

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205394Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 7, 2023

To: Laura Jawidzik, Clinical Reviewer
Division of Neurology 2 (DN2)

Alina Walizada, Regulatory Project Manager, DN2

Tracy Peters, Associate Director for Labeling, DN2

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for RizaFilm (rizatriptan) oral film

NDA: NDA 205394

In response to DN2's consult request dated December 16, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for RizaFilm (rizatriptan) oral film.

PI/PPI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 23, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/Medication Guide/IFU, and comments were sent under separate cover on April 5, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on April 3, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	April 6, 2023
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 205394
Product Name and Strength:	RizaFilm (rizatriptan) oral film, 10 mg
Applicant/Sponsor Name:	IntelGenx Corp
TTT ID #:	2022-3091-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 3, 2023 for RizaFilm. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for RizaFilm (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 ASSESMENT AND CONCLUSION

The Applicant implemented all of our recommendations and we have no recommendations at this time.

^a Weitzman, B. Label and Labeling Review for RizaFilm (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2(US); 2023 March 9. TTT ID No.: 2022-3091.

APPENDIX A. LABEL AND LABELING AND COVER LETTER

A.1 List of Labels and Labeling and Response to Agency's Recommendations Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following RizaFilm label and labeling submitted by IntelGenx Corp. received on April 3, 2023.

- Response to the Agency's recommendations available from docuBridge via:
<\\CDSESUB1\EVSPROD\nda205394\0027\m1\us\12-cover-letters\cover-letter-0027.pdf>
- Container (pouch) label
- Carton labeling

A.2 Label and Labeling Images

Container (pouch) label

(b) (4)



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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 5, 2023

To: Alina Walizada, MS, RPh
Regulatory Project Manager
Division of Neurology II (DN2)

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Lonice Carter, MS, RN, CNL, NHDP-BC
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Sheneé Toombs, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): RizaFilm (rizatriptan)

Dosage Form and Route: oral film

Application Type/Number: NDA 205394

Applicant: IntelGenx Corp.

1 INTRODUCTION

On October 17, 2022, IntelGenx Corp. submitted for the Agency's review a Class 2 Resubmission for New Drug Application 205394 RizaFilm (rizatriptan) oral film, in response to the Complete Response Letter issued by the Agency dated March 24, 2020. With this Class 2 Resubmission, the Applicant proposes an indication for the acute treatment of migraine with or without aura.

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 Neurology II (DN2) on December 17, 2022 and December 16, 2022, respectfully for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RizaFilm (rizatriptan) oral film.

2 MATERIAL REVIEWED

- Draft RizaFilm (rizatriptan) PPI received on October 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on March 23, 2023.
- Draft RizaFilm (rizatriptan) PPI received on October 17, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on March 23, 2023.
- Draft RizaFilm (rizatriptan) Prescribing Information (PI) received on October 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on March 23, 2023.
- Draft RizaFilm (rizatriptan) Prescribing Information (PI) received on October 17, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on March 23, 2023.
- Approved MAXALT (rizatriptan benzoate) tablets, for oral use, and MAXALT-MLT (rizatriptan benzoate) orally disintegrating tablets comparator labeling dated October 1, 2019.

3 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.

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.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is 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 is 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.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
04/05/2023 11:17:55 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 9, 2023
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 205394
Product Name and Strength:	RizaFilm (rizatriptan) oral (b) (4) film, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	IntelGenx Corp
FDA Received Date:	October 17, 2022
TTT ID #:	2022-3091
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

On October 17, 2022, the Applicant submitted revised container label, carton labeling, prescribing information (PI) and patient information (PPI) as part of the Class 2 resubmission for RizaFilm (rizatriptan) oral (b) (4) film under NDA 205394 in response to the Agency's Complete Response Letter (CRL), issued March 24, 2020.^a

The Division of Neurology 2 (DN 2) requested that we review the revisions to the container label, carton labeling, PI and PPI to determine if they are acceptable from a medication error perspective (see Appendix A for labels and labeling).

1.1 REGULATORY HISTORY

NDA 205394 is a 505(b)(2) NDA, and the listed drug product is Maxalt-MLT (NDA 020864). NDA 205394 was originally submitted on March 27, 2013. We completed a review of the labels and labeling for this application on January 10, 2014.^b However, the application received a complete response (CR) letter on January 31, 2014.^c As such, our recommendations for (b) (4) 10 mg strength container labels and carton labeling were sent to the Applicant as part of the CR letter. The CR letter noted that the FDA reserved comment on the proposed labeling (i.e., PI and PPI) until the application is otherwise adequate. Therefore, our recommendations for the PI and PPI were not communicated to the Applicant.

In response to the CR letter issued on January 31, 2014, IntelGenx Corp submitted NDA 205394 as a Class 2 resubmission on October 1, 2018. Under the Class 2 resubmission, the Applicant submitted 10 mg strength (b) (4) container label and carton labeling which were revised in response to our recommendations sent to the Applicant in the January 31, 2014, CR letter. We completed a review of the labels and labeling on December 11, 2018.^e However, the application received a second CR letter on March 28, 2019.^f As such, our recommendations for the container label and carton labeling were sent to the Applicant as part of the CR letter. We note our recommendations for the PI were not communicated to the Applicant as part of the CR letter.

