

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205394Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number	205394		
Applicant Name	IntelGenx Corp.		
Drug Product Name	RIZAFILM		
Dosage Form	Oral film		
Proposed Strength	10 mg		
Route of Administration	Oral		
Maximum Daily Dose	30 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Acute treatment of migraine with or without aura in adults and in pediatric patients (b) (4) 12 to 17 years of age		
Drug Product Description	White to off-white, rectangular strips, 2.2 cm x 2.75 cm, with "RIZA10" printed in blue ink on one side		
Co-packaged product information	Not applicable		
Device information	Not applicable		
Storage Temperature/ Conditions	Controlled room temperature, 20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Zhixing Shan	Gaetan Ladouceur
	<i>Drug Product/ Labeling</i>	Eric Bow	Martha Heimann
	<i>Manufacturing</i>	Qin (Stefanie) Liang / Erin Kim	Cassandra Abellard / Lane Christensen
	<i>Biopharmaceutics</i>	N/A this review cycle	N/A
	<i>Microbiology</i>	N/A	N/A



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	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

18 months when stored at 20°C to 25°C

b. Additional Comments for Action

There are no additional comments.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends **APPROVAL** of NDA 205394 for RIZAFILM (rizatriptan) oral film 10 mg. The applicant has provided adequate information to address deficiencies identified in previous review cycles and to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

This is the fourth review cycle for NDA 205394. The Applicant, IntelGenx Corporation (IntelGenx), seeks approval for a Rizatriptan Oral Film formulation that they developed. The NDA was initially submitted by Redhill Pharma in March 2013, with IntelGenx acting as the U.S. agent. Subsequently, the application was transferred to IntelGenx. Extensive CMC deficiencies were identified during the previous review cycles, including issues with the manufacturing process for the oral films, specifications, drug product stability, (b) (4), and a withhold recommendation for the original drug substance (DS) manufacturer (b) (4) during the first review cycle. In the first resubmission, IntelGenx then switched to (b) (4) as DS supplier and moved drug product (DP) manufacture from the original contract manufacturer to an IntelGenx facility. (b) (4) and IntelGenx facilities both received withhold recommendations during the second and third review cycles.



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In the 10/17/2022 resubmission, the applicant added (b) (4) as an alternate DS supplier. The (b) (4) DS has been reviewed and is acceptable for manufacture of the DP. Additionally, both the (b) (4) facilities are acceptable and recommended for approval.

To address control of the (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4). The modified manufacturing process is adequate and the IntelGenx DP manufacturing facility was recommended for approval following a recent PAI³.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

- Drug Substance** - Adequate
- Drug Product** - Adequate
- Quality Labeling** - Adequate
- Manufacturing** - Adequate
- Biopharmaceutics** - Adequate after previous review cycles.
- Microbiology** - N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: There are no additional lifecycle concerns

¹ MDI: maximum daily intake

² PDE: permissible daily exposure per ICH Q3D(R2) Elemental Impurities

³ PAI: pre-approval inspection



Martha
Heimann

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	Adequate	

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		
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1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another	N/A	

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i> .	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

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

² Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Inadequate	Need to add oral film to pouch container label.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	Move salt equivalency statement to side or back panel and correct formatting "10 mg rizatriptan (equivalent to 14.53 mg rizatriptan benzoate"
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Does not match PI instructions of 20-25°C, and need excursion statement. Recommend adding USP controlled room temperature
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

³ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap over seal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Adequate with outstanding IRs

Primary Labeling Assessor Name and Date: Eric Bow

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Martha Heimann*



Eric
Bow

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Martha
Heimann

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RECOMMENDATION: Complete Response

NDA 205394

Review 3

Drug Product Name	Rizaport™ (rizatriptan) oral film
Dosage Form	Oral film
Strength	10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	IntelGenx Corporation
US agent, if applicable	Ross C. D'Emanuele

QUALITY TEAM (Review 3)

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	Stephanie Emory	Julia Pinto
Manufacturing	Tianhong Tim Zhou	Aditi Thakur
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-36, Resubmission After Complete Response	9/26/2019	Product, Manufacturing
SD-37, Response to IR	10/8/2019	Manufacturing
SD-39, Quality Amendment	1/10/2020	Product

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	N/A ¹	
	III			N/A ¹	N/A ¹	

¹ Adequate information in application or no changes to information since previous adequate review.

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

Document	Application Number	Description
NDA	20865	Maxalt-MLT (rizatriptan benzoate orally disintegrating tablet). Referenced under 505(b)(2) for safety and efficacy of rizatriptan.
Pre-IND	110753	Type B pre-NDA meeting held on 11/7/2012. IntelGenx completed product development and bioequivalence studies prior to seeking Agency advice.

2. CONSULTS

Not applicable.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency issue a third **Complete Response Letter** (CRL) for NDA 205394 for Rizaport® (rizatriptan) oral film. From a quality perspective, the application remains inadequate to ensure that the Applicant can consistently manufacture a product that is suitable for use to treat the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Rizatriptan, a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist, was originally developed by Merck for acute treatment of migraine. It is currently marketed by Merck as 5 mg and 10 mg immediate-release tablets and as 5 mg and 10 mg orally disintegrating tablets under the trade names Maxalt® and Maxalt-MLT®, respectively. Generic versions of both products are available.

This is the third review cycle for NDA 205394. The Applicant, IntelGenx Corporation, seeks approval for a Rizatriptan Oral Film formulation that they developed. The NDA was initially submitted by Redhill Pharma in April 2013, with IntelGenx acting as U.S. agent for Redhill. Extensive CMC deficiencies, including CGMP problems with the original proposed drug substance manufacturer, were identified during the review of the original submission. and a CRL was issued on 1/31/2014. Redhill, and later IntelGenx as the application holder, submitted multiple incomplete responses to the CRL letter between 2/24/2014 and 11/30/2017. The 10/1/2018 resubmission was accepted as a complete response to the 1/31/2014; however, on review the OPQ review team again identified significant CMC and facility deficiencies. A second CRL was issued on 3/28/2019. On review of the 9/26/2019 resubmission, the application remains deficient and a CR action is recommended.

