in Quality/Response to Information request (0030) on May 12, 2020:



Reviewers' assessment: Applicant has provided all the relevant information and updated the Section 3.2.S.2.1 and Form 356h which are included in this submission. They also committed to submit an appropriate supplement should they wish to rely on testing from (b) (4) in the future.

1. (b) (4) is a contract testing lab that provides analytical and microbial testing of finished human pharmaceuticals and raw materials to various pharmaceutical customers. The firm has a good inspection history with three NAIs and one VAI inspections since (b) (4). The most recent inspection was conducted in (b) (4). It was a comprehensive routine surveillance inspection. During the inspection, various documents such as Standard operating procedures (SOPs), Change Controls, Investigations, Equipment Qualification, Analytical Methods, Instrument usage logs, Calibration records, Stability program and Employee training records, were reviewed. No FDA 483 form was issued to the firm at the end of the inspection. The firm is acceptable based on its inspection history and its testing capability to perform the (b) (4) testing.
2. (b) (4) is a contract testing lab that provides analytical and microbial testing of finished human pharmaceuticals and raw materials to various pharmaceutical customers. The most recent surveillance and PAI inspection was

conducted in (b) (4) The firm was initially classified as pOAI, however it was downgraded to VAI after the review of the response to the observations. This firm is listed as the (b) (4) testing facility in several approved submissions. Given the firm's acceptable compliance status, the firm is considered acceptable to perform the specified testing.

Recommendation:

Following a review of the application, pre-approval inspection results, and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 206966 are found to be acceptable.

Primary Drug Product Reviewer Name and Date: Aditi Thakur 05/28/2020

Secondary Reviewer Name and Date: Derek Smith 6/2/2020



**Aditi
Thakur**

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**Derek
Smith**

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Attachment II

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: Jun 03, 2020

From: Venkateswara R. Pavuluri, Ph.D., R. Ph.
Drug Product Reviewer
Office of New Drug Products
Branch IV/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Office of New Drug Products
Branch IV/DNDP II

To: CMC Labeling Review #1 of NDA 206966
for XEGLYZE® Lotion
Subject: Final Recommendation - APPROVAL

At the time when Labeling Review of NDA 206966 was completed upon resubmission, on 28-MAY-2020, this NDA was not recommended for approval per 21 CFR 314.125(b)(8). Specifically, it was noted that **Description** section and **Address** at the end of the Prescribing Information, and carton and container labels were not acceptable as presented and did not comply with the requirements under 21 CFR 201.10(g)(1) and 21 CFR 201.1(i) respectively. The NDA for this drug product was otherwise complete and adequate from the drug product perspective up on resubmission, in 2nd review cycle, per drug product review dated 10-APR-2020.

This labeling addendum is to document the most updated information in packaging insert (**Attachment-1**), and carton and container labels (**Attachment-2**) as submitted on Jun 1, 2020. The labeling and labels are now acceptable from the CMC labeling perspective.

Recommendation:

The outstanding CMC label/labeling issues have been satisfactorily resolved. This application is now recommended for **approval** from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, Ph. D., R. Ph.
Drug Product Reviewer
Branch IV, Division II, ONDP

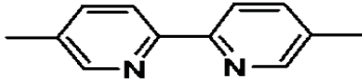
Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch IV, Division II, ONDP

Attachment-1: Prescribing Information /Package Insert submitted on Jun 1, 2020 SN0031:

11 DESCRIPTION

The active pharmacological ingredient in XEGLYZE (abametapir) Lotion is the pediculicide, abametapir, which is a dipyridyl compound. The chemical name of abametapir is 5,5'-dimethyl-2,2'-bipyridinyl.

The structural formula is:



The empirical formula is $C_{12}H_{12}N_2$ and the molecular weight is 184.24.

XEGLYZE is a white to off-white oil in water emulsion, containing 0.74% [weight by weight] of abametapir, intended for topical administration. XEGLYZE contains the following inactive ingredients: benzyl alcohol, butylated hydroxytoluene, carbomer 980, light mineral oil, polysorbate 20, trolamine and water.

Address after section 17

Manufactured by Groupe Parima Inc., for Dr. Reddy's Laboratories, S.A. Elisabethenanlage 11, 4051 Basel, Switzerland

Distributed by Dr. Reddy's Laboratories Inc., 107 College Road East, Princeton, NJ 08540

XEGLYZETM is a registered trademark of Dr. Reddy's Laboratories, S.A.

Issued: XX / 20XX

Product Insert Item Number Here

**Attachment-2: Carton and Container Labels submitted
on Jun 1, 2020 SN0031:**

Carton and Container Labels for XEGLYZE® Lotion

Carton:



Container Label:



APPEARS THIS WAY ON ORIGINAL



Venkateswara
Pavuluri

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Moo Jhong
Rhee

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Hamid
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/s/

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 4, 2020
From: Hamid Shafiei, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products 2
Office of New Drug Products

To: To Executive Summary, IQA for Assessment # 2 of NDA 206966

Subject: Final Recommendation of “Complete Response”

At the time of the review of the resubmission of this NDA, the Office Pharmaceutical Manufacturing Assessment had made a recommendation of “Withhold” for the drug substance manufacturing facility, Dr. Reddy’s Lab Ltd. CTO Unit VI (FEI 3002949085). As of April 30, the status for this manufacturing facility has been changed to “Compliant”. However, the following deficiencies still exist:

- 1) The required preapproval inspection of the drug substance testing facility [REDACTED] (b) (4) [REDACTED] still pending due to travel restrictions associated with COVID-19 pandemic, and OPMA has made a final recommendation of [REDACTED] (b) (4) for the facility (see the OPMA email recommendation in Attachments I and the signed OPMA review addendum in Attachment II).
- 2) The resolution of the currently pending CMC labels/labeling issues have been deferred to next review cycle.