In response to the CR letter issued March 28, 2019, IntelGenx Corp submitted a Class 2 resubmission under NDA 205394 on September 26, 2019. Under the Class 2 resubmission, the Applicant submitted container label and carton labeling which were revised in response to our recommendations sent to the Applicant in the March 28, 2019, CR letter. We completed a

^a Available via DARRTS: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8054f0ec>

^b Neshiewat, J. Label and Labeling Review for Rizatriptan (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 10. RCM No.: 2013-1082.

^c Available via DARRTS: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80315080>

^e Rider, B. Label and Labeling Review for Rizatriptan (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 11. RCM No.: 2018-2136.

^f Available via DARRTS: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804e8106>

review of the label and labeling on December 23, 2019.^g However, the application received a third CR letter on March 24, 2020.^h As such, our recommendations for the container label and carton labeling were sent to the Applicant as part of the CR letter. We note our recommendations for the PI were not communicated to the Applicant as part of the CR letter.

Subsequently, IntelGenx Corp submitted NDA 205394 as a Class 2 resubmission on October 17, 2022. Under the Class 2 resubmission, the Applicant submitted container label and carton labeling which were revised in response to our recommendations sent to the Applicant in the March 24, 2020, CR letter as well as PI and PPI labeling [subject of this review].

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C - NA
FDA Adverse Event Reporting System (FAERS)*	D -NA
Other	E -NA
Labels and Labeling	F

N/A=not applicable

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), Patient information (PPI), container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 (Table 2) for the Division and in Section 5 (Table 3) for IntelGenx Corp.

4 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

^g Baugh, D. Label and Labeling Review for Rizatriptan (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 23. RCM No.: 2018-2136-1.

^h Available via DARRTS: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8054f0ec>

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information (FPI) – Section 2 Dosage and Administration			
1.	In Section 2.1 (Dosing Information in Adults), the statement (b) (4)	We are concerned that this statement may cause confusion (b) (4)	We recommend removing the statement (b) (4) We defer to the review team for their input and final determination regarding this statement.
2.	In Section 2.3 (Administration of RizaFilm Oral (b) (4) Films), the instruction “the pouch should be folded and torn open...” does not clearly specify where the pouch should be folded or torn.	This instruction may be improved to increase clarity, and to minimize the risk of the film being damaged when opening the pouch.	We recommend revising the statement to read “The pouch should be folded on the dotted line and torn open at the notch...” to improve clarity, and to be consistent with the container label and patient information (PPI).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	We note that the storage statement “keep product in pouch until ready to use” is not included in Section 16.	Incomplete storage information may result in improper storage of the drug product which may lead to deteriorated drug medications errors.	We recommend adding the statement, “keep product in pouch until ready to use” as presented on the carton labeling and container label.
Full Prescribing Information – Section 17 Patient Counseling			
1.	Section 17 does not include instructions advising patients on how to open the pouch or proper administration of RizaFilm.	Including these instructions may minimize the risk of the film being damaged when opening the pouch and prevent wrong technique administration errors.	Consider including counseling instructions directed to the patient on how to open the pouch and administer RizaFilm oral (b) (4) film. <u>For example:</u>

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			“Advice patients that the pouch should be folded on the dotted line and torn open at the notch. Patients should be told administration with liquids is not necessary. Direct patients to place RizaFilm oral (b) (4) film on the tongue, where it will disintegrate and be swallowed with saliva” We defer to the review team for the final determination on the appropriate language for the instructions.
Patient Information (PPI)			
1.	The Section “How should I store RizaFilm?” does not include the storage statement “keep product in pouch until ready to use.”	Incomplete storage information may result in improper storage of the drug product which may lead to deteriorated drug medications errors.	We recommend adding the statement, “keep product in pouch until ready to use” as presented on your carton labeling and container label.

5 RECOMMENDATIONS FOR INTELGENX CORP

Table 3. Identified Issues and Recommendations for IntelGenx Corp (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The presentation of the letter “R” in the proprietary name, RizaFilm, can be improved for readability.	The artistic presentation of the letter “R” (i.e., top left is not closed) may detract from the readability and may distort the interpretation of the proprietary name.	We recommend you consider different styling for the “R” in the proprietary name. Consider the presentation of the “R” on your proposed container label and carton labeling submitted on September 26, 2019.

Table 3. Identified Issues and Recommendations for IntelGenx Corp (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	Carton: The product strength is located to the far-right of the proprietary name and directly to the left of the contains statement. Container: The product strength is located directly to the right of the contains statement.	The strength statement is not in the customary location (i.e., immediately following the dosage form) and may hinder a provider's ability to quickly and easily identify this information on the label and labeling.	We recommend relocating the strength statement to follow the dosage form. <u>For example:</u> RizaFilm (rizatriptan) oral (b) (4) film 10 mg OR RizaFilm (rizatriptan) oral (b) (4) film 10 mg Consider the location of the strength on your proposed container label and carton labeling submitted on September 26, 2019. Additionally, for the container label, refer to Container Label recommendations #1 and #2 below.
Container Label			
1.	The established name is missing from the container label.	The established name is required to appear on the container label in accordance with 21 CFR 201.10 (g)(1).	Revise the container label to include the established name to be in accordance with 21 CFR 201.10(g)(1). Also, ensure the presentation of the established name is at least half the size of the proprietary name. Additionally, refer to Carton Labeling recommendation #1 below.
2.	The dosage form (i.e., oral (b) (4) film) is not	The dosage form is critical information that should	Include the dosage form "oral (b) (4) film" immediately