Proposed indication(s) including intended patient population	Acute treatment of migraine with or without aura in adults and in pediatric patients 12 to 17 years of age
Duration of treatment	Chronic intermittent
Maximum daily dose	30 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate per Review #2**

No new information submitted.

Drug Product: **Inadequate**

The primary deficiency identified during the previous review cycle was the inadequate control strategy for (b) (4)

[REDACTED]

[REDACTED]. The Applicant submitted corrected stability data based on out of specification (OOS) investigations. However, as discussed below; the Manufacturing reviewer has identified process deficiencies that preclude reliance on the 2017 and 2018 exhibit batches for primary stability data and recommends manufacture of new exhibit batches.

Labeling: **Adequate per Review #2**

No new information submitted.

Manufacturing: **Inadequate**

Deficiencies identified during the previous review cycle included:

[REDACTED] (b) (4)

Additionally, the manufacturing facility recommendation was Withhold due to deficiencies observed during the preapproval inspection (PAI) of the IntelGenx facility and official action indicated (OAI) status of the drug substance manufacturing facility.

The Applicant [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] However,
based on the current deficiencies, it is recommended that the Applicant manufacture
new registration batches and submit in-process data for assurance of adequate
process control and consistency to support approval of the application.

The manufacturing facility recommendation remains Withhold for both the drug
substance manufacturing facility and the Intelgenx drug product manufacturing
facility. Based on the responses to deficiencies identified during the PAI for this
application and a subsequent PAI for a different application, the IntelGenx is not
ready for commercial production. A follow up inspection will be needed to verify the
facility has taken necessary corrective actions to ensure oral film product quality.

Biopharmaceutics: **Adequate per Review #2**

No new information submitted.

C. Risk Assessment

The risk assessment for the rizatriptan oral film is unchanged from Review 2.

D. List of Deficiencies for Complete Response

1) With respect to the manufacturing process:

(b) (4)

2) With respect to drug product stability:

We acknowledge the out of specification (OOS) investigations submitted in response the September 26, 2019 action letter. However, due to the manufacturing process deficiencies described in Item 1 above, we have determined that stability data obtained from testing of the existing exhibit batches cannot be used as primary data for establishment of product shelf life. Therefore, we recommend the following:

- a) Submit 12 months of long-term stability data for exhibit batches manufactured as recommended in Comment 1. Stability testing should be performed using fully validated methods and the suitability of analytical equipment should be verified prior to use. The product shelf life assigned will be based on review of this stability data.
- b) If you intend to use the 2017 or 2018 batch stability results as supportive data, provide the raw HPLC data for all corrected analytical results. Additionally, regarding INV-2019-017, in order to support disqualification of the OOS stability results obtained using (b) (4) for analysis of this product, further investigation is needed to identify the root cause.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
3/2/2020



Martha
Heimann

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Recommendation: Complete Response

NDA 205394

Review # 2

Drug Name/Dosage Form	Rizaport™ (rizatriptan) oral film
Strength	10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	IntelGenx Corporation
US agent, if applicable	Ross C. D'Emanuele

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Su Tran
Drug Product/Labeling	Stephanie Emory	Wendy Wilson-Lee
Process	Yaodong (Tony) Huang	Nallaperumal Chidambaram
Microbiology	N/A	
Facility	Yaodong (Tony) Huang	Ying Zhang
Biopharmaceutics	Parnali Chatterjee	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia A. Woody	N/A
Application Technical Lead	Martha Heimann	N/A
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-026, Resubmission, Class 2	10/1/2018	All
SD-033, Response to IR	1/22/2019	Biopharmaceutics
SD-034, Response to IR	2/5/2019	Biopharmaceutics

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	3/1/2019	Reviewed by R. Pragani
	III			N/A ¹	N/A ¹	

¹ Adequate information in application or no changes to information since previous reviews.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20865	Maxalt-MLT (rizatriptan benzoate orally disintegrating tablet). Referenced under 505(b)(2) for safety and efficacy of rizatriptan.
Pre-IND	110753	Type B pre-NDA meeting held on 11/7/2012. IntelGenx completed product development and bioequivalence studies prior to seeking Agency advice.

2. CONSULTS: N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

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II. Summary of Quality Assessments

A. Product Overview

Rizatriptan, a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist, was originally developed by Merck for acute treatment of migraine. It is currently marketed by Merck as 5 mg and 10 mg immediate-release tablets and as 5 mg and 10 mg orally disintegrating tablets under the trade names Maxalt® and Maxalt-MLT®, respectively. Generic versions of both products are available.

The applicant, IntelGenx Corporation, seeks approval for a Rizatriptan Oral Film formulation that they developed. NDA 305394 was initially submitted by Redhill Pharma in April 2013, with IntelGenx acting as US agent for Redhill. Extensive CMC deficiencies, including CGMP problems with the proposed drug substance manufacturer, were identified during the review of the original submission, and a CRL was issued on 1/31/2014. Redhill/IntelGenx submitted an incomplete response to the CRL letter on 2/24/2014. Subsequently, Redhill transferred ownership of the NDA to IntelGenx. On 11/30/2017, IntelGenx attempted to resubmit the NDA with significant changes proposed including new drug substance manufacturing, new manufacturing site and revised process for the drug product, increased limits for degradation products, and deletion (b) (4) proposed in the original NDA. Based on an initial examination, the 11/30/2017 submission did not contain sufficient information to allow for a complete review and was deemed an incomplete response. The Agency provided additional guidance during a teleconference with the applicant on 3/22/2018 prior to the current resubmission. During the current review cycle, the OPQ review team again identified significant CMC deficiencies. Additionally, the overall manufacturing inspection recommendation is Withhold due to deficiencies at two manufacturing facilities.