Therefore, from the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

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Attachment II: Signed OPMA Review Addendum (next page)



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Shafiei

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Manufacturing Assessment Review Addendum

NDA 206966

Abametapir 0.74%w/w

Dr. Reddy's Laboratories, SA

Reviewer's note:

NDA 206966 was reviewed and found inadequate per N206966 Manufacturing-R02 on 04/17/2020. This addendum review is documenting a modification to the assessment deficiencies due to change in the compliance status of the drug substance manufacturing facility, Dr. Reddy's Laboratories Limited (FEI 3002949085). The initial classification of the inspection date 01/20-28/2020 was pOAI. On 04/30/2020, the firm's responses and the proposed corrective actions were found to satisfactorily address the inspection observations, and consequently, the classification for the associated PAC code 56002 was downgraded to VAI for CGMP based on the surveillance coverage. The reclassification memo is still in draft however, the email notification was provided to the Office of Pharmaceutical Manufacturing Assessment by the Office of Manufacturing Quality on 04/30/2020 and alert was generated in panorama as well.

Most of the observations during the January 2020 inspection were related to the manufacturing of a different drug substance at the facility. Given that no manufacturing risk was noted for NDA 206966 operations, the data integrity assessment provided in support of NDA 206966 found no significant issues, OMQ has determined the facility is acceptable for CGMPs, this facility is now determined to be acceptable for NDA 206966.

While this recommendation has changed from the previous 4/17/2020 review, there remains a significant outstanding, facility risks that prevents approval of this application. Due to past inspection history noting data integrity concerns, a preapproval inspection of a drug substance testing facility (b) (4) was requested during the review cycle. However, due to the travel restrictions at the time of the current review cycle therefore the PAI could not be performed.

Therefore, the following deficiency, as well as an administrative comment, are still not resolved:

1. An inspection of (b) (4) facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel to (b) (4) we were unable to conduct an inspection during the current review cycle for your application. You may respond

to the other deficiencies in this Complete Response letter while the travel restrictions remain in effect. However, even if all other deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to your application.

2. Please note that there is a testing facility used for elemental impurities analysis included in your submission for Abametapir lotion 0.74% that was not included on your form 356h or Module 3. Please update your NDA (356h and Module 3) with all facilities and to include the specific their responsibilities.

Recommendation: The manufacturing facilities listed for NDA 206966 are not acceptable at this time

Primary Drug Product Reviewer Name and Date: Aditi Thakur 05/02/2020

Secondary Reviewer Name and Date: Derek Smith 05/04/2020



Aditi
Thakur

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Derek
Smith

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/s/

HAMID R SHAFIEI
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Office of Pharmaceutical Quality

New Drug Application (NDA)

Integrated Quality Assessment Template

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 206966 Assessment # 2

Drug Product Name	XEGLYZE® (abametapir)
Dosage Form	Lotion
Strength	0.74%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
NDA 206966 Resubmission	11/12/2019	All
Response to Quality Information Request	04/13/2020	OPQ - OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett, Ph.D.	Donna Christner, Ph.D.
Drug Product	Venkateswara Pavuluri, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Aditi Thakur, Ph.D.	
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Melinda Bauerlien, MS	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(1) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substance, abametapir and the drug product, Xeglyze (abametapir) Lotion, 0.74% for topical use.
- However, the Office of Pharmaceutical Manufacturing Assessment has made a “**Withhold**” recommendation for the drug substance manufacturing site, FEI 3002949085 due to unresolved cGMP issues. Additionally, there is a **pending of the required preapproval inspection** of drug substance testing site, FEI (b) (4) due to current travel restrictions.
- The CMC issues on labels/labeling have **not** been satisfactorily resolved in this review cycle.
- The applicant request’s for categorical exclusion from the environmental assessment has been granted (see the original IQA dated April 22, 2016).

Therefore, from the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Dr. Reddy’s Laboratories, Inc. has resubmitted this 505(b)(1) new drug application for Xeglyze® (abametapir) Lotion, 0.74% intended for the topical treatment of head lice in patients 6 months of age or older. The active ingredient, abametapir is a pediculicide (b) (4)

This application had been originally submitted on September 14, 2015 and received Complete Response on August 30, 2016 due to inadequate cGMP compliance of drug substance manufacturing facility, Dr. Reddy’s Lab Ltd. CTO Unit VI (FEI 3002949085). This application has been resubmitted on November 12, 2019 as a class 1 resubmission. This submission includes a new site as an alternative drug substance manufacturing facility, additional drug product information and stability data, and updated manufacturing process and facilities information.