Table 3. Identified Issues and Recommendations for IntelGenx Corp (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	included on the container label.	appear prominently to help identify the product.	following the established name. For example: RizaFilm (rizatriptan) oral (b) (4) film 10 mg OR RizaFilm (rizatriptan) oral (b) (4) film 10 mg Consider the presentation of the dosage form on the proposed container label and carton labeling submitted on September 26, 2019.
Carton Labeling			
1.	The established name lacks prominence commensurate with the proprietary name. Specifically, the established name is not at least half the size of the proprietary name.	As currently presented, the established name is not at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).	Increase the prominence (e.g., font size) of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Consider the presentation of the established name on the proposed container label and carton labeling submitted on September 26, 2019.
2.	The dosage form (i.e., oral (b) (4) film) lacks sufficient prominence and is difficult to read.	The dosage form is critical information that should appear prominently to help identify the product.	To increase readability, we recommend increasing the prominence/font size of the dosage form “oral (b) (4) film.” If more space is needed, you may consider placing the

Table 3. Identified Issues and Recommendations for IntelGenx Corp (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			dosage form underneath the established name. Consider the presentation of the dosage form on the proposed container label and carton labeling submitted on September 26, 2019.
3.	The net quantity statement (i.e., 18 Films, 12 Films, 6 Films) competes in prominence with important product information (i.e., proprietary name, established name, and product strength).	The prominence of the net quantity statement may detract from the important product information, specifically the product strength, which may cause numerical confusion.	We recommend decreasing the prominence of the net quantity statement (i.e., 18 Films, 12 Films, 6 Films).
4.	The statement (b) (4) appears on the back panel of the carton labeling.	The statement (b) (4) is unnecessary because "Rx only" replaces this cautionary statement and appears on the Principal Display Panel.	Consider removing the statement (b) (4)
5.	The statement "Dispense in (b) (4) container" can be improved for clarity.	This may be improved o accurately describe how to dispense the drug product (i.e., store pouches in carton) and prevent administration of deteriorated drug product.	Consider revising the statement "Dispense in (b) (4) container" to "Dispense in this sealed carton."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for RizaFilm that IntelGenx Corp submitted on October 17, 2022, and the listed drug, Maxalt MLT.

Table 4. Relevant Product Information for Rizatriptan and Listed Drug, Maxalt MLT ⁱ		
Product Name	RizaFilm	Maxalt MLT (NDA 020864)
Initial Approval Date	N/A	6/29/1998
Active Ingredient	rizatriptan	rizatriptan benzoate
Indication	Acute treatment of migraine with or without aura in adults and in patients 12 to 17 years of age	For the acute treatment of migraine with or without aura in adults and in pediatric patients 6 to 17 years old.
Route of Administration	oral	oral
Dosage Form	Oral (b) (4) film	Orally disintegrating tablet (ODT)
Strength	10 mg	10 mg
Dose and Frequency	Adults: single dose of 10 mg; may repeat every 2 hours up to a maximum of 30 mg in 24 hours Pediatric patients 12 to 17 years of age: 10 mg single dose in patients weighing 40 kg (88 lb.) or more	Although rizatriptan benzoate 5 orally disintegrating tablets are available in the marketplace, MAXALT-MLT Orally Disintegrating Tablets are no longer marketed in the 5 mg strength. <u>Adults:</u> The recommended starting dose of MAXALT MLT is either 5 mg or 10 mg for the acute treatment of migraines in adults. The 10-mg dose may provide a greater effect than the 5-mg dose, but may have a greater risk of adverse reactions. Redosing in Adults: If the migraine returns, a second dose may be administered 2 hours after the first dose. The

ⁱ Maxalt MLT (rizatriptan benzoate) orally disintegrating tablet (NDA 020864) Prescribing Information. Available from Dailymed: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=007b4644-e0e7-4863-9ae3-fe09676b3f5f>

		maximum daily dose should not exceed 30 mg in any 24-hour period. <u>Pediatric Patients</u> (Age 6 to 17 years) Dosing in pediatric patients is based on the patient's body weight. The recommended dose of MAXALT is 5 mg in patients weighing less than 40 kg (88 lb), and 10 mg in patients weighing 40 kg (88 lb) or more. <i>Dosage Adjustment for Patients on Propranolol:</i> <u>Adult Patients</u> In adult patients taking propranolol, only the 5-mg dose of MAXALT is recommended, up to a maximum of 3 doses in any 24-hour period (15 mg) <u>Pediatric Patients</u> For pediatric patients weighing 40 kg (88 lb) or more, taking propranolol, only a single 5-mg dose of MAXALT is recommended (maximum dose of 5 mg in a 24-hour period). MAXALT should not be prescribed to propranolol-treated pediatric patients who weigh less than 40 kg (88 lb)
How Supplied	Each oral film is individually packaged in an aluminum laminate pouch and supplied in cartons containing: 1 carton of 6 individually packaged films (NDC (b) (4)) 1 carton of 12 individually packaged films (NDC (b) (4)) and	10 mg: white to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch

	1 carton of 18 individually packaged films (NDC (b) (4))	(sachet). They are supplied as follows: 6 × unit of use carrying case of 3 orally disintegrating tablets (18 tablets total).
Storage	Room temperature; 59°F to 77°F (15°C to 25°C)	
Container Closure	Flexible laminate pouch that consists of a (b) (4) /foil laminate with medium strength Core-Peel® as the product contact layer.	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 13, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 205394 and rizatriptan. Our search identified three previous reviews^{j,k,l}, and we confirmed that our previous recommendations were implemented or considered.

