APPLICATION NUMBER:

206966Orig1s000

OTHER REVIEW(S)
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

<table>
<thead>
<tr>
<th>Date of This Memorandum:</th>
<th>June 3, 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Dermatology and Dental Products (DDDP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 206966</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Xeglyze (abametapir) lotion, 0.74%</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>Dr. Reddy’s Laboratories, SA</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2015-2383-3</td>
</tr>
<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Madhuri R. Patel, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Sevan Kolejian, PharmD, MBA</td>
</tr>
</tbody>
</table>
1 PURPOSE OF MEMORANDUM
The NDA 206966 received a Complete Response (CR) on August 30, 2016 for facility deficiencies. We previously reviewed the label and labeling and found the container label and carton labeling acceptable\(^a\). Subsequently, we reviewed label and labeling as part of the Class 2 Resubmission package on November 12, 2019\(^b\). This MEMO evaluates the revised label and labeling the Applicant submitted on June 1, 2020. The Division of Dermatology and Dental Products (DDDP) requested that we review the proposed Instructions for Use (IFU), Patient Package Insert (PPI), and revised container label, carton labeling, and Prescribing Information (PI) for Xeglyze (Appendix A) to determine if they are acceptable from a medication error perspective.

2 ASSESSMENT AND CONCLUSION
We note that “Xeglyze Lotion” has been revised to “Xeglyze” throughout the labeling. The patient information, distributor company name, and the National Drug Code (NDC) number have changed since our previous label and labeling review.

The revised PI, PPI, IFU, and container label are acceptable from a medication error perspective. However, we note that the carton labeling can be improved to enhance clarity (see section 3).

3 RECOMMENDATIONS FOR DR. REDDY’S LABORATORIES, SA
We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling
   a. To ensure consistency with the Prescribing Information, revise the statement, “Dosage and Administration: See package insert and instructions for use, including the patient information section, for dosing information” to read “Recommended Dosage and Administration: See prescribing information, including the patient information section, and instructions for use.” If space is limited, the statement may read “Recommended Dosage and Administration: See prescribing information and instructions for use.”

\(^a\) Mehta, H. Label and Labeling Review for Xeglyze (NDA 206966). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUL 15. RCM No.: 2015-2383-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 1, 2020

Prescribing Information (Image not shown):
Available at "\cdsesub1\evsprod\nda206966\0031\m1\us\114-labeling\draft-labeling\draft-labeling-text\draft-label-track-chg.docx"

Patient Package Insert (Image not shown):
Available at "\cdsesub1\evsprod\nda206966\0031\m1\us\114-labeling\draft-labeling\draft-labeling-text\draft-patient-info-track-chg.doc"

Instructions for Use (Image not shown):
Available at "\cdsesub1\evsprod\nda206966\0031\m1\us\114-labeling\draft-labeling\draft-labeling-text\draft-ifu-track-chg.doc"

Container label

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
06/03/2020 11:04:05 AM

SEVAN H KOLEJIAN
06/03/2020 05:50:30 PM
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 10, 2020
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 206966
Product Name and Strength: Xeglyze (abametapir) lotion, 0.74%
Applicant/Sponsor Name: Dr. Reddy’s Laboratories, SA
OSE RCM #: 2015-2383-2
DMEPA Safety Evaluator: Madhuri R. Patel, PharmD
DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM
The NDA 206966 received a Complete Response (CR) on August 30, 2016 for facility deficiencies. This MEMO evaluates the labels and labeling the Applicant submitted as part of the Class 2 Resubmission package on November 12, 2019. We previously reviewed the revised label and labeling and found the container label and carton labeling acceptable. The Division of Dermatology and Dental Products (DDDP) requested that we review the proposed container label, carton labeling, and revised Prescribing Information (PI) for Xeglyze (Appendix A) to determine if they are acceptable from a medication error perspective.

2 ASSESSMENT AND CONCLUSION
We note that the patent information, distributor company name, and the National Drug Code (NDC) number have changed since our previous label and labeling review.
The revised PI and container label are acceptable from a medication error perspective. However, we note that the carton labeling can be improved to enhance clarity (see section 3).

3 RECOMMENDATIONS FOR DR. REDDY’S LABORATORIES, SA

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling
   a. To ensure consistency with the Prescribing Information, revise the statement, “Dosage and Administration: See package insert and instructions for use, including the patient information section, for dosing information” to read “Recommended Dosage and Administration: See prescribing information including the patient information section, for dosing information.” If space is limited, the statement may read “Recommended Dosage and Administration: See prescribing information.”
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
03/10/2020 12:06:09 PM

SEVAN H KOLEJIAN
03/10/2020 12:13:08 PM
MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:    July 15, 2016
Requesting Office or Division:  Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:  NDA 206966
Product Name and Strength:  Xeglyze (abametapir) 0.74% w/w topical lotion
Submission Date:            July 8, 2016
Applicant/Sponsor Name:     Dr. Reddy’s Laboratories
OSE RCM #:                  2015-2383-1
DMEPA Primary Reviewer:     Hina Mehta, PharmD
DMEPA Team Leader:          Mishale Mistry, PharmD. MPH

1 PURPOSE OF MEMO
Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels for Xeglyze (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The revised container labels for Xeglyze is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Mehta, H. Label and Labeling Review for Xeglyze (NDA 206966). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 March 16. 10 p. OSE RCM No.: 2015-2383.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HINA S MEHTA
07/15/2016