Xeglyze® will be packaged and marketed as (b) (4) lotion in a 250 mL single-use amber USP Type (b) (4) glass bottle affixed with a

polypropylene child resistant closure featuring a Tri-Foil (b) (4) liner.

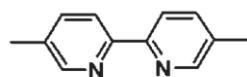
Refer to the original IQA by Dr. Yichun Sun dated April 22, 2016 for information regarding the previous review of this application.

Proposed Indication(s) including Intended Patient Population	Topical treatment of head lice infestation in patients 6 months of age and older.
Duration of Treatment	Massage XEGLYZE Lotion into the scalp and throughout the hair; Leave the lotion on the hair and scalp for 10 minutes and then rinse off with warm water.
Maximum Daily Dose	One 250-mL bottle containing up to 210mL of lotion
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The active ingredient, abametapir is a pediculicide (b) (4). Abametapir is a white to pale yellow solid that has an empirical formula of $C_{12}H_{12}N_2$, a molecular weight of 184.24, and the chemical structure below:



It has a melting temperature range of (b) (4) °C and it is not a hygroscopic drug substance. Abametapir is insoluble in water; sparingly soluble in hexane and petroleum ether; soluble in acetonitrile, diethyl ether, dimethyl sulfoxide, isopropyl alcohol, and propylene glycol; freely soluble in acetic acid, acetone, benzene, benzyl alcohol, chloroform, dimethylformamide, dioxane, ethanol, ethyl acetate, methanol and tetrahydrofuran. The partition coefficient (logP) of the drug is determined to be 2.13 at pH 7.0.

Abametapir is produced by (b) (4)

The equivalency of the drug substance manufactured at the new proposed alternative site, (b) (4) and the original site, Dr. Reddy's Lab Ltd. CTO Unit VI has been established.

Abametapir is tested against an adequate specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months.

The drug substance section of this resubmission has been reviewed by Dr. Friedrich Burnett. Dr. Burnett has found the drug substance section of this resubmission adequate to support the approval of this application. Dr. Burnett's review is provided in the Drug Substance Chapter of the IQA.

Refer to Dr. Yichun Sun's IQA dated April 22, 2016 for information regarding the review of the drug substance in the original submission of this application.

Drug Product: Adequate

The drug product, XEGLYZE (abametapir) Lotion, is a viscous, white to off-white oil in water emulsion, containing 0.74% w/w of abametapir. Abametapir is a pediculicide and is indicated for the topical treatment of head lice infestation (*Pediculus humanis capitis*) in patients 6 months of age and older.

The inactive ingredients used in XEGLYZE lotion are water, light mineral oil, polysorbate 20, carbomer 980, trolamine, butylated hydroxytoluene and benzyl alcohol.

XEGLYZE lotion is packaged in a 250 mL single-use amber USP Type (b) (4) glass bottle affixed with a polypropylene child resistant closure featuring a Tri-Foil (b) (4) liner for a single use. The bottle is safety coated with (b) (4) polyvinyl chloride (PVC) (b) (4)

XEGLYZE lotion is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 36 months. The applicant has provided sufficient stability data in support of the proposed drug product expiration dating period.

The drug product section of this resubmission has been reviewed by the Drug Product Reviewer, Dr. Venkateswara Pavuluri. Dr. Pavuluri has found the information provided the drug product section of this resubmission adequate to support the approval of this application. Dr. Pavuluri has requested that the following comment to be conveyed to applicant regarding the post-approval stability commitment.

“Provide a written commitment under section 3.2.P.8.2 Post Marketing stability commitments, (b) (4)

Dr. Pavuluri’s review is provided in the Drug Product Chapter of this resubmission IQA.

For information regarding the drug product review of the original submission of this application, refer Dr. Yichun Sun’s IQA dated April 22, 2016.

Labeling: Inadequate

The PI labeling as well as container and carton labels deficiencies noted the original IQA dated April 22, 2016 were not appropriately addressed since this application received CR in August 30, 2016. This application will be receiving CR again in the current review cycle, and therefore, PI labeling as well as container and carton label deficiencies will not be addressed at this time.

Manufacturing: Inadequate

The manufacturing process for XEGLYZE (abametapir) Lotion comprises of the (b) (4) The manufacturing process for this application was previously reviewed during the first review cycle by Dr. Yaodong Huang. Dr Huang had found the manufacturing process and the proposed process controls for the control of the critical manufacturing steps adequate to support the approval of the application from the process perspective. Dr. Huang’s review is captured in the original IQA dated April 22, 2016.

The drug substance and drug product facilities involved in this application were previously reviewed by Dr. Quallyna N. Porte during the first review cycle. Based on the results from the inspection of the drug substance manufacturing site, Dr. Reddy’s Lab Ltd. CTO Unit VI (FEI 3002949085), Dr. Porte had found this site inadequate to support the approval of this application from the facilities perspective until satisfactory resolution of all cGMP deficiencies noted by the field investigator. Due to recommendation of withhold for this site, this application received a CR during the first review cycle. Dr. Porte’s review is also captured in the original IQA dated April 22, 2016.