^j Neshiewat, J. Label and Labeling Review for Rizatriptan (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 10. RCM No.: 2013-1082.

^k Rider B. Label and Labeling Review for RIZAPORT (rizatriptan) (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 11. RCM No.: 2018-2136.

^l Baugh, D. Label and Labeling Review for Rizatriptan (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 23. RCM No.: 2018-2136-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^m along with postmarket medication error data, we reviewed the following RizaFilm labels and labeling submitted by IntelGenx Corp. received on October 17, 2022.

- Container label
- Carton labeling
- Annotated and Clean Prescribing Information (Image not shown) available from
 - o <\\CDSESUB1\EVSPROD\nda205394\0023\m1\us\114-labeling\draft\annotated\presc info annotated.docx>
 - o <\\CDSESUB1\EVSPROD\nda205394\0023\m1\us\114-labeling\draft\labeling\prescribing-info-clean.pdf>
- Annotated and Clean Patient Information (image not shown) available from
 - o <\\CDSESUB1\EVSPROD\nda205394\0023\m1\us\114-labeling\draft\annotated\patient-info-annotated.docx>
 - o <\\CDSESUB1\EVSPROD\nda205394\0023\m1\us\114-labeling\draft\labeling\patient-info-clean.pdf>

F.2 Label and Labeling Images

Container (pouch) label



^m Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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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)

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Date of This Review:	December 23, 2019
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 205394
Product Name, Dosage Form, and Strength:	Rizatriptan oral (b) (4) film, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	IntelGenx Corp.
FDA Received Date:	September 26, 2019
OSE RCM #:	2018-2136-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

This review is in response to a request from the Division of Neurology 2 (DN2) to review the proposed labels and labeling for rizatriptan oral (b) (4) film for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

IntelGenx Corp. submitted NDA 205394 on March 17, 2013. The Agency subsequently issued a Complete Response (CR) letter on January 31, 2014. IntelGenx Corp submitted NDA 205394 as a Class 2 resubmission on October 1, 2018. The Agency issued a CR letter March 28, 2019 and DMEPA's previous recommendations for the container label and carton labeling were included in the CR letter. IntelGenx Corp submitted their response to the CR letter as a Class 2 resubmission on September 26, 2019.

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 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our 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 reviewed the proposed label and labeling for their vulnerability to medication errors and to determine if our previous recommendations were implemented or considered^a.

^a Rider B. Label and Labeling Review for RIZAPORT (rizatriptan) (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 11. RCM No.: 2018-2136.

Prescribing Information (PI)

- Section 2.1 of the Full Prescribing Information (FPI) [REDACTED] (b) (4)
- Section 2.3 of the FPI can be improved to clearly state how the pouch should be opened prior to administration. We are concerned this lack of clarity poses risk of the film being damaged.
- We note the presence of dashes between the numerical dose and the unit of measure (e.g., 10-mg) used throughout the PI and may lead to dose misinterpretation or confusion.
- We note the container label states “Keep product in pouch until ready to use.” However, this information is not present in Section 16 *How Supplied/Storage and Handling* of the PI.
- Section 17 *Patient Counseling Information* lacks information on how to open the pouch.

Carton Labeling and Container Label

- The temperature scale statements do not include the temperature scale designation (i.e., ‘C’ or ‘F’) after each numerical value, which could lead to misinterpretation and may pose a risk of drug degradation.
- The usual dose statement can be improved to ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information labeling.

Carton Labeling

- It is unclear what information will be included in the area titled ‘serialization area’. Therefore, we are unable to assess the acceptability of this information.
- We note a product identifier is not present as required by the Drug Supply Chain Security Act.
- There is no placeholder (“LOT” and “EXP”) for the lot number and expiration date, which are required per 21 CFR 10(i)(1) and 21 CFR 211.137, respectively.
- We note the statement [REDACTED] (b) (4) on the side panel and are concerned that this may be interpreted as the proprietary name, which could lead to confusion.

Container Label

- As currently presented, the format for the expiration date is “YYYY MM.” However, it is unclear whether the month (that is, MM) will be displayed using numerical (for example, 06) or alphabetical (for example, JU) characters. Therefore, we were not able to assess the appropriateness of the proposed expiration date format from a medication safety perspective.

See Sections 4.1 and 4.2 below for our detailed recommendations to address the aforementioned concerns.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling where additional important information should be added or further clarified to help ensure the safe use of this product. See our recommendations in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

A. Prescribing Information

1. Dosage and Administration Section

- a. Section 2.1 of the Full Prescribing Information (FPI) states (b) (4)

[REDACTED]

We recommend removing this statement from the PI.

- b. Section 2.3 of the FPI states (b) (4)

[REDACTED] However, this statement does not specify where the pouch should be folded or torn, which poses the risk of the film being damaged. We recommend revising the statement to read: “The pouch should be folded on the dotted line and torn open at the notch...” for consistency across the labels and labeling.

- c. We note the presence of dashes between the numerical dose and the unit of measure (e.g., 10-mg) used throughout the PI. We recommend removal of the dashes between the numerical dose and unit of measure to avoid dose misinterpretation and confusion.

2. How Supplied/Storage and Handling Section

- a. We note the container label states “Keep product in pouch until ready to use.” However, this information is not present in Section 16 of the PI. We recommend adding this statement, or a similar one, to Section 16 of the PI to decrease the risk of administration of a degraded product.