MISHALE P MISTRY
07/15/2016
Clinical Inspection Summary

Date: June 16, 2016
From: Roy Blay, Ph.D., Reviewer, GCPAB\OSI
       Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI
       Susan D. Thompson, M.D.
       Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To: DDDP\Project Manager\Cristina Attinello
    DDDP\Medical Officer\Kevin Clark
    DDDP\Team Leader\Gordana Diglisic
    Division of Dermatology and Dental Products

NDA/BLA #: NDA 206966
Applicant: Hatchtech Pty Ltd.
Drug: Abametapir lotion, 0.74%, (Xeglyze)
NME (Yes/No): Yes
Therapeutic Classification: Standard Review
Proposed Indication(s): Treatment of head lice infestation
Consultation Request Date: November 13, 2015
Summary Goal Date: June 24, 2016
Action Goal Date: September 2, 2016
PDUFA Date: September 14, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Seiler and Perry were inspected in support of this NDA and the final classification of these inspections was No Action Indicated (NAI).

Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this NDA to support the use of abametapir lotion, 0.74%, (Xeglyze) for the treatment of head lice infestation.

Protocols Ha03-001 and Ha03-002, both entitled, “A Randomized, Double-Blind, Multicenter, Vehicle-Controlled Study of the Efficacy and Safety of Abametapir Lotion 0.74% Administered for the Treatment of Head Lice Infestation” were inspected in support of this application.
The primary objectives of Protocols Ha03-001 and Ha03-002 were the same; i.e., to evaluate the efficacy of at-home administration of a single application of abametapir lotion 0.74% for the treatment of head lice. Protocol Ha03-1 involved approximately 106 index subjects along with involved household members (approximately 381 subjects). Subjects were first enrolled in February of 2014 and completed the study in June of 2014. Subjects included in this study were healthy male or female subjects 6 months of age or older with active head lice infestation who belonged to a household with an eligible index subject. Subjects were treated with either abametapir lotion 0.74% or the matching vehicle lotion. The maximum study duration was 23 days which included a 7 day Screening period, 1 day Treatment period and Follow-up Visits 1, 7, and 14 days after treatment application. The primary efficacy variable was the lice assessment at all visits through Day 14. The primary efficacy endpoint was defined as the proportion of index subjects who were lice-free at all follow-up visits through to the Day 14 Visit. The sponsor’s conclusion was that the study demonstrated that abametapir lotion 0.74% was significantly more effective in treating head lice infestation than vehicle (81.1% of index subjects were lice-free at all follow-up visits through to Day 14 versus 50.9%, respectively; p = 0.001).

Dr. Seiler’s site (107) was selected because of its large enrollment and a relatively large treatment effect, and Dr. Perry’s site (205) was selected because of its large enrollment and unusually high vehicle response rate.

3. RESULTS (by site):

<table>
<thead>
<tr>
<th>Site #/ Name of CI/ Address</th>
<th>Protocol #/ # of Subjects (enrolled)</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>107/ Jeffry Seiler, MD, MBA LSRN Research 6758 North Military Trail, Suite 110 West Palm Beach, FL 33407</td>
<td>Ha03-001/ 24</td>
<td>22-25 Feb 16</td>
<td>NAI</td>
</tr>
<tr>
<td>205/ Patti Perry, MD Cactus Kids Pediatrics 1830-1932 S. 8th Ave. Yuma, AZ. 85364</td>
<td>Ha03-002/ 16</td>
<td>1-3 Feb 16</td>
<td>NAI</td>
</tr>
</tbody>
</table>

**Compliance Classifications**

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.
1. **Jeffry Seiler, M.D., M.B.A.**

At this site for Protocol Ha03-001, there were 25 subjects screened, 24 subjects were enrolled along with 77 index-related household subjects. All 24 index subjects and 77 index-related household subjects completed the study.

The study records of all 24 index subjects were reviewed in detail. Source data was compared to line listings. Records reviewed included, but were not limited to, source documents, case report forms (CRFs), training documents, sponsor, monitor, and IRB correspondence, financial disclosure, eligibility criteria, primary efficacy endpoints, protocol deviations, adverse events, concomitant medications, and test article accountability and storage. The electronic data capture (EDC) system named (b) (4) was also reviewed. This system was used to transmit data originally captured in source documents to the sponsor.

Review of the records of all 24 index subjects indicated that informed consent forms were completed prior to any study-related testing. No deficiencies were noted regarding the use of the EDC system.

A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Patti Perry, M.D.**

At this site for Protocol Ha03-002, there were 96 subjects screened across 19 households. The records of the subjects in the 19 households involved were reviewed. Source data was compared against line listings. Records reviewed included, but were not limited to, financial disclosure forms, training records, inclusion/exclusion criteria, medical histories, concomitant medications, monitor and IRB communications, primary efficacy data (scalp/lice evaluation), adverse events, and drug accountability and storage.

Review of the records of all 96 subjects indicated that informed consent forms were completed prior to any study-related testing.