The additional manufacturing process and facilities information including information regarding the proposed new alternative drug substance manufacturing site, (b) (4) provided in the resubmission has been

reviewed by Dr. Aditi Thakur. Dr. Thakur has found the manufacturing process provided in the resubmission adequate. However, Dr. Thakur has again found the drug substance manufacturing site Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) as inadequate and has made a recommendation of "withhold" for this site due to outstanding cGMP deficiencies. Also, due to travel restrictions, there is a pending of a required PAI of the drug substance testing site, (b) (4). In addition to facilities deficiencies, Dr. Thakur has also requested that the following comment be conveyed to the applicant:

"Please note that there is a testing facility used for elemental impurities analysis included in your submission for Abametapir lotion 0.74% that was not included on your form 356h or Module 3. Please update your NDA (356h and Module 3) with all facilities and each facility's specific responsibility."

In summary, Dr. Thakur has found the overall facilities involved in this NDA inadequate to support the approval of the application.

Biopharmaceutics: Adequate

No biopharmaceutics review is performed in this review cycle since no additional biopharmaceutics information was provided in the resubmission of this application. For biopharmaceutics review, refer to the original IQA dated April 22, 2016.

Microbiology (if applicable): Adequate

No microbiology review is performed in this review cycle since no additional microbiology information was provided in the resubmission of this application. For microbiology review, refer to the original IQA dated April 22, 2016.

C. Risk Assessment: See the IQA by Dr. Yichun Sun Date April 22, 2016

D. List of Deficiencies for Complete Response

1. Drug Product

The following information request should be included in the CR letter as an additional comment:

- Provide a written commitment under section 3.2.P.8.2 Post Marketing Stability Commitments, to immediately discuss any deviations of batches from the approved specifications with the Agency and to withdraw the affected lots from the market as warranted.

2. Labeling Deficiencies

CMC PI labeling as well as container and carton labels deficiencies were delineated in the first cycle of labeling/label by Dr. Bhavishy Mittal. However, these deficiencies were not discussed with the applicant as this application received CR.

No additional labeling/label review is conducted at this time since this application will again receive CR during this review cycle.

3. Manufacturing Deficiencies

- 1) Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) has been given a "Withhold" recommendation until cGMP deficiencies of the site is satisfactorily resolved.
- 2) PAI of the drug substance testing site, (b) (4) is conducted with a satisfactory inspection conclusion.
- 3) Please note that there is a testing facility used for elemental impurities analysis included in your submission for Abametapir lotion 0.74% that was not included on your form 356h or Module 3. Please update your NDA (356h and Module 3) with all facilities and each facility's specific responsibility

Application Technical Lead:

Hamid Shafiei, Ph.D.
Brach V/DNDP II/ONDP/OPQ



Hamid
Shafiei

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QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	Adequate	Refer to the IQA dated April, 2016	Assessed during the first review cycle
	III			Adequate	Refer to the IQA dated April, 2016	Assessed during the first review cycle
	III			Adequate	Refer to the IQA dated April, 2016	Assessed during the first review cycle
	III			Adequate	Refer to the IQA dated April, 2016	Assessed during the first review cycle
	III			Adequate	Refer to the IQA dated April, 2016	Assessed during the first review cycle

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
EOP2 Meeting Minutes	77510	Discussions of the clinical development plan for IND 77510
Advice/Information Request Letter	77510	Requesting the sponsor to add additional tests to the drug product specification
Pre-NDA Meeting Minutes	77510	Discussion of the content and format of the proposed

		NDA submission for Xeglyze (abametapir) topical lotion, 0.74%

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

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Aditi
Thakur

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Derek
Smith

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/s/

HAMID R SHAFIEI
04/23/2020 11:14:04 AM

**Recommendation:**

This 505(b)(1) NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(6),(13).

NDA 206966

Review 1

Drug Name/Dosage Form	ABAMETAPIR LOTION (XEGLYZE)
Strength	0.74%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	9/14/2015	N/A
Amendment	1/20/2016	Drug product, process and quality microbiology
Amendment	2/2/2016	Biopharmaceutics
Amendment	2/19/2016	Drug product (labeling and labels)
Amendment	2/24/2016	Process
Amendment	3/10/2016	Quality microbiology
Amendment	3/30/2016	Drug product
Amendment	3/30/2016	Environmental assessment
Amendment	4/10/2016	Drug product

Quality Review Team

Discipline	Reviewer	Secondary	Branch/Division
Drug Substance	Xavier Ysern	Donna Christner	Branch II/Division of New Drug API
Drug Product	Bhavishya Mittal	Moo-Jhong Rhee	Branch V/Division of New Drug Products II
Process	Tony (Yaodong) Huang	Nallaperumal Chidambaram	Branch VIII/Division of Process Assessment III
Microbiology	Eric Adeeku	Jesse Wells	Branch I/Division of Microbiology Assessment
Facility	Quallyna Porte	Christina Capacci-Daniel	Branch II/Division of Inspection Assessment
Biopharmaceutics	Vidula Kolhatkar	Kelly Kitchens	Branch II/Division of Biopharmaceutics
Regulatory Business Process Manager	Maria Cowan	N/A	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Moo-Jhong Rhee	Branch V/Division of New Drug Products II
Environmental Assessment (EA)	Raanan Bloom	Scott Furness	Environmental Assessment Team/Office of New Drug Products

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
(b) (4)	Type III		(b) (4)	3	Adequate	Last review in DAARTS was done by Dr. G. Gill-Sangha on 09/04/2013.
	Type III		4	Adequate	Last review in DAARTS was done by Dr. D. Chiapperino on 02/27/2004. However, this review is not available electronically.	
	Type III		3	Adequate	Last review in DAARTS was done by Dr. P. Jiang-Baucom on 03/25/2016.	
	Type III		4	Adequate	This DMF has never been reviewed in DAARTS. However, the colorant is part of the cap and sufficient information is provided for the cap in the NDA.	
	Type III		4	Adequate	Last review in DAARTS was done by Dr. D. N. Klein on 10/02/2012 for F-217 liner and was found to be adequate.	