Proposed Indication(s) including Intended Patient Population	Acute treatment of migraine with or without aura in adults and in pediatric patients 12 to 17 years of age
Duration of Treatment	Chronic intermittent
Maximum Daily Dose	Adult: 30 mg; Pediatric (≥ 40 kg): 10 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

(b) (4)

Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to drug master file (DMF) (b) (4). The DMF was reviewed to support this NDA and is deemed adequate. Information submitted by the applicant directly to the NDA includes a summary of general properties, an outline of the (b) (4) potential impurities, and the applicant's acceptance specification, which meets USP monograph requirements. The information provided in the application is consistent the DMF.

Drug Product

The proposed product is a 2.75 cm x 2.2 cm white rectangular oral (b) (4) film containing 10 mg of rizatriptan (as 14.53 mg of rizatriptan benzoate) and printed with RIZA10 in blue ink (colorant FD&C Blue No. 1). Inactive ingredients include copovidone and hydroxypropyl cellulose (b) (4) triacetin (b) (4), titanium dioxide (b) (4) sucralose (b) (4) L-menthol and ammonium glycyrrhizate (flavoring agents), BHT (b) (4) isopropyl alcohol and methyl ethyl ketone. (b) (4)

The films are individually packaged in a child-resistant flexible laminate pouch comprised of (b) (4) foil, and medium strength Core-Peel (product contact surface). The applicant has adequately addressed deficiencies from the CRL related to the qualitative and quantitative composition of the product, and controls for noncompendial excipients.

The manufacturing process for Rizatriptan Oral Films consists of: (b) (4)

Manufacturing changes made since the 1/31/2014 CRL include site change from a contract facility to an IntelGenx facility located in Canada, change

from (b) (4) changes to equipment, and changes to process parameters. Given the extensive nature of the changes, the Agency recommended that the applicant perform a new bioequivalence (BE) study versus the listed drug, Maxalt-MLT, rather than relying on in vitro dissolution comparison. The applicant submitted a new BE study (Study 2259).

During the manufacturing review, extensive deficiencies related to the manufacturing process and manufacture of the exhibit batches at the new site. The deficiencies include (b) (4)

(b) (4) discrepancies between the process description provided in Module 3.2.P.3 and proposed master batch records. It is also noted that the applicant failed to update the manufacturing development section to reference the biobatch for the second BE study.

The proposed specification for Rizatriptan Oral Films is typical for a solid oral dosage. For most test parameters (e.g., assay, content uniformity, related substances, and dissolution), the analytical methods and acceptance criteria were deemed suitable for regulatory purposes during review of the original submission. The applicant has addressed CRL deficiencies related to establishment of controls for (b) (4). The applicant has also addressed the CRL deficiency regarding absence of tests for physical integrity of the film by supplying adequate data to justify omission of such tests. However, the applicant proposes a limit of NMT (b) (4) %, for the (b) (4)

Based on stability data for exhibit batches manufactured by IntelGenx it does not appear that the product will remain within this limit for a commercially viable shelf life. (b) (4) levels were reported as (b) (4) % for all three exhibit batches at the 9-month long-term stability test point and one batch exceeded the limit at 12 months (Lot 10117, (b) (4) % reported). The applicant contends that the 12-month OOS result is an outlier and should be disregarded because the results for the 18-month time point were lower. However, the applicant has not provided any justification for this conclusion. It is noted that (b) (4) levels in previous batches manufactured by a contract facility for the original NDA submission were significantly lower (maximum level (b) (4) % at 36 months). Due to the significant changes in (b) (4) impurity level and OOS results, a statistical evaluation would be required to support shelf-life assignment, and exclusion of any OOS results as outliers must be supported statistically. The applicant has not submitted a statistical evaluation and a shelf-life cannot be established.

Facilities

The overall manufacturing inspection is Withhold due to inspection observations at the Intelgenx drug product manufacturing and a potential official action indicated (pOAI) alert for the drug substance manufacturer, Aurobindo.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31(a). Approval of the application is not expected to increase use of the active moiety, as the product would be used in place of currently approved products and there are no extraordinary circumstances. The claim is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment

An initial risk assessment was not performed prior to review of the original NDA submission. Therefore, a final risk assessment will not be done.

E. List of Deficiencies to be Communicated

The following deficiencies are reasons for a CR action. Comment 12.b (qualification of
(b) (4) may require editing by the nonclinical team.



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10. We recommend you revise the microbiological limits in the drug product specification to comply with USP<1111> for dosage forms appropriate to your finished drug product.
11. The overall control strategy for (b) (4) is inadequate. Based on the available stability data for the IntelGenx 2017 batches, particularly the OOS results at 12 months for all storage conditions, a viable shelf-life cannot be assigned for this product. Insufficient data is available for the IntelGenx 2018 batches, and the (b) (4) batches are not equivalent in terms of in-process and initial impurity levels. Therefore, these batches cannot provide the basis for shelf-life assignment.
12. An adequate control strategy must be developed by either or both of the following options:



13. During recent inspections of the (b) (4) (FEI: (b) (4) drug substance manufacturing facility) and Intelgenx Corp., (FEI: 3005721224, drug product manufacturing facility) for this NDA, our field investigators conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this NDA may be approved. Please list communications submitted to, or held with, the agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facilities.

Additional Comment for Action Letter

These is not an approvability issues but should be addressed when the NDA is resubmitted.

1. Provide the full report for the elemental impurities risk assessment summarized in section 3.2.P.5.6 Justification of Specification. We note that this assessment was provided in the previous 3.2.P.2 Pharmaceutical Development document submitted October 31, 2017, which has been removed from the submission but not in the current version of this document submitted October 1, 2018.

2. (b) (4)

(b) (4)

Clarify this discrepancy and update the application accordingly.