A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

\{See appended electronic signature page\}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 3947295
CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm\NDA 206966
DDDP\Division Director\Kendall Marcus
DDDP\Team Leader\Gordana Diglisic
DDDP\Medical Officer\Kevin Clark
DDDP\Project Manager\Cristina Attinello
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROY A BLAY
06/16/2016

JANICE K POHLMAN
06/16/2016

SUSAN D THOMPSON
06/16/2016
Division of Pediatric and Maternal Health Memorandum

Date: March 31, 2016
Date consulted: October 20, 2015

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD,
Director, Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products (DDDP)

Drug: Xeglyze (abametapir) Lotion 0.74%

NDA: 206966

Applicant: Hatchtech Pty Ltd/Dr. Reddy’s Laboratories SA

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: For the topical treatment of head lice infestation in patients 6 months of age and older.

Materials Reviewed:
- DDDP consult request dated October 20, 2015
- Applicant’s response to Division’s information request of November 23, 2015, dated December 16, 2015
- Annotated draft labeling text to comply with the Pregnancy and Lactation Labeling Rule (PLLR), dated December 16, 2015
- Application submission dated September 14, 2015
Consult Question:
DDDP requests that DPMH review the content and format of the proposed labeling and supporting data and make recommendations regarding the section 8 USE IN SPECIFIC POPULATIONS, subsections 8.1, 8.2 and 8.3 of the labeling.

INTRODUCTION
The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 20, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Xeglyze (abametapir) Lotion 0.74% to comply with the Pregnancy and Lactation Labeling Rule format (PLLR).

REGULATORY HISTORY
On September 14, 2015, Hatchtech Pty Ltd submitted the NDA 206966, under the 505(b)(1) pathway of the Federal Food, Drug, and Cosmetic Act (FDCA) for the new molecular entity (NME) Xeglyze (abametapir) Lotion, 0.74%.

DDDP sent the Applicant an information request (IR) on November 23, 2015, requesting:
- A review and summary of all available published literature regarding Xeglyze (abametapir) Lotion, 0.74% use in pregnant and lactating women;
- The estimated background risk of major birth defects and miscarriage for the indicated population; and
- Revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

In response, the Applicant provided the requested information and in addition to other responses to the IR, submitted revisions to the Pregnancy and Lactation sections of the labeling on December 16, 2015, per FDA’s Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling, December 2014. The NDA for Xeglyze (206966) was filed on November 23, 2015.

BACKGROUND
Head Lice
The first evidence of existence for the Human head louse (Pediculus humanus capitis) was found in the well-preserved body of an Inca prince in Chile from the 15-century AD (Anno Domini). The head louse was well adapted for survival on its host. Today, in the United States alone, it is estimated that several million people, mainly children 3 to 12 years of age, are infected each year. The entire life cycle of the head louse is approximately 30 days and starts when an egg is laid by a female louse on a hair shaft, close to the scalp. The eggs stick to the hair shaft by an adhesive produced by the female louse at the time of laying. The eggs are then incubated by body heat and take approximately 1 week (range 7 to 10 days) to hatch and release a nymph (also known as an instar), which is about the size of a pinhead. The nymph undergoes 3 molting

Reference ID: 3923988
cycles (3 to 4 days each cycle) as it develops to an adult louse. Emerging from the nymph stage as an adult, the reproductive phase of the louse begins. The female lays her first eggs 1 to 2 days after mating and can lay 3 to 8 eggs per day for the next 16 days. A head louse must feed regularly on the host’s blood and, once detached from the host, they are highly vulnerable to dehydration and die.\(^5\)

In order to successfully eliminate an infestation of head lice, both the crawling stages of the louse as well as the egg stage must be targeted, breaking the life cycle of the louse. Different drugs have been approved by FDA for the treatment of lice, but many of them require multiple applications. Xeglyze is proposed to be effective with one application only.

**Drug Characteristics**

The active pharmacological ingredient in Xeglyze Lotion 0.74%, is the pediculicide, abametapir, which is a dipyridyl compound from the class of bipyridinium molecules. The molecular weight is 184.24. Abametapir, a metalloproteinase inhibitor, \(^6\) Abametapir targets ion channels of the nerve or muscle to result in hyper-excitation, paralysis, and subsequent death of the insect. It also inhibits lice from closing their respiratory spiracles, allowing the vehicle to obstruct the spiracles thereby causing the lice to asphyxiate. In addition, abametapir is believed to cause chelation of metal cations that result in inhibition of metalloproteinases critical to louse egg development and survival. \(^7\)

Abametapir is applied topically, and is systemically absorbed. In clinical studies, abametapir absorption was rapid with a median Tmax of 0.57 to 1.54 hours. Abametapir plasma maximum concentration (Cmax) and area under the concentration time curve in adults was 41 (66%) ng/ml and 121 (50%) ng*h/mL, respectively. Abametapir plasma protein binding ranged from 91.3 – 92.3%, while for its metabolite, abametapir carboxyl, the plasma protein binding ranged from 96.0 – 97.5%. The unconjugated abametapir carboxyl accounts for the vast majority of drug related plasma exposure in humans. The mean half-life in adults was 21 (11%) hours. For detailed PK analysis, the reader is referred to the Clinical Pharmacology Review by Tran, D. Ph.D. in DARRTS.\(^8\)

**Pregnancy and Lactation**

On June 30, 2015, the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”\(^9\) also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006

---

\(^5\) Nash B. Treating head lice. BMJ. 2003 June 7;326(7401);1256-7.
\(^6\) Proposed Xeglyze labeling, Section 12 Clinical Pharmacology, December 16, 2015
\(^7\) NDA Submission, September 14, 2015
\(^8\) Tran, D. Clinical Pharmacology Review: DARRTS: April, 2016.
\(^9\) Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).
Physicians Labeling Rule\textsuperscript{10} format to include information about the risks and benefits of using these products during pregnancy and lactation.