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 N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP2 Meeting Minutes	77510	Discussions of the clinical development plan for IND 77510
Advice/Information Request Letter	77510	Requesting the sponsor to add additional tests to the drug product specification
Pre-NDA Meeting Minutes	77510	Discussion of the content and format of the proposed NDA submission for Xeglyze

		(abametapir) topical lotion, 0.74%.

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	-----	N/A	-----	-----
Pharmacology/Toxicology	-----	N/A	-----	-----
CDRH	-----	N/A	-----	-----
Clinical	-----	N/A	-----	-----
Other	-----	N/A	-----	-----

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product.

However, the Office of Process and Facility has made a “**Withhold**” recommendation for the drug substance manufacturing site due to unresolved cGMP issues.

Also, the issues on labels/labeling are not completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved. (See the **List of Deficiencies** on Page 114)

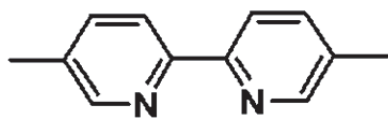
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance/active pharmaceutical ingredient (API) used in the drug product, (abametapir lotion), is abametapir. The chemical name of abametapir is: 5, 5'-dimethyl-2,2'-bipyridinyl. It has the following structural formula:



Abametapir is a white to pale yellow solid that has an empirical formula of $C_{12}H_{12}N_2$ and a molecular weight of 184.24. Abametapir melts in the temperature range of (b) (4)

C. Abametapir is insoluble in water; sparingly soluble in hexane and petroleum ether; soluble in acetonitrile, diethyl ether, dimethyl sulfoxide, isopropyl alcohol, and propylene glycol; freely soluble in acetic acid, acetone, benzene, benzyl alcohol, chloroform, dimethylformamide, dioxane, ethanol, ethyl acetate, methanol and tetrahydrofuran. The partition coefficient (logP) of the drug is determined to be 2.13 at pH 7.0. Abametapir drug substance is not hygroscopic.

The drug substance is chemically produced (b) (4)

implemented are: (b) (4)

In-process tests

(b) (4)

(b) (4)

The identity, strength, purity and quality of the drug substance are deemed assured by the drug substance specification. (b) (4)

(b) (4)

A re-test period of (b) (4) months is recommended for the drug substance when stored at (b) (4) in the proposed package.

B. Drug Product Quality Summary

The drug product, XEGLYZE (abametapir) Lotion, is a viscous, white to off-white oil in water emulsion, containing 0.74% w/w of abametapir. Abametapir is a pediculicide and is indicated for the topical treatment of head lice infestation (*Pediculus humanis capitis*) in patients 6 months of age and older. The inactive ingredients used in XEGLYZE lotion are water, light mineral oil, polysorbate 20, carbomer 980, trolamine, butylated hydroxytoluene and benzyl alcohol.

XEGLYZE lotion is packaged in a PVC safety-coated round amber glass bottle affixed with a white polypropylene child resistant cap featuring a tri-foil inner liner for single patient use. Approximately 7 oz. or 210 mL (200 g) of the lotion is filled into each bottle. (b) (4)

(b) (4)

XEGLYZE lotion is prepared by (b) (4) as shown below:

(b) (4)



(b) (4)

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. (b) (4)
 is being developed. The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on long-term and accelerated stability data obtained from 3 registration batches of the drug product, and 6 supportive batches of the drug product. The Environmental Assessment (EA) team finds that the NDA applicant's request for a categorical exclusion from an EA is acceptable.

However, the facility review team from the Office of Process and Facilities has recommended withholding approval of this application due to cGMP issues related to Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) manufacturing facility. Therefore, **Complete Response** is recommended for this NDA from the OPQ perspective.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	XEGLYZE
Non Proprietary Name of the Drug Product	Abametapir lotion
Non Proprietary Name of the Drug Substance	Abametapir
Proposed Indication(s) including Intended Patient Population	XEGLYZE Lotion is a pediculicide indicated for the topical treatment of head lice infestation in patients 6 months of age and older.
Duration of Treatment	Massage XEGLYZE Lotion into the scalp and throughout the hair; Leave the lotion on the hair and scalp for 10 minutes and then rinse off with warm water.
Maximum Daily Dose	210 mL (one bottle)
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: N/A
 - Drug Product: N/A

2. Biowaivers/Biostudies
 - Biowaiver Requests: N/A
 - PK studies: N/A

- IVIVC: N/A

(b) (4)



E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

Do not refrigerate or freeze.