3. Patient Counseling Information Section

- a. Section 17 *Patient Counseling Information* lacks information on how to open the pouch. We recommend adding the instruction to “fold on dotted line and tear open at notch” to open the pouch, to minimize the risk of delay of therapy medication errors.

4.2 RECOMMENDATIONS FOR INTELGENX CORP.

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

A. General Comments (Container labels and Carton Labeling)

1. The usual dose statement can be improved to ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information labeling. We recommend you revise the usual dose statement: “Usual Dosage: See package insert for dosage information.” to read “Recommended Dosage: See prescribing information.”
2. The current temperature statements do not contain the temperature scale designation (i.e., “°C” or “°F”) after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. Ensure that the degree symbol and temperature scale follow each numeric value denoting temperature ranges to increase clarity. For example, revise “59° - 77°F (15° - 25°C)” to read “59°F to 77°F (15°C to 25°C)”.

B. Container Labels

1. As currently presented, the format for the expiration date is “YYYY MM.” However, it is unclear whether the month (that is, MM) will be displayed using numerical (for example, 06) or alphabetical (for example, JU) characters. Therefore, we were not able to assess the appropriateness of the proposed expiration date format from a medication safety perspective. Please clarify whether you propose to use only numerical characters for the expiration date, or whether you propose to use alphabetical characters for the month. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day, if space permits. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

C. Carton Labeling

1. It is unclear what information will be contained within the “Serialization Area.” Therefore, we are unable to assess the acceptability of the information. Please clarify the specific information you intend to display in the “Serialization Area.”
2. As currently presented, there is no product identifier on the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The draft guidance is available from:
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.

3. We did not identify a placeholder (“LOT” or “EXP”) for the lot number and expiration date on the carton labeling. The lot number and expiration date are required per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively. Ensure that the lot number and expiration date are present on the carton labeling in accordance with 21 CFR 10(i)(1) and 21 CFR 211.137.
4. We note the statement (b) (4) on the side panel and are concerned that this may be interpreted as the proprietary name, which could lead to confusion. Consider relocating this statement to the back panel, deleting the statement altogether, or address this concern by other means.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rizatriptan received on September 26, 2019 from IntelGenx Corp.

Table 2. Relevant Product Information for Rizatriptan	
Initial Approval Date	N/A
Active Ingredient	rizatriptan
Indication	Acute treatment of migraine with or without aura in adults and in patients 12 to 17 years of age
Route of Administration	oral
Dosage Form	Oral (b) (4) film
Strength	10 mg
Dose and Frequency	Adults: single dose of 10 mg; may repeat every 2 hours up to a maximum of 30 mg in 24 hours Pediatric patients 12 to 17 years of age: 10 mg single dose in patients weighing 40 kg (88 lb.) or more
How Supplied	Each oral film is individually packaged in an aluminum laminate pouch and supplied in cartons containing: • 1 carton of 6 individually packaged films (NDC (b) (4)) • 1 carton of 12 individually packaged films (NDC (b) (4)) and • 1 carton of 18 individually packaged films (NDC (b) (4))
Storage	Room temperature; 59°F to 77°F (15°C to 25°C)
Container Closure	Flexible laminate pouch that consists of a (b) (4) /foil laminate with medium strength Core-Peel® as the product contact layer.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 12, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, 'rizatriptan'. Our search identified one previous review^b and we considered our previous recommendations to see if they are applicable for this current review.

^b Rider B. Label and Labeling Review for RIZAPORT (rizatriptan) (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 11. RCM No.: 2018-2136.

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,^c along with postmarket medication error data, we reviewed the following Rizatriptan labels and labeling submitted by IntelGenx Corp.

- Container label received on September 26, 2019
- Carton labeling received on September 26, 2019
 - o 18 count carton
 - o 12 count carton
 - o 6 count carton
- Prescribing Information (Image not shown) received on September 26, 2019, available from <\\cdsesub1\evsprod\nda205394\0016\m1\us\114-labeling\draft\labeling\prescribing-info-clean.pdf>
- Patient Information (image not shown) received on September 26, 2019

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DENISE V BAUGH
12/23/2019 02:23:05 PM

BRIANA B RIDER
12/24/2019 09:03:41 AM

MEMORANDUM

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

DATE: 1/14/2019

TO: Office of Drug Evaluation I
Division of Neurology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 205394

OSIS received an inspection request consult from the Division of Neurology Products dated January 7, 2019 for the below clinical and analytical site. The requested review goal date is March 15, 2019.

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct an inspection of the clinical and analytical site listed in the consult. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in (b) (4) and the analytical inspection was conducted in (b) (4) which fall within the surveillance interval. The inspections were conducted under the following submissions: (b) (4)

The final classification for the inspections was No Action Indicated (NAI).

In addition, the requested review goal date outlined in the consult does not provide sufficient time for the inspections to be completed and for OSIS to submit an Establishment Inspection Report review to the review division.

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted.

Inspection Site

Facility Type	Facility Name	Facility Address
		(b) (4)

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/s/

SHILA S NKAH
01/14/2019 11:15:42 AM

LABEL AND LABELING 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:	December 11, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 205394
Product Name and Strength:	Rizaport (rizatriptan) oral (b) (4) film, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	IntelGenx Corp.
FDA Received Date:	October 1, 2018 and November 6, 2018
OSE RCM #:	2018-2136
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

This review is in response to a request from the Division of Neurology Products (DNP) to review the proposed labels and labeling for Rizaport (rizatriptan) oral (b) (4) film for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

IntelGenx Corp. submitted NDA 205394 on March 27, 2013. The Agency subsequently issued a Complete Response (CR) letter on January 31, 2014.