3. We note that you provide data demonstrating that disintegration time is not a meaningful test for this product. We request that you remove the test from the specification.
 4. (b) (4)
 5. Provide justification for not including bubbles and other visible defects in the proposed appearance testing in the specification. We refer you to comment #13 in the Complete Response Letter dated January 31, 2014.
 6. Although you propose to omit physical testing such as folding endurance, elongation at break, and tensile strength from the product specification, justification is based on data collected up to 12 months at long-term conditions and 6 month's accelerated condition. Therefore, physical testing should continue in parallel with primary stability studies to support future shelf-life extensions, per ICH Q1E.
- (b) (4)
8. We request that you upload the original method validation reports for the assay and dissolution methods (ITG-17-0002, ITG-17-0004, resp.) into eCTD format.
 9. In section 3.2.P.8.3, the long-term results for assay and impurities at approximately 2 months appear to be missing for the four batches manufactured at IntelGenx in 2018. Provide this data, if available, and update the application accordingly.



Martha
Heimann

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LABELING**I. Package Insert (“prescribing-info-clean” submitted 01OctNov2018)****1. Highlights of Prescribing Information**

Item	Information Provided in NDA
Product Title	
Proprietary name and established name	(b) (4) (rizatriptan) oral (b) (4) film
Dosage form, route of administration	<i>Revise the proprietary name throughout all labels and labeling, as use of the name (b) (4) was denied.</i>
Controlled drug substance symbol	
Dosage Forms and Strengths	
Summary of the dosage form and strength	(b) (4) oral (b) (4) film 10 mg

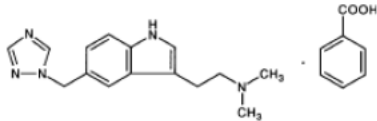
2. Section 2 Dosage and Administration

Item	Information Provided in NDA
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	For (b) (4) oral (b) (4) films, administration with liquid is not necessary. Oral (b) (4) films are packaged in individual child (b) (4) aluminum pouch with tear notch (b) (4) (b) (4) (b) (4) (b) (4) swallowed with the saliva.

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
Available dosage forms	10 mg oral (b) (4) films are white to off-white, rectangular strip of 2.2 cm x 2.75 cm with a blue identifier “RIZA10” on one side.
Strengths: in metric system	
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	

4. Section 11 Description

Item	Information Provided in NDA
Proprietary name and established name	(b) (4) oral (b) (4) film is available for oral administration in a 10 mg strength ((b) (4)
Dosage form and route of administration	to 14.53 mg of the benzoate salt).
Active moiety expression of strength with equivalence statement (if applicable)	<i>Revise the equivalence statement to refer to "rizatriptan" and "rizatriptan benzoate."</i>
Inactive ingredients listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each oral (b) (4) film contains the following inactive ingredients: ammonium glycyrrhizate, butylated hydroxytoluene, copovidone, ethylcellulose, fd&c blue no. 1, hydroxypropyl cellulose, isopropyl alcohol, (b) (4) methyl ethyl ketone, sodium acetate, sucralose, titanium dioxide and triacetin. <i>Revie to capitalize "FD&C."</i>
Pharmacological/therapeutic class	(b) (4) contains rizatriptan benzoate, a selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist.
Chemical name, structural formula, molecular weight	Rizatriptan benzoate is described chemically as: N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1Hindole-3-ethanamine monobenzoate and its structural formula is: 
Other important chemical or physical properties (such as pKa or pH)	Its empirical formula is C ₁₅ H ₁₉ N ₅ •C ₇ H ₆ O ₂ , representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
Strength of dosage form	(b) (4) oral (b) (4) film, 10 mg is a white flexible rectangular strip of 2.2 cm × 2.75 cm with an imprint "RIZA10" in edible blue ink on one side. Each oral film is individually packaged in an aluminum laminate pouch. It is supplied as follows:
Available units (e.g., bottles of 100 tablets)	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC (b) (4) 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. <i>Revise to remove the word "edible."</i>
Special handling (e.g., protect from light)	<i>Revise to include a statement to keep out of reach of children.</i>
Storage conditions	Store (b) (4) at room temperature, 59-86°F (15-30°C).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	(b) (4) oral (b) (4) films are manufactured by: IntelGenx Corp. Saint-Laurent, Quebec H4S 1Y2 Canada

6. Patient Information ("patient-info-clean" submitted 01Oct2018)

Information Provided in NDA	
How should I store (b) (4)?	Store (b) (4) at room temperature between (b) (4) (b) (4).
What are the ingredients in RIZAPORT?	Active ingredient in (b) (4) oral (b) (4) film: rizatriptan (b) (4). Inactive ingredients in (b) (4): ammonium glycyrrhizate, butylated hydroxytoluene, copovidone, ethylcellulose, fd&c blue no. 1, hydroxypropyl cellulose, isopropyl alcohol, (b) (4) methyl ethyl ketone, sodium acetate, sucralose, titanium dioxide and triacetin. <i>Revise to capitalize "FD&C."</i>
Manufacturer/distributor name	(b) (4) oral (b) (4) films are manufactured by: IntelGenx Corp. Saint-Laurent, Quebec H4S 1Y2 Canada

Reviewer's Assessment of Package Inserts: *Adequate, pending the applicant's acceptance of the revisions noted above in red. The applicant has adequately addressed the general labeling comments provided in the previous CR letter.*



Item	Information provided in Pouch and Carton Labels
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	See representative examples above
Dosage strength	
Net contents	
“Rx only” displayed prominently on the main panel	
NDC number (21 CFR 207.35(b)(3)(i))	
Lot number and expiration date (21 CFR 201.17)	
Storage conditions	
Bar code (21CFR 201.25)	
Name of manufacturer/distributor	

Reviewer’s Assessment of Labels: *Adequate, pending update of the proprietary name. The applicant has adequately addressed the general labeling comments provided in the previous CR letter.*



Stephanie
Emory

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Wilson- Lee

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QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics



BIOPHARMACEUTICS

NDA: 205394-ORIG-01-RESUB-25

Drug Product Name / Strength: Rizaport® (rizatriptan) Oral (b) (4) Film, 10 mg

Route of Administration: Oral

Applicant Name: IntelGenx Corp.

Primary Reviewer: Parnali Chatterjee, Ph.D.

Secondary Reviewer: Ta-Chen Wu, Ph.D.