G. Life Cycle Knowledge Information (see Attachment A)



OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Complete response is recommended for this NDA from the OPQ perspective.

**Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
4/20/2016**

**Yichun
Sun -S**

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ASSESSMENT OF THE BIOPHARMACEUTICS

(b) (4)

**Reviewer's Assessment:****The reviewer**

(b) (4)

24. *Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?*

The proposed commercial formulation was used in all clinical studies including Phase 3 studies except an initial tolerability Phase 1 study.

Applicant's Response: N/A



QUALITY ASSESSMENT



Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The reviewer

(b) (4)

Reviewer's Signature

Vidula Kolhatkar, Ph.D.

Branch II

Division of Biopharmaceutics/ONDP

04/12/16

**Tapash K.
Ghosh -S**

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Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics assessment, and I concur with the comments conveyed to the Applicant.

Kelly M. Kitchens, Ph.D.

Quality Assessment Lead (Acting)

Division of Biopharmaceutics, Branch II

April 12, 2016

**Tapash K.
Ghosh -S**

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ASSESSMENT OF MICROBIOLOGY

The Agency’s 01/08/2016 and 02/04/2016 information requests addressed in the body of the review as comments (in italics) were responded to in the applicant’s 01/20/2016 and 03/10/2016 submissions respectively.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

Description of drug product –

(section 3.2.P.1)

Abametapir lotion 0.74 % is a white to off-white lotion consisting of an oil in water emulsion intended for external application to the skin. Xeglyze Lotion 0.74% is a lousicide and an ovicide indicated for the topical treatment of head lice infestation (*Pediculosis humanis capitis*) in patients 6 months of age and older.

Xeglyze Lotion 0.74% has demonstrated activity against head lice (b) (4)

**Drug product composition –
(section 3.2.P.1).**

Component	Quantity		Function
	Amount/unit (g/bottle)	% w/w	
Abametapir (5,5'-Dimethyl-2,2'- dipyridyl) (in-house)	(b) (4)	0.74	(b) (4)
Light mineral oil, NF (b) (4)		(b) (4)	
Polysorbate 20, NF			
Benzyl alcohol, NF			
Butylated Hydroxytoluene, NF			
Carbomer 980, NF (b) (4)			
Trolamine, NF			
Purified water, USP			

Description of container closure system –

(section 3.2.P.1; section 3.2.P.7).

The container closure system for the drug product consists of a 250 mL single-use amber USP Type (b) (4) glass bottle affixed with a polypropylene child resistant closure (CRC) featuring a tri-foil inner liner.

Component	Description	Manufacturer
Bottle	250 mL/45mm USP type (b) (4) amber glass bottle	(b) (4)
Cap	45 mm white polypropylene CRC cap	

Acceptable.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Antimicrobial Effectiveness Testing -

(section 3.2.P.2.5).

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

(section 1.14.1.3).

Xeglyze Lotion, 0.74 %, is a white to off-white liquid emulsion supplied in a PVC safety-coated ^{(b) (4)} (250 mL) amber glass ^{(b) (4)} with a polypropylene child resistant cap.

Store upright at room temperature 20 – 25 °C (68 – 77 °F) with allowable excursions between 15 °C and 30 °C (59 – 86 °F).

For single use. Discard any unused portion.

Do NOT refrigerate or freeze.

Keep out of reach of children.

Acceptable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: This NDA is recommended for approval.
No outstanding issues remain.

Reviewer's Signature

Adeeku, Eric, Ph.D.

Branch I

Division of Microbiology Assessment/OPF

Eric K. Adeeku - A

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Secondary Review Comments and Concurrence:

Supervisor's Signature

Jesse Wells, Ph.D.

Microbiology Secondary Reviewer, Branch I

Division of Microbiology Assessment/OPF

Jesse Wells -S

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ASSESSMENT OF ENVIRONMENTAL ANALYSIS

25. Is the applicant's claim for categorical exclusion acceptable?

26. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response: The applicant responded (3/30/16, SN0014) to the Agency's 3/21/16 IR by submitting an appropriate claim for categorical exclusion and statement of no extraordinary circumstances. In addition, the applicant confirmed that the production for sale volume is the highest quantity of the active moiety expected to be produced for use in any of the first five years. The applicant stated that there are currently no applications for this drug in other regulatory regions in response to the IR question pertaining to the availability of environmental risk assessments or summaries of environmental studies conducted in support of applications for this drug in other regulatory regions.

Reviewer's Assessment: Abametapir (5,5'-dimethyl 2,2'-bipyridinyl) is a metalloproteinase inhibitor with activity against head lice and their ova (eggs). It is extensively and rapidly metabolized, primarily by the cytochrome P450 enzyme CYP1A2 to a mono-hydroxylated metabolite (abametapir hydroxyl) and further to a mono-carboxylated metabolite (abametapir carboxyl). Excretion of drug-related material from rats following dermal administration of abametapir was primarily via urine (45%) and to a lesser extent via feces (18%). Environmental introduction of parent and metabolites would be expected through waste water systems.