IntelGenx Corp. submitted NDA 205394 as a Class 2 resubmission on October 1, 2018.

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 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling identified areas which may be improved to decrease risk of medication error.

Prescribing Information

- Section 2.1 of the Full Prescribing Information (FPI) (b) (4)
- Section 2.3 of the FPI can be improved to clearly state how the pouch should be opened prior to administration. We are concerned this lack of clarity poses risk of the film being damaged.

- We note the presence of dashes between the numerical dose and the unit of measure (e.g., 10-mg) used throughout the PI and may lead to dose misinterpretation or confusion.
- We note the container label states “Keep product in pouch until ready to use.” However, this information is not present in Section 16 *How Supplied/Storage and Handling* of the PI.
- Section 17 *Patient Counseling Information* lacks information on how to open the pouch.

Container Label

- The container label does not indicate the intended expiration date format and may pose risk of degraded drug medication administration errors.
- The immediate container label lacks a barcode. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the pouch label as required per 21 CFR 201.25(c)(2).
- The established name, finished dosage form, and strength are not displayed in accordance with our current draft Guidance for Industry: “Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors”
- We note the container label lacks instruction on how to use the film, which poses risk of wrong technique administration errors.

Carton Labeling

- The net quantity statement (i.e., 18 Films, 12 Films, 6 Films) competes in prominence with important product information.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to ensure safe use and handling of the proposed product. We provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

- a. Section 2.1 of the Full Prescribing Information (FPI) states (b) (4)

[REDACTED]

We recommend removing this statement from the PI.

- b. Section 2.3 of the FPI states (b) (4). However, this statement does not specify where the pouch should be folded or torn, which poses risk of the film being damaged. We recommend revising the statement to read: “The pouch should be folded on the dotted line and torn open at the notch...” for consistence across the labels and labeling.
- c. We note the presence of dashes between the numerical dose and the unit of measure (e.g., 10-mg) used throughout the PI. We recommend removal of the dashes between the numerical dose and unit of measure to avoid dose misinterpretation and confusion.
- 2. How Supplied/Storage and Handling
 - a. We note the container label states “Keep product in pouch until ready to use.” However, this information is not present in Section 16 of the PI. We recommend adding this statement, or a similar one, to Section 16 of the PI to decrease risk of administration of degraded product.
- 3. Patient Counseling Information Section
 - a. Section 17 *Patient Counseling Information* lacks information on how to open the pouch. We recommend adding the instruction to “fold on dotted line and tear open at notch” to open the pouch, to minimize the risk of delay of therapy medication errors.

4.2 RECOMMENDATIONS FOR INTELGENX CORP.

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

A. Container Labels

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2. The immediate container label lacks a barcode. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product’s linear barcode to each individual pouch as required per 21CFR 201.25(c)(2).
3. The layout of the strength is not consistent with our current guidance for the presentation of the proprietary name, established name, dosage form, and

strength for drug products.^a Relocate the strength statement to follow the established name on the principal display panel as this is the customary placement of the strength statement, and therefore the location most familiar to users. See example below:

RIZAPORT
(rizatriptan)
oral  film
10 mg

4. We note the container label lacks instruction on how to use the film, which poses risk of wrong technique administration errors. We recommend adding a statement such as “How to use: Use dry hands. Place film on tongue. Keep in place until film dissolves.” or any other relevant statements should be added to the container label to minimize the risk of wrong technique administration errors.
- B. Carton Labeling
1. The net quantity statement (i.e., 18 Films, 12 Films, 6 Films) competes in prominence with the proprietary name, established name, and product strength and takes away from important product information. ^aDecrease the prominence of the net quantity statement (i.e., 18 Films, 12 Films, 6 Films).

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 336-342). Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rizaport received on October 1, 2018 from IntelGenx Corp.

Table 2. Relevant Product Information for Rizaport	
Initial Approval Date	N/A
Active Ingredient	rizatriptan
Indication	Acute treatment of migraine with or without aura in adults and pediatric patients 12 to 17 years of age.
Route of Administration	oral
Dosage Form	oral (b) (4) film
Strength	10 mg
Dose and Frequency	Adults: 10 mg single dose; separate repeat doses by at least two hours; maximum dose in a 24-hour period: 30 mg Pediatric patients (12 to 17 years): 10 mg single dose in patients 40 kg (88 lb.) or more
How Supplied	Each oral film is individually packaged in an aluminum laminate pouch and supplied in cartons containing: • 1 carton of 18 individually packaged films (NDC (b) (4)) • 1 carton of 12 individually packaged films (NDC (b) (4)) • 1 carton of 6 individually packaged films (NDC (b) (4))
Storage	Store at room temperature, 59°F to 86°F (15°C to 30°C)
Container Closure	Flexible laminate pouch that consists of a (b) (4) /foil laminate with medium strength Core-Peel® as the product contact layer.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 23, 2018, we searched for previous DMEPA reviews relevant to this current review using the term, NDA 205394. Our search identified one previous reviews^b, and we considered our previous recommendations to see if they are applicable for this current review.

^b Neshiewat, J. Label and Labeling Review for Rizatriptan oral films (NDA 205394). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 10. RCM No.: 2013-1082.