**XEGLYZE AND PREGNANCY LITERATURE REVIEW**
The Applicant was requested to provide a review and summary of all available published literature regarding Xeglyze (abametapir) Lotion, 0.74\% use in pregnant and lactating women. In the December 16, 2015 response, the Applicant stated that abametapir is a New Chemical Entity. Therefore, no published literature regarding the use of Xeglyze (abametapir) Lotion, 0.74\% is available outside the clinical trials. DPMH also conducted a review of PubMed, ReproTox\textsuperscript{11}, and TERIS\textsuperscript{12} for published literature regarding Xeglyze and use in pregnancy. No publications were identified.

**CLINICAL STUDIES**
A serum and/or urine pregnancy test was performed on all female subjects of child-bearing potential who participated in 9 of the studies conducted. Subjects who were pregnant were not excluded from study participation in the Phase 3 studies. A total of 2 pregnant subjects were enrolled into the Phase 3 studies. Both subjects completed the study. At the time of study completion, the pregnancy was ongoing. One subject complained of no adverse events (AE) while the other experienced 2 AEs while enrolled in the study: elevated alkaline phosphatase and low protein. Both events were considered nonserious, mild in severity and not related to study drug by the investigator. Additionally, 1 subject reported a pregnancy during participation in the Phase 2 PK study. The subject reported using birth control (condom with spermicide) during the study. The subject was discontinued from the study as soon as the pregnancy test was found positive. Eleven days after discontinuation of the drug, the subject experienced a spontaneous abortion. The subject has a history of miscarriages. No reason was reported for the spontaneous abortion at this time. No concomitant medications were taken. This reviewer agrees with the investigator and the Applicant that the spontaneous abortion is unlikely to be related to the drug.

On January 20, 2016, Dr. Reddy's Laboratories provided to the NDA file the 120-day safety update confirming that no additional nonclinical or clinical studies have been conducted after submission of the NDA and no additional subjects have been exposed under any other means (e.g., compassionate use). No new literature has been published. No follow up on the above pregnancies has been provided.

**Reviewer Comment**
The limited data available, at this time, on the use of abametapir lotion 0.74\% in pregnant women have not demonstrated an association with abametapir and any risk of miscarriage or major birth defects.

\textsuperscript{10} Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).
\textsuperscript{11} ReproTox database, Truven Health analytics, Micromedex solutions, 2016
\textsuperscript{12} TERIS database, Truven Health Analytics, Micromedex Solutions, 2016.
XEGLYZE AND ANIMAL STUDIES
During the product development cycle, systemic embryo-fetal development studies were conducted with oral administration of abametapir during organogenesis in rats and rabbits. No evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50-times and equivalent to the maximum recommended human dose (MRHD), respectively.

Oral doses of 4, 16, and 40 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 19) to pregnant rabbits. No treatment related effects on embryo-fetal toxicity or malformations were noted at 40 mg/kg/day (~1 times the MRHD based on C_{max} comparisons). The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used. In the presence of maternal toxicity, embryo-fetal toxicity (lower fetal body weights and delayed ossification) was noted at 75 mg/kg/day.

**Reviewer Comment**
There is no evidence of fetal harm or malformations, independent of maternal toxicity, in animal reproduction studies.

XEGLYZE AND LACTATION
DPMH reviewed Thomas Hale’s book on *Medication and Mother’s Milk*, regarding abametapir and lactation. No entries were identified.

A review of LactMed\(^{13}\) did not identify any entries.

XEGLYZE Lotion contains benzyl alcohol, which with systemic exposure, has been associated with serious adverse reactions and death in neonates and low birth-weight infants. Because there is no known minimum amount of benzyl alcohol at which toxicity may occur, there is a potential of benzyl alcohol toxicity for premature and low-birthweight infants who are exposed via breastmilk. For more information on benzyl alcohol toxicity, the reader is referred to the DPMH Pediatric review by E. Radden, MD.

**Reviewer Comment**
There are no adequate and well-controlled studies conducted to investigate the effects of abametapir lotion 0.74% on lactating women by the Applicant. There is no other information on Xeglyze and Lactation. During the clinical trials in patients aged 6 months and older, adverse reactions occurring in ≥1% of the Xeglyze Lotion treatment group (except the local reactions of skin erythema, rash, skin burning sensation and contact dermatitis) included systemic adverse reactions of vomiting in 1.7% and eye irritation in 1.2%. Xeglyze Lotion is indicated only for a single application. Even though abametapir is systemically absorbed, lactation is not contraindicated during its use. Xeglyze and its metabolites are bound to plasma proteins more than 92% and it has a short half-life (21 hours), which suggests that the amount of the drug

\(^{13}\) [http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT](http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT). The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
present in human milk after 2 days may be low. However, physicochemical properties alone are not sufficient to establish the quantity of drug that may be transferred to breast milk. Therefore, DPMH recommends that the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Xeglyze Lotion and any potential adverse effects on the breastfed child from Xeglyze Lotion or from the underlying maternal condition. However, a lactating mother may minimize exposure to the infant by pumping and discarding breastmilk for 2 days. Afterwards, she may continue with breastfeeding safely. DPMH also recommends a postmarketing clinical lactation study to better characterize the amount of abametapir transferred into breastmilk and any potential risk associated with breastfeeding. The Applicant should be encouraged to provide a study protocol for this lactation study.