Background:

On April 03, 2013, the Applicant submitted NDA 205394 for Rizaport® (rizatriptan) Oral (b) (4) Film, (b) (4) 10 mg (b) (4) via the 505(b)(2) pathway. The Applicant referenced Maxalt-MLT® (rizatriptan benzoate) Orally Disintegrating Tablet (ODT) as the Listed Drug (LD) that was approved under NDA 020865 for 5 mg and 10 mg strengths (**Note:** The 5 mg strength of the LD is discontinued as per the Orange Book). FDA noted deficiencies in the NDA 205394 and issued a Complete Response (CR) letter to the Applicant on January 31, 2014. In the CR letter (01/31/2014), the Biopharmaceutics Reviewer conveyed the following comments to the Applicant:

1. The acceptance criterion for the dissolution in the drug product specification was revised to Q (b) (4)% in 15 minutes. Update the drug product release and stability specifications to reflect this change and provide dissolution data for the last time point on the stability samples with this method.
2. Provide dissolution data using the revised dissolution method from samples at the end of their shelf life or the latest stability time point to support your expiry

The current re-submission contains the Applicant's responses to the FDA's CR letter (01/31/2014) and provides (i) addition of an alternate drug substance manufacturing site, (b) (4) (ii) addition of an alternate drug product manufacturing site, IntelGenx Corp., Canada, (iii) (b) (4) (iv) (b) (4). However, the resubmission was found to be incomplete. It should be noted that the Applicant (b) (4)

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated the need for bridging the formulations due to manufacturing sites and manufacturing processes changes for the proposed drug product.

Dissolution Method and Dissolution Acceptance Criterion:

In the previous review cycle (12/03/2013), the following dissolution method and dissolution acceptance criterion was approved for Rizaport® (rizatriptan) Oral (b) (4) Film, 10 mg by Dr. John Duan, CDER/ONDQA Biopharmaceutics Reviewer:

Parameters	Proposed Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle over disk)/50 rpm
<i>Media/Volume</i>	25 mM phosphate buffer, pH 7.0/500 mL
<i>Bath temperature</i>	37.0±0.5 C
<i>Dissolution Acceptance Criterion</i>	Q= (b) (4) % in 15 minutes

➤ ***Bridging of the Formulations Due to Manufacturing Site and Processes Changes:***

The Applicant provided in vitro dissolution data at batch release and on stability for four registration batches and the bio-batch manufactured at the alternate manufacturing site used in the comparative bioavailability/bioequivalence (BA/BE) Study 2259 that demonstrate >85% release of rizatriptan in 15 minutes. Additionally, the Applicant conducted a comparative bioavailability/bioequivalence (BA/BE) study (Study 2259) with the bio-batch manufactured at the alternate manufacturing site that demonstrated BE to Maxalt-MLT® ODT 10 mg (LD), based on point estimate and 90% confidence interval between 80-125%. *Based on the totality of evidence, adequate in vitro dissolution data were provided to 'bridge' the formulation and manufacturing site changes.*

➤ ***Biopharmaceutics Risk Assessment:***

From a Biopharmaceutics perspective, the risk of dissolution failure during batch release and stability testing is 'low' because the proposed drug product is an orally soluble film and the drug substance is highly soluble.

➤ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 205394 for Rizaport® (rizatriptan benzoate) Oral (b) (4) Film 10 mg is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

➤ **LIST OF SUBMISSIONS REVIEWED:**

Submissions Reviewed	Reference ID
NDA 205394 Resubmission	Dated 10/31/2017, SDN 21 (\cdsesub1\evsprod\nda205394\0001\m1\us\12-cover-letters\cl-2017-10-31.pdf)
NDA 205394 Resubmission/Class 2	Dated 10/01/2018, SDN 25 (\cdsesub1\evsprod\nda205394\0005\m2\27-clin-sum\summary-biopharm.pdf)
Response to Information Request Comment #1	Dated 01/22/2019, SDN 33 (\cdsesub1\evsprod\nda205394\0013\m1\us\111-information-amendment\val-report-disso-hplc-0000.pdf; (\cdsesub1\evsprod\nda205394\0013\m1\us\111-information-amendment\val-report-disso-hplc-0003.pdf)
Response to Information Request Comment #2	Dated 02/05/2019, SDN 34 (\cdsesub1\evsprod\nda205394\0014\m1\us\12-cover-letters\resp-cmc-ir-2019-02-05.pdf)

Current Submission:

The resubmission provided for the (i) addition of an alternate drug substance manufacturing site, (b) (4) (ii) change in the drug product manufacturing site from (b) (4) and its associated testing sites to IntelGenx Corp., Canada, (iii) increase in the dimensions of the drug product from (b) (4) to 2.2 cm×2.75 cm (6.05 cm²), and (iv) (b) (4). However, the resubmission was found to be incomplete on November 30, 2017.

As per the CMC Reviewers, the proposed changes were considered as Level 3 changes according to the SUPAC IR guidance document and were significant enough that the in vivo performance of the drug product could be potentially impacted. Per FDA's advice at the Type A Meeting (T-con) held on 03/22/2018, to qualify the proposed changes in the drug product, the Applicant conducted another comparative bioavailability (BA) study (No. 2259) using the TBM drug product manufactured at the IntelGenx Corp., (Quebec, Canada) manufacturing site and Maxalt-MLT[®] Orally Disintegrating Tablet (ODT), 10 mg as the LD in healthy male and female volunteers under fasting conditions. Additionally, the Applicant provided comparative dissolution profile data using the approved dissolution method for four registration batches of the TBM drug product manufactured at the IntelGenx Corp., (Quebec, Canada) manufacturing site.

The Applicant manufactured four commercial scale batches (Lot 10073, Lot 10110, Lot 10117, and Lot 10208) at IntelGenx Corp., (Quebec, Canada) manufacturing site. The formulation composition in the proposed TBM drug product batches is similar to the formulation

composition used for the bio-batch ITG-1001 manufactured at (b) (4) in the original NDA 205394 submission (see **Appendix I**, Table A and Table B).