Carcinogenic studies have not been conducted with Xeglyze lotion. Abametapir and abametapir carboxyl are not genotoxic. These compounds were not mutagenic in vitro in bacterial reverse mutation assays, and they were not clastogenic in an in vivo chromosome aberration assay in rats. No effects on fertility have been observed in rats following repeated doses of up to 75 mg/kg/day. No E, A, or T activity is noted. Interestingly, the toxic effects of 5,5'-dimethyl 2,2'-bipyridinyl is shown to be reversible following the addition of the metal ions. Environmental metals may thus modify the toxic properties of abametapir.

The applicant submitted a 5th year production estimate of (b) (4) kg. The provided Expected Introduction Concentration (EIC) of (b) (4) ug/L is in error. The value should be (b) (4) ug/L or an EEC of (b) (4) ng/L. A literature review did not result in any information indicating ecotox concern at the estimated levels of exposure. At these exposure concentrations, ecotox impacts would not be anticipated.

Abametapir will be introduced into the environment primarily through patient use. To minimize the amount of waste Xeglyze lotion that enters the environment, a recommendation is made to modify the label text, carton, and container instructions ("For single use. Discard any unused portion.") by adding the following phrase: "Do not flush contents down sink or toilet." In addition, the 'Patient Counseling Information' includes the following addition to the existing text ("Discard container after use."): "Do not flush contents down sink or toilet. Use a take-

back program or household waste.”

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the anticipated amount of abametapir to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL**Reviewer's Assessment and Signature:**

The claim of categorical exclusion is acceptable.

Reviewer's Signature**Raanan Bloom, Ph.D.****Environmental Assessment Team, ONDP****Raanan A.
Bloom -S**

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062595, cn=Raanan A. Bloom -S
Date: 2016.04.20 14:59:35 -04'00'

Secondary Review Comments and Concurrence:

Concur.

Supervisor's Signature**Scott Furness, Ph.D.****Deputy Director, ONDP****Michael S.
Furness -S**

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cn=Michael S. Furness -S
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**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1
Labeling Package Insert**

For NDA only

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

The highlights from the package insert are given below:



(b) (4)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	XEGLYZE (abametapir)	Adequate
Dosage form, route of administration	Lotion, Topical	Adequate
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	1 dosage form only (0.74% w/w)	Adequate

Conclusion:

The package insert is tentatively acceptable as it is going through a thorough review by all relevant disciplines.

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

Lotion, 0.74%.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Only one dosage form is available	Adequate
Strengths: in metric system	0.74% w/w	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Abametapir lotion 0.74% is a white to off white lotion consisting of homogeneous oil in water emulsion intended for external application to the skin. It is packaged in a 250 mL single-use amber USP (b) (4) glass bottle affixed with a 45 mm polypropylene child resistant closure (CRC) featuring a tri-foil inner liner. The container is filled to a nominal 200 g.	Adequate

Conclusion:

Satisfactory.

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

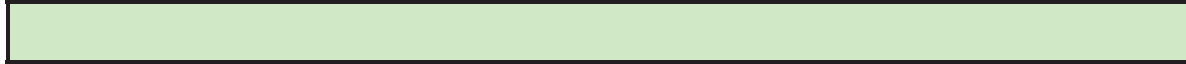


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	XEGLYZE (abametapir)	Adequate
Dosage form and route of administration	Lotion, Topical	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Yes, information is provided	Adequate
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	Abametapir is a metalloproteinase inhibitor with activity against head lice (b) (4)	Adequate
Chemical name, structural formula, molecular weight	Formula: C ₁₂ H ₁₂ N ₂ Molecular Weight: 184.24 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	White to pale yellow solid Melting point = (b) (4) °C Partition Coefficient (Log P @ pH = 7) = 2.13	Adequate

Conclusion:

Satisfactory.



#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Store upright at room temperature 20°C to 25°C (68° to 77°F) with allowable excursions between 15°C and 30°C (59°F and 86°F). Do NOT refrigerate or freeze.

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	0.74% w/w	Adequate
Available units (e.g., bottles of 100 tablets)	250 mL single-use amber USP (b) (4) glass bottle affixed with a 45 mm polypropylene child resistant closure (CRC) featuring a tri-foil inner liner. The container is filled to a nominal 200 g.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Abametapir lotion 0.74% is a white to off white lotion consisting of (b) (4) oil in water emulsion intended for external application to the skin. NDC # (b) (4)	Adequate
Special handling (e.g., protect from light, do not freeze)	Do NOT refrigerate or freeze.	Adequate
Storage conditions	Store upright at room temperature 20°C to 25°C (68° to 77°F) with allowable excursions between 15°C and 30°C (59°F and 86°F).	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by Groupe Parima, for Dr. Reddy's Laboratories, S.A. Basel, Switzerland (b) (4)	Adequate

Conclusion:

Satisfactory.