XEGLYZE AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy Testing and Contraception

There are no data informing of a potential risk of fetal harm. Therefore, there is no need for recommendations for pregnancy testing or contraception.

Infertility

There is no information on Xeglyze and infertility.

XEGLYZE AND ANIMAL STUDIES

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term Carcinogenic studies in animals have not been conducted to evaluate the carcinogenic potential with of Xeglyze Lotion or abametapir.

Abametapir was not mutagenic or clastogenic based on the results of two in vitro genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on \(C_{\text{max}}\) comparisons)

Reviewer Comment

There is no information about Xeglyze use and females and males of reproductive potential. This section should be omitted.

CONCLUSIONS

Xeglyze labeling has been updated to comply with the PLLR format. A review of the literature revealed no data with Xeglyze use in pregnant or lactating women. From the clinical studies during the development cycle of the drug, limited data exists for Xeglyze exposure in pregnant women. In clinical trials, the only systemic adverse events observed were rare vomiting and eye irritation. There is no data on lactation in humans or animals with use of Xeglyze. The existing data are not sufficient to determine any drug-associated risk.

However, Xeglyze Lotion is rapidly systemically absorbed and contains benzyl alcohol, which with systemic exposure, has been associated with serious adverse reactions and death in neonates.
and low birth-weight infants. Therefore, DPMH recommends the following Clinical Lactation Study PMR language:

*A single dose, pharmacokinetic, open-label, clinical study in lactating women who require treatment with Xeglyze lotion.*

*Concentrations of abametapir will be assessed in maternal plasma and breast milk so as to estimate potential infant exposure.*

**Protocol Submission:** (6 months post approval date)

**Study Start:** (~6 months post approval date)

**Final Report Submission:** (2 years post approval date)


DPMH has the following recommendations for Xeglyze Lotion labeling:

- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of Xeglyze Lotion was formatted in the PLLR format to include “Risk Summary,” and “Data”. The Human Data subsection has been deleted because there is no information to be reported.\(^{14}\)

- **Lactation, Section 8.2**
  - The “Lactation” subsection of Xeglyze Lotion labeling was formatted in the PLLR format to include the “Risk Summary”. The data subsection has been deleted because there is no information to be reported.

- **Females and Males of Reproductive Potential, Section 8.3**
  - The “Females and Males of Reproductive Potential” subsection of Xeglyze Lotion labeling is omitted because there are no recommendations for pregnancy testing or contraception, and no adverse effects on fertility to be conveyed to the prescriber.

**RECOMMENDATIONS**

DPMH revised sections 8.1 and 8.2 of Xeglyze Lotion labeling for compliance with the PLLR (see below). DPMH refers to the NDA action for final labeling.
DPMH Proposed Xeglyze Lotion Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-USE IN SPECIFIC POPULATIONS---------

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on XEGLYZE Lotion use in pregnant women to inform a drug associated risk. In embryo-fetal development studies conducted with oral administration of abametapir during organogenesis, no evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the maximum recommended human dose (MRHD) in rats and rabbits, respectively. The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used in the study [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Systemic embryo-fetal development studies were performed in rats and rabbits. Oral doses of 10, 25, and 75 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 17) to pregnant rats. In the presence of maternal toxicity, embryofetal toxicity (lower fetal body weights and delayed ossification) was noted at 75 mg/kg/day. No treatment related effects on malformations were noted at 75 mg/kg/day (50 times the MRHD based on C_{max} comparisons).

Oral doses of 4, 16, and 40 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 19) to pregnant rabbits. No treatment related effects on embryofetal toxicity or malformations were noted at 40 mg/kg/day (~1 times the MRHD based on C_{max} comparisons). Maternal toxicity related to the vehicle limited the maximum dose in pregnant rabbits.

In a perinatal and postnatal development study in rats, oral doses of 10, 25, and 75 mg/kg/day were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryo-fetal lethality, and decreased fetal body weight gain were noted at 75 mg/kg/day. No treatment related effects on postnatal development were noted at 75 mg/kg/day (47 times the MRHD based on C_{max} comparisons).
8.2 Lactation
Risk Summary
No data are available regarding the presence of abametapir in human milk, or the effects of abametapir on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for XEGLYZE Lotion and any potential adverse effects on the breastfed child from XEGLYZE Lotion or from the underlying maternal condition.

Clinical Considerations
To minimize potential infant exposure to abametapir, a woman may pump and discard breastmilk for 2 days after Xeglyze use, before resuming to breastfeed her infant.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOS MASTROYANNIS
04/28/2016

TAMARA N JOHNSON
04/28/2016

LYNNE P YAO
04/28/2016
MEMORANDUM

From: Erica Radden, M.D.
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: Donna Snyder, M.D., Acting Pediatric Team Leader,
John Alexander, M.D., M.P.H., Acting Deputy Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division Dermatology and Dental Products (DDDP)

Drug: Xeglyze (abametapir) lotion, 0.74%

Application number: NDA 206966

Applicant: Dr. Reddy’s Laboratories, SA

Proposed Indication: For the topical treatment of head lice infestation in patients 6 months of age and older.

Proposed Dosage Form and Route of Administration: Lotion: 0.74% w/w, administered topically.