Approved Dissolution Method and Dissolution Acceptance Criterion:

The following dissolution method and dissolution acceptance criterion (see **Table 1**) was approved in the previous review cycle (12/03/2013, see Dr. J. Duan's review¹) for batch release and stability testing of the proposed drug product:

Table 1. Approved dissolution method (ITG-17-0004) and dissolution acceptance criterion for batch release and stability testing of the proposed drug product

Parameters	Proposed Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle over disk)/50 rpm
<i>Media/Volume</i>	25 mM phosphate buffer, pH 7.0/500 mL
<i>Bath temperature</i>	37.0±0.5 °C
<i>Dissolution Acceptance Criterion</i>	Q= (b) (4)% in 15 minutes

Dissolution Profile Data to Bridge the Changes in the To-Be-Marketed Drug Product Batches at Batch Release:

The mean dissolution profile data for the newly manufactured commercial scale batches at IntelGenx Corp., (Quebec, Canada) manufacturing site, i.e., Lot 10073, Lot 10110, Lot 10117, and Lot 10208, are provided in **Table 2**.

Table 2a. Mean dissolution profile data for four registration batches of Rizaport (rizatriptan) Oral (b) (4) Film, 10 mg

Time(min)	% Drug Release				
	Test #1 Lot: 10073	Test #2 Lot: 10110	Test #3 Lot: 10117	Test #4 Lot: 10208	Test #5 Lot: ITG1001
0	0	0	0	0	0
2.5	42	41	36	40	34
5	70	71	64	74	60
7.5	81	85	82	92	Not Sampled
10	85	91	91	99	92
15	87	94	96	104	98
20	89	96	98	106	100
30	90	96	99	108	101

From **Table 2a**, all four registration batches exhibit >85% release of rizatriptan in 15 minutes.

The similarity factor ' f_2 ' value between the four registration batches manufactured at IntelGenx Corp., (Quebec, Canada) manufacturing site was not calculated by this Reviewer as the dissolution for registration batches are very rapid (>85% in 15 minutes).

Table 2b. Dissolution data at 15 minutes for the bio-batch 0007-01-01-01 of Rizaport (rizatriptan) Oral (b) (4) Film, 10 mg

Test	Specification	10mg (release testing)			
Lot #		0007-01-01-01	0008-01-01-01	0008-01-01-02	0010-01-01-01
Batch size				(b) (4)	
Mfg date		2018-06-18	2018-06-26	2018-06-26	2018-07-16
Dissolution	≥ (b) (4)% in 15 min	(b) (4)			

The dissolution data at 15 minutes for the bio-batch 0007-01-01-01 of the TBM drug product exhibits >85% release of rizatriptan, indicating that the bio-batch is similar to the registration batches (see **Table 2b**).

Dissolution Data for the To-Be-Marketed Drug Product Batches on Stability:

The mean dissolution data for the four registration batches (Lot 10073, Lot 10110, Lot 10117, and Lot 10208) manufactured at IntelGenx Corp., (Quebec, Canada) manufacturing site exhibit >85% release of rizatriptan at 15 minutes on long-term stability conditions of 25 °C/60% RH for up to 18 months and accelerated stability conditions of 40 °C/75% RH for up to 6 months.

Bioequivalence Study:

The BE was established between between the TBM drug product batch 0007-01-01-01 manufactured at IntelGenx Corp., (Quebec, Canada) and Maxalt-MLT® Orally Disintegrating Tablet (ODT) 10 mg (LD), based on BE acceptance criterion (see **Table 3**).

Table 3. Statistical analysis of the comparative bioavailability (BA) study (No. 2259) in healthy using the TBM drug product batch 0007-01-01-01 manufactured at IntelGenx Corp., (Quebec, Canada) manufacturing site and Maxalt-MLT® Orally Disintegrating Tablet (ODT), 10 mg as the LD under fasting conditions

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C _{max}	18.34	22.72	22.19	102.37	93.85	111.67
AUC _T	10.64	80.91	77.46	104.46	99.30	109.90
AUC _∞	10.40	82.88	79.01	104.90	99.82	110.23

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Reviewer's Comment:

Based on the dissolution data and the bioequivalence study, the Applicant adequately 'bridged' the aforementioned proposed changes.

➤ **BIOPHARMACEUTICS RISK ASSESSMENT:**

From the Biopharmaceutics perspective, because the proposed drug product is an oral (b) (4) film product, the risk of dissolution failure during batch release and stability testing is considered low. Additionally, because the proposed drug substance exhibits high aqueous solubility, the risk of dissolution failure is low.

➤ **POST-APPROVAL COMMITMENTS: None**

➤ **LIST OF DEFICIENCIES: None**

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Wu

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NDA 205-394

Rizatriptan Benzoate Oral Film
 ^{(b) (4)} **10 mg**

RedHill Biopharma Ltd.

Sherita D. McLamore-Hines, Ph.D.

Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA: 205-394
2. REVIEW: #1
3. REVIEW DATE: December 11, 2013
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

n/a

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission
Amendment

Document Date

March 29, 2013
October 16, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:

RedHill Biopharma Ltd.