2. Container and Carton Labels

1) Immediate Container Label

The following container label was provided with Amendment 10 (dated 02/19/2016) of the NDA



Reviewer's Assessment:

There are a few noticeable issues with the label:

- In the inactive material list, “Mineral Oil” should be listed as “Light Mineral Oil”
- In the inactive material list, “BHT” should be listed as “butylated hydroxytoluene”
- In the inactive material list, “Carbomer” should be listed as “Carbomer 980”
- In the manufactured by section, it should be “Groupe Parima” and not “Groupe Parima Inc.”
- In the Warning Section, it may be advantageous to list that “XEGLYZE SHOULD BE USED ON CHILDREN, **6 MONTHS AND OLDER**, UNDER”
- Need to add line “Do not flush contents down sink or toilet”

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Complies	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Complies	Adequate
Route of administration (21.CFR 201.100(b)(3))	Complies	Adequate
Net contents* (21 CFR 201.51(a))	Complies	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Complies but corrections are pointed out for how the names should be listed	Not Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot number	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Complies	Adequate
Storage (not required)	Provided. Excursions limits are justified based on data.	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Complies	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Complies	Adequate
Others	Key instructions such as (b) (4) and “warning” are included in the label	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The labeling information is inadequate.

Not Satisfactory

2) Carton Labeling

There are a few noticeable issues with the label:

- In the inactive material list, “Mineral Oil” should be listed as “Light Mineral Oil”
- In the inactive material list, “BHT” should be listed as “butylated hydroxytoluene”
- In the inactive material list, “Carbomer” should be listed as “Carbomer 980”
- In the manufactured by section, it should be “Groupe Parima” and not “Groupe Parima Inc.”
- In the Warning Section, it may be advantageous to list that “XEGLYZE SHOULD BE USED ON CHILDREN, **6 MONTHS AND OLDER**, UNDER”
- Need to add line “Do not flush contents down sink or toilet”

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Complies	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Complies	Adequate
Net contents (21 CFR 201.51(a))	Complies	Adequate
Lot number per 21 CFR 201.18	Space is reserved for lot number	Adequate
Expiration date per 21 CFR 201.17	Space is reserved for expiration date	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(d)(2)]	Complies but corrections are pointed out for how the names should be listed	Not Adequate
Sterility Information (if applicable)	Not applicable	Not applicable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Complies	Adequate
Storage Conditions	Provided. Excursions limits are justified based on data.	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Complies	Adequate
Name of manufacturer/distributor	Complies	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Complies	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Complies	Adequate

Conclusion:

The labeling information is inadequate.

Not Satisfactory

OVERALL ASSESSMENT AND SIGNATURES: LABELING**Reviewer's Assessment and Signature:**

The labeling information is inadequate. The deficiencies have been noted in the review.

Reviewer's Signature**Bhavishya Mittal, Ph.D.****Branch V****Division of New Drug Products II/ONDP****April 18, 2016**

**Bhavishya
a Mittal -S**

Digitally signed by Bhavishya Mittal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001708640, cn=Bhavishya Mittal -S
Date: 2016.04.20 13:07:58 -04'00'

Secondary Review Comments and Concurrence:

I concur with Dr. Mittal's recommendation on the labels and labeling.

Supervisor's Signature**Moo-Jhong Rhee, Ph.D.****Chief, Branch V****Division of New Drug Products II/ONDP**

**Moojhong
Rhee -S**

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.04.22 09:03:03 -04'00'

II. List of Deficiencies To Be Communicated

A. Regarding Facility:

Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) manufacturing facility for this NDA is not considered acceptable to manufacture the drug substance for NDA 206966. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

B. Regarding Label/Labeling:

Immediate Container Label:

There are a few noticeable issues with the label:

- In the inactive material list, "Mineral Oil" should be listed as "Light Mineral Oil"
- In the inactive material list, "BHT" should be listed as "butylated hydroxytoluene"
- In the inactive material list, "Carbomer" should be listed as "Carbomer 980"
- In the manufactured by section, it should be "Groupe Parima" and not "Groupe Parima Inc."
- In the Warning Section, it may be advantageous to list that "XEGLYZE SHOULD BE USED ON CHILDREN, **6 MONTHS AND OLDER**, UNDER"
- Need to add line "Do not flush contents down sink or toilet"

Carton Label:

There are a few noticeable issues with the label:

- In the inactive material list, "Mineral Oil" should be listed as "Light Mineral Oil"
- In the inactive material list, "BHT" should be listed as "butylated hydroxytoluene"
- In the inactive material list, "Carbomer" should be listed as "Carbomer 980"
- In the manufactured by section, it should be "Groupe Parima" and not "Groupe Parima Inc."
- In the Warning Section, it may be advantageous to list that "XEGLYZE SHOULD BE USED ON CHILDREN, **6 MONTHS AND OLDER**, UNDER"
- Need to add line "Do not flush contents down sink or toilet"

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking (RPN Value)	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay (abametapir)	• Formulation • Raw materials	M (36)	(b) (4)	Acceptable	N/A

	• Process parameters • Scale/equipment • Site		(b) (4)		
Degradation Products 	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (45)		Acceptable	N/A
	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (27)		Acceptable	N/A
	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L (18)		Acceptable	N/A
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (36)		Acceptable	N/A
pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (36)		Acceptable	N/A
Apparent Viscosity (cps)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (48)		Acceptable	N/A
Content Uniformity in the Container, USP <3>	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (32)		Acceptable	N/A
Microscopic Observation (Particles or agglomerates of API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (27)		Acceptable	N/A
Droplet Size 	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M (32)		Acceptable	N/A

			(b) (4)		

RPN: Risk Priority Number

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Low Risk- $RPN \leq 25$

Moderate Risk - $25 < RPN \leq 60$

High Risk - $RPN > 60$