Proposed Dosing Regimen: Apply XEGLYZE Lotion to dry hair in an amount sufficient to thoroughly coat the hair and scalp. Massage XEGLYZE Lotion into the scalp and throughout the hair; leave on the hair and scalp for 10 minutes and then rinse off with warm water.
Consult Request:
DDDP requests Division of Pediatric and Maternal Health (DPMH)-Pediatric Team’s input on pediatric use labeling, particularly regarding the benzyl alcohol excipient and the associated neonatal toxicity.

Materials Reviewed:
- Applicant’s draft Xeglyze (abametapir) labeling (September 15, 2015)
- Natroba (spinosad) labeling (December 30, 2014)
- Sklice (ivermectin) labeling (February 7, 2012)

Background:
Hatchtech Pty, Ltd. submitted an NDA on September 15, 2015, for Xeglyze (abametapir) lotion, a new molecular entity and pediculocide with a proposed indication for the treatment of head lice infestation in patients 6 months of age and older. Subsequently, on December 30, 2015, ownership of the NDA was changed from Hatchtech Pty Ltd to Dr. Reddy’s Laboratories, SA.

Each bottle (200 g) of abametapir lotion contains benzyl alcohol. Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis, encephalopathy and respiratory depression with gasping leading to death in infants at doses of 99 to 234 mg/kg/day. Benzyl alcohol toxicity has been particularly associated with low birth-weight infants, because of the greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature. Additionally, infants in hospital settings may be exposed to benzyl alcohol through routine administration of multiple medications and may be at increased risk of toxicity.

In May, 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a Drug Bulletin containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible. In 1997, the AAP Committee on Drugs published a review of the available published literature on neonatal benzyl alcohol toxicity and reported that most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death; however, the effects of lower amounts of benzyl alcohol have not been adequately studied.

DDDPM consulted DPMH-Pediatric Team to provide input on the sponsor’s proposed labeling related to pediatric use, particularly regarding benzyl alcohol toxicity.

**Pediatric Assessment:**
An Agreed iPSP letter was issued on May 8, 2014, in which the Agency agreed that studies should be waived in patients <6 months of age because:
1. necessary studies are impossible or highly impracticable due to the low prevalence of head lice infestation in infants less than 6 months of age, and
2. the potential of increased systemic absorption due to a high ratio of skin surface to body mass and the potential for an immature skin barrier in pediatric subjects from birth to 6 months.
The sponsor completed pediatric studies in patients 6 months and older, and the pediatric assessment is complete.

*Reviewer comment: Because studies were waived due to a safety concern, that concern should be described in labeling.*

**DPMH Review of Pediatric Use Labeling:**
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013)

See Appendix 1 for proposed applicant labeling for Xeglyze (September 15, 2015).

**Discussion on Pediatric Use Labeling Recommendations:**
The DPMH labeling review will focus on edits to section 5 (Warnings and Precautions), subsection 8.4 (Pediatric Use), and Highlights of Prescribing Information.

Because the proposed indication will include pediatric patients down to 6 months of age, information regarding pediatric use for this indication should be placed throughout labeling. Labeling for other lice treatment products, such as Natroba (spinosad) and Sklice (ivermectin), was considered in order to align the language among these products as much as possible to limit any suggestion of differences in safety.

(2);268-78.

Reference ID: 3921216
Comments on the Warnings and Precautions Section
Xeglyze contains benzyl alcohol [bracketed text], and language regarding the associated potential for neonatal toxicity (as discussed above) should be included in the Warnings and Precautions section and the Pediatric Use subsection. Furthermore, because this warning pertains to an unapproved subpopulation (i.e., patients < 6 months of age), labeling should state that safety and effectiveness have not been established in this subpopulation. To be consistent with the labeling for other lice treatment products, a statement that use is not recommended in patients < 6 months of age can be included in the warning for benzyl alcohol toxicity, but should clarify that the recommendation is due to the potential for increased systemic absorption of the product.

The guidance for industry titled Head Lice Infestation: Developing Drugs for Topical Treatment states that the risk of accidental ingestion should be discussed in the Warnings and Precautions and Patient Counseling Information sections, and should include a recommendation to administer the drug to pediatric patients only under direct adult supervision. This concern is particularly relevant to Xeglyze because the design of the container (i.e., an amber glass bottle [bracketed text]) and viscosity of the product limited the use of additional preventive measures, such as an orifice-reducing plug, or a squeezable container with flow restrictor. There is no specific concern identified for toxicity with ingestion of abametapir (the active ingredient); however, the division notes a concern for increased systemic exposure to benzyl alcohol with ingestion of Xeglyze, which is relevant to all populations. Additionally, accidental ingestion is unlikely to occur with neonates and infants, but rather in older patients. Therefore, we recommend discussing the risk of accidental ingestion in the Warnings and Precautions section under a heading separate from the warning regarding neonatal benzyl alcohol toxicity.

Comments on the Pediatric Use Subsection
The Pediatric Use subsection (8.4) should state that safety and effectiveness have been established in patients 6 months of age and older with cross-references to more detailed information supporting approval in the Clinical Pharmacology and Clinical Studies sections. Subsection 8.4 should also state that safety and effectiveness have not been established in patients < 6 months of age. Additionally, because studies were waived in patients < 6 months of age due to the potential concern for increased systemic absorption, labeling should describe this safety concern. Furthermore, because the potential for benzyl alcohol toxicity and the concern for accidental ingestion are particularly relevant to the pediatric population, these risks should also be discussed in subsection 8.4.