Address:

Reza Fathi
21 Haarbaa St.
Tel Aviv
Israel
64739

US Agent:

Dr. Reze Fathi
88 North Franklin Turnpike
HoHoKus, New Jersey 07423

Telephone:

609.462.1143

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name (USAN): Rizatriptan benzoate
- c) Code Name/# (ONDC only): RIZ105
- d) Chem. Type/Submission
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Migraine

11. DOSAGE FORM: Oral Film

12. STRENGTH/POTENCY: (b) (4) 10 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

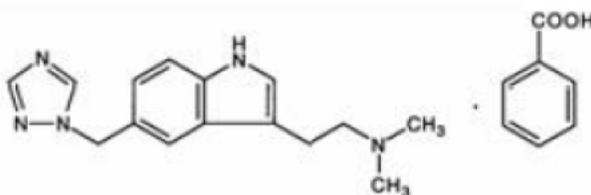
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: *N,N*-Dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate

Molecular Formula: C₁₅H₁₉N₅ · C₇H₆O₂

Molecular Weight: 391.47

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	6/28/2013	N/A

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A

Chemistry Review Data Sheet

EES	Pending	Pending	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	12/03/2013	Acceptable	John Duan
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Pending	Pending	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	

Executive Summary Section

The Chemistry Review for NDA 205394**The Executive Summary****A. Recommendation and Conclusion on Approvability**

A complete response is recommended from a Chemistry, Manufacturing, and Controls (CMC) perspective for NDA 205394. The complete response recommendation is due to several CMC deficiencies, though the facilities inspection is also pending on a recommendation from the Office of Compliance. The CMC deficiencies are outlined below:

Process Description Deficiencies:

(b) (4)

Formulation Deficiencies:

(b) (4)

Deficiencies Regarding Impurities:

(b) (4)

Executive Summary Section

12. Provide information pertaining to the characterization of impurities in the drug product (section P.5.5)

Drug Product Specification Deficiencies:

13. Update the drug product specifications to include tests and acceptance criteria for physical characteristics of the film (e.g., flexibility, tensile strength, acceptable level of bubbles, etc) or provide justification, supported by data, for not monitoring these parameters in the finished product.
14. The proposed acceptance criterion for the disintegration is overly broad. Tighten the specification for disintegration to a limit that is justified data and patient requirements.

(b) (4)

17. The acceptance criterion for the dissolution in the drug product specification was revised to Q ^{(b) (4)}% in 15 minutes. Update the drug product release and stability specifications to reflect this change and provide dissolution data for the last time point on the stability samples with this method.

Container Closure Deficiencies:

18. Provide a detailed description of the drug product container closure system including manufacturers, materials of construction, specifications for materials and parts, certificates of compliance, certificates of analyses, DMF references and the corresponding letters of authorization for the DMF references.
19. Provide a description of any secondary packaging used for the drug product

Stability Deficiencies:

20. Revise the post approval stability commitment to provide for placement of the first three commercial batches of each strength on stability under long-term and accelerated conditions.
21. Your application is devoid of photostability data for the drug product. Provide photostability on at least one batch of the drug product as per ICH Q1A(R2) and Q1B or justification for the exclusion of this data.
22. Provide dissolution data using the revised dissolution method from samples at the end of their shelf life or the latest stability time point to support your expiry.

Environmental Impact Assessment:

23. Amend your application to request a categorical exclusion from preparing an environmental impact considerations, citing the specific citation under 21 CFR 25.31.

Executive Summary Section

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

There are no CMC Phase 4 activity recommendations.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

NDA 205-394 is submitted for the approval of a oral film formulation of rizatriptan benzoate. Currently there is no USP monograph for this API however it is approved for use in an immediate release tablet and orally disintegrating tablet (ODT) in NDAs 20-864 and 20-865, respectively. Rizatriptan benzoate is a well characterized molecular entity, which is manufactured, packaged and release tested by (b) (4). It is a non-hygroscopic, white to off white powder with a molecular weight of 391.47 and a melting range of 178-180°C. Based on solubility and the permeability studies, Rizatriptan benzoate has a BCS classification as Class 1 (high solubility, high permeability) according to the FDA Guidance¹ for Biopharmaceutics Classification System (BCS). Five crystalline forms (b) (4) as well as an amorphous form have been described in the literature. Each of the forms is distinguishable by (b) (4). The applicant references DMF (b) (4) for a complete description of the manufacturing process and all relevant characterization data pertaining to Rizatriptan benzoate. DMF (b) (4) has been reviewed in conjunction with this application and was determined to be adequate to support this application.

The drug product, Rizatriptan Benzoate Oral Film, is being developed for the treatment of migraine headaches. Rizatriptan benzoate is currently approved in an immediate release tablet and orally disintegrating tablet (ODT) under the brand names Maxalt[®] and Maxalt MLT[®], respectively. The drug product is presented as (b) (4) containing (b) (4) 14.53 mg of rizatriptan benzoate, USP which is equivalent to (b) (4) 10 mg of rizatriptan, (b) (4)

The drug product formulation is comprised of a blend of the (b) (4)

The common drug product specification test for (b) (4) include appearance, identification by HPLC and UV, uniformity of dosage units, assay, dissolution, disintegration, related substances, residual solvents and microbiological examination (b) (4)

Executive Summary Section

The manufacturing of the drug product is outsourced to

(b) (4)

The proposed packaging for the drug product is a laminate pouch. The pouch consists of

(b) (4)

aluminum

(b) (4)

The sponsor proposes a storage condition of 25°C with excursions permitted in the range of 15°C – 30°C and a (b) (4) month expiry for the (b) (4) 10 mg drug product. The applicant included 12 months of long term and 6 months of accelerated primary stability data for the drug product. The stability protocol includes a stability matrix in which 3 batches (b) (4) of the drug product are tested at each time point. The samples were tested for description, tightness of primary packaging, identification, assay, (b) (4) dissolution, disintegration (at release only), related substances, (b) (4) and microbial limits. In addition to the primary stability data, the applicant included a comparison of long term and accelerated data of a batch printed with the identifier (batch 8207912) and an unprinted batch (batch 8208012). Both batches were for 10 mg films. This data will be viewed as supportive stability data as these are not primary stability batches. While all data were within the proposed specification limits and there were no unexpected stability trends observed, the applicant has not adequately responded to the Biopharm request that was included in the 74-Day Letter pertaining to the dissolution specification.

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

Rizatriptan benzoate is being developed as an immediate release oral film for treatment of migraine attacks in adults. (b) (4)

(b) (4) 10 mg as a single dose with re-dosing separated by at least 2 hours later up to a maximum daily dose of 30 mg.