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,^c along with postmarket medication error data, we reviewed the following Rizaport labels and labeling submitted by IntelGenx Corp. on October 1, 2018 and November 6, 2018.

- Container label
- Carton labeling
 - o 18-count carton
 - o 12-count carton
 - o 6-count carton
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container Label

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BRIANA B RIDER
12/11/2018

LOLITA G WHITE
12/11/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: January 10, 2014

Acting Team Leader: Julie Neshiewat, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Rizatriptan Oral Film (b) (4) 10 mg

Application Type/Number: NDA 205394

Applicant: RedHill Biopharma

OSE RCM #: 2013-1082

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	INTRODUCTION	1
1.1	Product Information.....	1
2	METHODS AND MATERIALS REVIEWED	1
2.1	Selection of Medication Error Cases	1
2.2	Labels and Labeling	2
3	MEDICATION ERROR RISK ASSESSMENT	2
3.1	Medication Error Cases	2
3.2	Integrated Summary of Medication Error Risk Assessment	3
4	CONCLUSIONS	4
5	RECOMMENDATIONS.....	4
	Appendices.....	6

1 INTRODUCTION

This review evaluates the proposed labels and labeling for Rizatriptan Oral Films, NDA 205394, for areas of vulnerability that could lead to medication errors in response to a request from the Division of Neurology Products (DNP).

1.1 PRODUCT INFORMATION

Rizatriptan Oral Films is a 505(b)(2) application and the referenced drug is Maxalt-MLT (Rizatriptan Benzoate Oral Disintegrating Tablets). The following product information is provided in the July 10, 2013 insert labeling submission.

- Active Ingredient: Rizatriptan
- Indication of Use: Acute treatment of migraine with or without aura in adults
- Route of Administration: Oral
- Dosage Form: Films
- Strength: (b) (4) 10 mg
- Dose and Frequency: (b) (4) 10 mg single dose; separate repeat doses by at least two hours; maximum dose in a 24-hour period is 30 mg
- How Supplied: Carton containing 18 pouches; each pouch contains 1 film
- Storage: Room temperature
- Container and Closure System: child resistant packaging material containing (b) (4) aluminum. (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Maxalt-MLT medication error cases. We also reviewed the Rizatriptan labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS† Search Strategy	
Date	November 12, 2013
Drug Names	Maxalt-MLT (product name) *Maxalt-MLT* (product verbatim)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues NEC (HLT)

† See Appendix A for a description of the FAERS database

The FAERS database search identified 18 cases. Each case was reviewed for relevancy and duplication. After individual review, 15 cases were not included in the final analysis for the following reasons:

- Wrong drug error associated with Maxalt and Maxalt-MLT
- Intentional overdose
- Wrong patient
- Wrong technique with orally disintegrating tablet
- Product quality issue unrelated to a medication error
- Adverse event unrelated to a medication error
- Not enough information to determine if a medication error occurred
- Duplicate case

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Pouch Labels submitted October 30, 2013 (Appendix B)
- Carton Labeling submitted October 30, 2013 (Appendix C)
- Prescribing Information submitted July 10, 2013 (No image)
- Patient Information submitted July 10, 2013 (No image)

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes the results of our FAERS search and the risk assessment of the Rizatriptan labels and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, three medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Appendix D provides listings of all case numbers for the cases summarized in this review.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Overdose (n = 3)

In two of the three cases, the health care provider prescribed more than a 10 mg dose. In the third case, the patient took 15 to 17 doses of rizatriptan per month due to increased migraine attack frequency. Outcomes of the cases include amnestic episodes and throat irritation.

We reviewed the insert labeling and it states that the single dose is (b) (4) 10 mg, and the maximum dose in a 24 hour period is 30 mg. The insert labeling further states that the safety of treating more than four headaches in a 30 day period has not been established. The patient information leaflet states that the maximum dose in a 24 hour period is 30 mg. It may be helpful to also state in the patient information leaflet that the safety of treating more than four headaches in a 30 day period has not been established.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Based on the overdose cases, it may be helpful to state in the patient information leaflet that the safety of treating more than four headaches in a 30 day period has not been established.

The Chemistry, Manufacturing, and Controls (CMC) reviewer indicated that the active ingredient for the product should be consistent with the expression of potency and therefore should use the active ingredient “Rizatriptan” on the labels and labeling. We note the active ingredient “Rizatriptan” would be in compliance with the Manual of Policies and Procedures (MAPP) for Naming of Drug Products Containing Salt Drug Substances. However, this would appear different from the listed active ingredient “Rizatriptan Benzoate” on the labels and labeling for the referenced drug, Maxalt MLT. This information was communicated to the Labeling and Nomenclature Committee (LNC). Since the strength on the labels and labeling of both the proposed product and referenced drug, Maxalt MLT, refer to “Rizatriptan,” it was determined to use “Rizatriptan” as the active ingredient on the labels and labeling for the proposed product.

The colored text against the background colors for (b) (4) is difficult to read and should be revised for better contrast. Statements in all upper case should be revised to title case for improved readability. The strength statement should appear beneath the dosage form statement for customary placement. Adequate and clear instructions for opening the pouch should appear on the labels and labeling. The labels and labeling should also state the product should be kept in the pouch until ready to use to help maintain the product’s integrity. The labeling can be revised for clarity indicating that subsequent doses, up to 30 mg in a 24 hour period, can be administered 2 hours after the previous dose. Since the Applicant is no longer proposing a (b) (4) the how supplied section of the full prescribing information will need to be updated based on this information. Negative warnings, such as “do not do that” can be misread as an affirmative warning “do this.”² and therefore, negative warnings should be revised in the labeling.