Comments on the Highlights of Prescribing Information
Our labeling recommendations for the Highlights of Prescribing Information section summarize the labeling proposed for the Warnings and Precautions section. Additionally, we recommend deleting the Use in Specific Populations and Pediatric Use headings from the Highlights section because per the Labeling Review Tool,
the absence of information about the safety and effectiveness of a drug in a specific population (e.g., pregnant women, pediatric patients, hepatic or renal impairment) ordinarily should not be included under this heading, and

information about Use in Specific Populations included under other headings in the Highlights section (e.g. Contraindications, Warnings and Precautions, Dosage and Administration) should not be repeated under this heading.

DPMH Actions and Labeling Recommendations:
DPMH reviewed the sponsor’s draft labeling and participated in the internal meetings between October, 2015 and April, 2016. DPMH provided labeling recommendations for the pediatric population per 21 CFR 201.57(c)(9)(iv). The following recommendations were provided to DDDP based on labeling discussions between DDDP and DPMH. DPMH’s input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-------------------------WARNINGS AND PRECAUTIONS-------------------------

- **Neonatal Benzyl alcohol toxicity**: Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants. Safety and effectiveness in pediatric patients below the age of 6 months have not been established. Not recommended in pediatric patients under 6 months of age; potential for increased systemic absorption. (5.1)

- **Accidental Ingestion**: Administer only under direct supervision of an adult. (5.2)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.1 **Neonatal Benzyl Alcohol Toxicity**
Each bottle (200 g) of XEGLYZE Lotion contains benzyl alcohol. Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including “gasp syndrome” in neonates and low birth weight infants. The “gasp syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants may be more likely to develop toxicity [see Use in Specific Populations (8.4)]. The safety and effectiveness of XEGLYZE Lotion have not been established in pediatric patients below the age of 6 months. Use is not recommended in pediatric patients under 6 months of age because of the potential for increased systemic absorption.

5.2 **Accidental Ingestion**

[The division will include language on the adverse effects reported with benzyl alcohol in large quantities, and advice to contact the local Poison Control Center if accidental... ]
In order to prevent ingestion in pediatric patients, XEGLYZE Lotion should only be administered under direct supervision of an adult.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of XEGLYZE Lotion have been established in pediatric patients 6 months of age and older [see Clinical Pharmacology (12) and Clinical Studies (14)].

The safety and effectiveness of XEGLYZE Lotion have not been established in pediatric patients below the age of 6 months. XEGLYZE Lotion is not recommended in pediatric patients under six months of age because of the potential for increased systemic absorption due to a high ratio of skin surface to body mass and the potential for an immature skin barrier.

Each bottle (200 g) of XEGLYZE Lotion contains benzyl alcohol. Benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants. The “gasp ing syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low birth weight infants when administered intravenously. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity.

Because of the risk of accidental ingestion, XEGLYZE Lotion should be administered to pediatric patients only under direct adult supervision.
Appendix 1: Applicant’s Proposed Labeling for Xeglyze (September 15, 2015)

HIGHLIGHTS OF PRESCRIBING INFORMATION
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERICA D RADDEN
04/22/2016

DONNA L SNYDER
04/22/2016

JOHN J ALEXANDER
04/22/2016
Date: April 18, 2016

To: Kendall A. Marcus, MD  
   Director  
   Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
         Associate Director for Patient Labeling  
         Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD  
       Patient Labeling Reviewer  
       Division of Medical Policy Programs (DMPP)

Tara Turner, PharmD, MPH  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): XEGLYZE (abametapir)

Dosage Form and Route: lotion, for topical use

Application Type/Number: NDA 206966

Applicant: Dr. Reddy’s Laboratories SA
INTRODUCTION
On September 14, 2015, Dr. Reddy’s Laboratories SA submitted for the Agency’s review a New Drug Application (NDA) 206966 for XEGLYZE (abametapir) Lotion. The proposed indication for XEGLYZE (abametapir) Lotion is for the topical treatment of head lice infestation in patients 6 months of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on January 28, 2016 for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for XEGLYZE (abametapir) Lotion.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

MATERIAL REVIEWED
• Draft XEGLYZE (abametapir) Lotion PPI and IFU received on September 14, 2015 revised by the Review Division throughout the review cycle and received by DMPP and OPDP on April 4, 2016.
• Draft XEGLYZE (abametapir) Prescribing Information (PI) received on September 14, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 4, 2016.
• Approved NATROBA (spinosad) comparator labeling dated December 30, 2014.

REVIEW METHODS
To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we have:
• simplified wording and clarified concepts where possible
• ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI and IFU meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
• ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.
• The appended IFU review incorporates DMPP and DMEPA comments.

4 CONCLUSIONS
The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROWELL MEDINA
04/18/2016

TARA P TURNER
04/18/2016

BARBARA A FULLER
04/18/2016

LASHAWN M GRIFFITHS
04/18/2016
Memorandum

Date: April 18, 2016

To: Cristina Attinello, MPH
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Pharm.D., BCPS, RAC, Team Leader, OPDP

Subject: NDA 206966
XEGLYZE (abametapir) lotion, for topical use

On January 28, 2016, DDDP consulted OPDP to review the draft Package Insert (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for XEGLYZE (abametapir) lotion, for topical use (Xeglyze) for the original NDA submission.