C. Basis for Approvability or Not-Approval Recommendation

CMC recommends a complete response for NDA 205394 from a CMC perspective due to deficiencies related to the manufacture and control of the drug product as outlined in this review. A recommendation from the Office of Compliance is still pending and will be captured once it is rendered.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date

OStephens

Executive Summary Section

C. CC Block

Orig. NDA 205394

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

/s/

SHERITA D MCLAMORE
12/11/2013

OLEN M STEPHENS
12/11/2013
CMC recommendation is for a complete response
Draft letter attached.

ONDQA BIOPHARMACEUTICS REVIEW

NDA#: 205-394/S-000
Submission Date: 3/26/2013, 7/10/2013, 10/30/2013, 11/22/2013
Drug Name: Rizatriptan Benzoate oral film
Formulation: Oral film
Strength: (b) (4) 10 mg
Applicant: RedHill Biopharma
Reviewer: John Duan, Ph.D.
Submission Type: Original NDA 505(b)(2)

SYNOPSIS

Submission: NDA 205-394 Rizatriptan Benzoate oral film submitted on 3/26/2013 is proposed for the indication of the treatment of migraine attacks in adults.

Review: The Biopharmaceutics review is focused on the evaluation of the proposed dissolution methodology and the acceptance criteria.

COMMENTS

2. Through multiple communications between the FDA and the Applicant, the following dissolution method and acceptance criterion are acceptable for release and on stability.

USP Apparatus 5: Paddle over disk
Rotation speed: 50 rpm
Medium: 25 mM Phosphate Buffer pH =7.0
Volume: 500 mL
Temperature: $37.0 \pm 0.5^{\circ}\text{C}$
Acceptance criterion: $Q = (b) (4) \%$ at 15 minutes

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the information submitted under NDA 205-394 for Rizatriptan Benzoate oral film and found it acceptable. From the Biopharmaceutics perspective this NDA is recommended for approval.

John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Angelica Dorantes, Ph.D.
Team Leader
ONDQA Biopharmaceutics

cc: NDA 205-394 DARRTS

BIOPHARMACEUTICS EVALUATION

1. Introduction

The Applicant developed an immediate release oral film formulation of rizatriptan for the treatment of migraine attacks in adults. Rizatriptan is a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist. The therapeutic activity of rizatriptan in migraine can be attributed to agonist effects at 5-HT_{1B/1D} receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system.

Rizatriptan is currently marketed as the active pharmaceutical ingredient in Maxalt® (rizatriptan benzoate) Tablets and Maxalt-MLT® (rizatriptan benzoate) Orally Disintegrating Tablets. Both formulations are available in 5 mg and 10 mg dosage units for oral administration. According to the labeling, dosing is one tablet upon acute migraine attack with re-dosing separated by at least two hours and up to 30 mg a day.

2. Physiological properties of the drug substance

Physical description: The drug substance is white to off-white powder.

Solubility: The drug substance is soluble in methanol and soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

Reviewer's Comments: *The solubility of the drug substance is considered high in water. Although the Applicant claimed it is a (b) (4) drug, the classification cannot be concluded because the permeability information was not provided.*

3. Pharmacokinetics of the reference drug

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of rizatriptan following administration of MAXALT-MLT® Orally Disintegrating Tablets is about 45%, and mean peak plasma concentrations (C_{max}) are reached after approximately 1 - 1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by one hour. In clinical trials, MAXALT was administered without regard to food. The area under the curve (AUC) of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred following multiple dosing.

Rizatriptan is minimally bound (14%) to plasma proteins and the primary route of its metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-HT_{1B/1D} receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of the parent compound at the 5-HT_{1B/1D} receptor, is formed to a minor degree. Other minor metabolites are not active at the 5-HT_{1B/1D} receptor.

Rizatriptan is mainly eliminated in the urine, and partially in the feces. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan, while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

The plasma half-life of rizatriptan in males and females averages 2-3 hours.

Reviewer's Comments: *It seems that the high solubility of the drug plays a role for the rapid absorption with a tmax of 1-1.5 hours.*

4. The Composition

The composition of Rizatriptan Benzoate oral film is shown in the following table.

(b) (4)

Reviewer's Comments:

(b) (4)

5. The biowaiver request

(b) (4)

Your proposed dissolution method using paddle over disk with a rotation speed of (b) (4) rpm is not acceptable. Based on the data provided, the following method and acceptance criterion are recommended. Implement this method for the drug product release and ongoing stability program. Update the relevant section of your NDA.

Apparatus:	Paddle over disk
Rotation speed:	50 rpm
Medium:	25 mM Phosphate Buffer pH =7.0
Volume:	500 mL
Temperature:	37.0 ± 0.5°C
Acceptance criterion:	Q = (b) (4)% at 15 minutes

The amendment dated July 10, 2013, included the Applicant's response to the FDA's request for information stating that "Your recommended method is being implemented (on-going), and relevant sections of the NDA will be updated in the next amendment."

The amendment dated October 10, 2013 includes a response to the requests for information stating that "The report is awaiting approval for release and [the] will be provided in the next amendment." (\\cdsesub4\NONECTD\NDA205394\5395585\m1\12-cover-letter)

The amendment dated October 30, 2013, included the updated dissolution method and validation report. However, the drug product specification table listed "(b) (4)% in 15 minutes" instead of "Q = (b) (4)% at 15 minutes." The following information request was sent to the Applicant on 11/18/2013.

You should update the dissolution acceptance criterion in your product specification table to "Q = (b) (4)% at 15 minutes" as we recommended on June 14, 2013. We request your response before November 26, 2013.

The amendment dated November 22, 2013, provided the correction from "(b) (4)% in 15 minutes" to "Q = (b) (4)% at 15 minutes". Sections 3.2.P.5.1 and 3.2.P.8.2 were updated.

The Reviewer's Comments:

The Applicant has accepted the FDA recommended dissolution method (with rotation speed of 50 rpm) and acceptance criterion of Q = (b) (4)% at 15 minutes. The Applicant has also updated the NDA's specification table for the drug product with the revised dissolution method and acceptance criteria.

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

/s/

JOHN Z DUAN
12/03/2013

ANGELICA DORANTES
12/03/2013