² Institute for Safe Medication Practices (ISMP). August 12, 2010. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Medication Safety Alert, 15(16).

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to clarify information and to increase the readability of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

DMEPA provides the recommendations below for consideration by the review division prior to approval of the NDA:

A. Comments to the Division

1. Full Prescribing Information: Dosage and Administration

- a. Consider revising the statement (b) (4) for clarity.
- b. We recommend revising the statement (b) (4) to read similar to “The pouch should be folded on the dotted line and torn open at the notch...” for clarity.

2. Full Prescribing Information: How Supplied/Storage and Handling

- a. Since the Applicant is no longer proposing (b) (4) the NDC number will need to be updated for consistency with the carton labeling. In addition, we recommend revising (b) (4) to read “carton containing 18 oral films” for accuracy.
- b. We recommend adding a statement similar to “Keep product in pouch until ready to use.” to help maintain the integrity of the product.

3. Full Prescribing Information: Patient Counseling Information

- a. Consider including a section to instruct patients on how to open the pouch and administer the film.

4. Patient Information Leaflet

- a. In the How should I take RIZ105 section, we recommend revising the statement (b) (4) to read similar to “Remove the film from the aluminum pouch by folding on the dotted line and tearing it open at the notch...”
- b. In the How should I take RIZ105 section, we recommend revising the statement “For adults: a second dose may be taken 2 hours after the first dose.” to read “For adults: another dose may be taken 2 hours after the previous dose.” for clarity.

- c. Negative warnings, such as “do not do that” can be misread as an affirmative warning “do this.”³ In the How should I take RIZ105 section, we recommend revising the negative statement “Do not take more than 30 mg of RIZ105 in a 24 hour period” to read similar to “The total maximum dose of RIZ105 in a 24 hour period is 30 mg.”
- d. In the How should I store RIZ105? Section, we recommend adding a statement similar to “Keep product in pouch until ready to use.” to help maintain the integrity of the product.

B. Comments to the Applicant

1. General Comments for Labels and Labeling

- a. (b) (4) against the (b) (4) background for the 10 mg strength is difficult to read. Change the background colors or change the colored text for better contrast and to improve readability.
- b. Revise the active ingredient from (b) (4) to “Rizatriptan.”
- c. Relocate the strength to beneath the dosage form for customary placement.

2. Pouch Labels

- a. It is unclear where the pouch should be folded before tearing open at the notch. Add a dotted line to show where it should be folded. Revise the statement (b) (4) to read similar to “To open: Fold on the dotted line and tear open at the notch.” for clarity. In addition, the dotted line and instructions for opening the pouch should appear on the principal display panel instead of the back panel. In order to accommodate this information, relocate the net quantity to the lower third of the principal display panel, away from the strength.
- b. Add the statement “Keep product in pouch until ready to use.” to the back panel, similar to the carton labeling, to help maintain the integrity of the product.

3. Carton Labeling

- a. Revise statements in all upper case to sentence case to improve readability.

If you have further questions or need clarifications, please contact Ermias Zerislassie, OSE Regulatory Project Manager, at 301-796-0097.

³ Institute for Safe Medication Practices (ISMP). August 12, 2010. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Medication Safety Alert, 15(16).

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JULIE V NESHIEWAT
01/10/2014

MEMORANDUM

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

DATE: September 26, 2013

TO: Eric P. Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I

FROM: Arindam Dasgupta, Ph.D., Pharmacologist
Division of Bioequivalence and GLP Compliance
(DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 205-394, Rizatriptan
Benzoate oral film 10 mg, (b) (4) sponsored by
RedHill Biopharma Ltd., Tel Aviv, Israel

At the request of the Division of Neurology Products,
Office of New Drugs, DBGLPC audited the clinical and
analytical portions of the following comparative
bioavailability study.

Study #: RZA-P9-688
Study Title: Single dose crossover comparative
bioavailability study of Rizatriptan 10 mg
immediate release oral film and Maxalt-MLT®
10 mg orally disintegrating tablets in
fasting state in healthy male and female
volunteers

The clinical and analytical portions of the study were audited at [REDACTED] (b) (4) by ORA Investigator George C. Amedro and OSI/DBGLPC scientist Arindam Dasgupta).

The audit included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

Following the inspections at the clinical and analytical sites no Form FDA-483 was issued and there were no significant findings at either site.

Conclusions:

Following the above inspections, I recommend that data for clinical and analytical portions of study RZA-P9-688 are acceptable for further agency review.

Arindam Dasgupta Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

Clinical

NAI: [REDACTED] (b) (4)

Analytical

NAI: [REDACTED] (b) (4)

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Skelly/Choi/Bonapace/Dasgupta/Dejernet/CF
OND/ODEI/DNP/Bastings/Lana Chen
OCP/DCP1/Mehta/ Xinning Yang/ Angela Y. Men
ORA/NE-FO/NYK-DO/NYK-DIB/SYR-NY/Amedro
Draft: AD 09/26/2013
Edit: MFS 9/26/2013
OSI: BE6467; 0:\BE\EIRCOVER\205394red.riz.doc
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
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/s/

ARINDAM DASGUPTA

09/26/2013

MICHAEL F SKELLY

09/26/2013

Skelly signing on behalf of Dr. Haidar

WILLIAM H TAYLOR

09/26/2013