OPDP reviewed the proposed substantially complete version of the PI, PPI, and IFU provided by DDDP via e-mail on April 4, 2016. OPDP also reviewed the proposed carton and container labeling submitted to the electronic document room by the sponsor on September 14, 2015. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the PPI and IFU for Xeglyze under separate cover. OPDP’s comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP’s comments, please contact Tara Turner at 6-2166 or at Tara.Turner@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TARA P TURNER
04/18/2016
LABEL, LABELING AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: March 16, 2016
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 206966
Product Name and Strength: Xeglyze (abametapir) 0.74% w/w topical lotion
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Dr. Reddy’s Laboratories, SA
Submission Date: September 14, 2015 and February 19, 2016
OSE RCM #: 2015-2383
DMEPA Primary Reviewer: Hina Mehta, PharmD
DMEPA Team Leader: Mishale Mistry, PharmD, MPH

Reference ID: 3903075
1 REASON FOR REVIEW
Hatchtech Pty Ltd submitted NDA 206966 for Xeglyze (abametapir) lotion on September 14, 2015. There was a change in ownership of the NDA from Hatchtech Pty Ltd to Dr. Reddy's Laboratories, SA on December 30, 2015. The Division of Dermatology and Dental Products (DDDP) requested we evaluate the container labels, carton labeling, and prescribing information for vulnerabilities that could lead to medication errors.

2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C-N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
We performed a risk assessment of the proposed container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified areas in the labels and labeling that can be improved to increase the readability and prominence of important information and promote the safe use and handling of the product. We defer to Pharmaceutical Quality/CMC for appropriateness of the term “single use” on the labels and labeling. We provide recommendations in Section 4.1 for the Prescribing Information and 4.2 for the container label and carton labeling to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS
DMEPA concludes that the proposed labels and labeling can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION
A. Highlights of Prescribing Information, Dosage and Administration Section

1. For increased readability, we recommend listing the use and administration instructions as follows:
   - For topical use only. Not for oral, ophthalmic, or intravaginal use.
   - For single use. Discard any unused portion.
   - Shake well before use.
   - Apply XEGLYZE Lotion to dry hair in an amount sufficient to thoroughly coat the hair and scalp. Avoid contact with eyes. Massage XEGLYZE Lotion into the scalp and throughout the hair; leave on the hair and scalp for 10 minutes and then rinse off with warm water.

4.2 RECOMMENDATIONS FOR THE HATCHTECH PTY LTD

We recommend the following be implemented prior to approval of this NDA 206966:

A. Container Label

1. We recommend relocating “FOR SINGLE USE ONLY. Discard bottle after use.” to the Principal Display Panel (PDP) so this information is not overlooked.

2. We recommend replacing “” with “NOT FOR ORAL, OPHTHALMIC, OR INTRAVAGINAL USE” for consistency with other topical products.

3. We recommend relocating the warning statement, “Warning: Keep out of reach of children. Xeglyze should be used on children under direct supervision of an adult.” to the side panel to ensure adequate space for statements identifying the correct route of administration and how the product should be safely handled and used.

4. Replace “” with “Do not refrigerate or freeze” to be consistent with the prescribing information.

5. In the storage section, add the temperature unit after each numerical temperature reading. For example: “Store upright at room temperature 20°C to 25°C (68°F to 77°F)”.

B. Carton Labeling

1. We recommend reducing the size of the graphic on the bottom of the principal display panel in order to ensure adequate space for statements identifying the route of administration and how the product should be safely used and handled. Additionally, we recommend removing any overlaying text on the graphic as it affects the readability of the information.
2. We recommend adding the statements, “FOR SINGLE USE ONLY. Discard bottle after use.” on the PDP below the “For topical use on the scalp hair and scalp only” statement, so this important information is not overlooked.

3. We recommend replacing “(b) (4)” with “NOT FOR ORAL, OPHTHALMIC, OR INTRAVAGINAL USE” for consistency with other topical products.

4. We recommend re-locating the warning statement, “Warning: Keep out of reach of children. Xeglyze should be used on children under direct supervision of an adult.” to the side panel to ensure adequate space for statements identifying the correct route of administration and how the product should be safely handled and used.

5. Replace “(b) (4)” with “Do not refrigerate or freeze” to be consistent with the prescribing information.

6. In the storage section, add the temperature unit after each numerical temperature reading. For example: “Store upright at room temperature 20°C to 25°C (68°F to 77°F)”.

Reference ID: 3903075
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 2 presents relevant product information for Xeglyze (abametapir) that Hatchtech Pty Ltd submitted on September 14, 2015.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Xeglyze (abametapir)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td><strong>Container Closure</strong></td>
</tr>
</tbody>
</table>
APPENDIX B.  PREVIOUS DMEPA REVIEWS

B.1 Methods
On November 17, 2015, we searched the L:drive and AIMS using the terms, Xeglyze to identify reviews previously performed by DMEPA.

B.2 Results
Our search did not identify any previous label/labeling reviews relevant to this review.
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Xeglyze (abametapir) labels and labeling submitted by Hatchtech Pty Ltd on September 14, 2015.

- Container Label
- Carton Labeling
- Prescribing Information Labeling

G.2 Label and Labeling Images

Xeglyze (abametapir) 0.74% container label

Xeglyze (abametapir) 0.74% carton labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HINA S MEHTA
03/16/2016

MISHALE P MISTRY
03/21/2016

Reference ID: 3903075