CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205394Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 20, 2019
From	Heather Fitter, M.D.
Subject	Cross-Discipline Team Leader Review
NDA # and Supplement#	205394
Applicant	IntelGenx Corp
Date of Submission	September 29, 2018
PDUFA Goal Date	April 1, 2019
Proposed Proprietary Name	Rizaport
Established or Proper Name	Rizatriptan
Dosage Form(s)	10 mg (b) (4) film
Route of Administration	Oral
Recommended Proposed Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Recommended Proposed Dosing Regimen(s)	10 mg single dose
Recommendation on Regulatory Action	*Complete Response*

1. Introduction/Background

A 505(b)(2) application was originally submitted by RedHill BioPharm (with IntelGenx acting as the US agent) for Rizaport, an immediate-release oral film formulation of rizatriptan for the acute treatment of migraine on April 3, 2013. A Complete Response (CR) was issued on January 31, 2014, due to Product Quality deficiencies related to process description, formulation, impurities, product specification, container closure, stability and the environmental impact assessment. Since then, the applicant has submitted two incomplete responses (2/26/2014 and 10/31/2017), and has had several meetings with the Agency to discuss these incomplete responses. In the final incomplete response letter, the Division recommended that the applicant conduct another relative bioavailability (BA) study using the final to-be-marketed drug product, as the overall CMC changes were significant since the original BA study was conducted. Ownership of this NDA was transferred from Redhill to IntelGenx following the first incomplete response to the CR letter (CRL).

IntelGenx Corp submitted the current class 2 resubmission to their 505(b)(2) application on September 29, 2018. This applicant proposes to rely on rizatriptan, a 5-HT1B/1D receptor agonist, approved for the acute treatment of migraine with and without aura, which is available as a tablet and an orally disintegrating tablet. The applicant proposes to use Maxalt-MLT oral disintegrating tablet at as the listed drug. (b) (4) , the applicant only includes a 10-mg formulation with the current resubmission. This submission includes a comparative BA study of Rizaport to Maxalt-MLT and (b) (4) in addition to the requested CMC information.

The following are the key primary reviewers for this resubmission of the Rizaport NDA:

Clinical: Dr. Laura Jawidzik
Clinical Pharmacology: Dr. Priya Brunsdon is the primary reviewer and Dr. Sreedharan Sabarinath is the secondary reviewer.
CMC:

- Drug Substance primary reviewer was Dr. Rajan Pragani and the secondary reviewer was Dr. Su Tran
- Drug Product/Labeling primary reviewer was Dr. Stephanie Emory, and the secondary reviewer was Dr. Wendy Wilson-Lee
- Process primary reviewer was Dr. Yaodong Huang and the secondary reviewer was Dr. Nallaperumal Chidambaram
- Facility primary reviewer was Dr. Yaodong Huang, and the secondary reviewer was Dr. Ying Zhang
- Biopharmaceutics primary reviewer was Dr. Parnali Chatterjee and the secondary reviewer was Dr. Ta-Chen Wu
- The regulatory business process manager reviewer was Dr. Dahlia Woody
- The application technical lead was Dr. Martha Heimann

Office of Study Integrity and Surveillance (OSIS): Dr. Shila Nkah
Division of Medication Error Prevention and Analysis (DMEPA): Dr. Briana Rider was the primary reviewer and Dr. Lolita White was the secondary reviewer
Project Manager: Dr. Lana Chen

2. Nonclinical Pharmacology/Toxicology

N/A

3. Product Quality

The proposed product submitted for review in this application is an oral (b) (4) film containing 10 mg of rizatriptan. The applicant has adequately addressed deficiencies from the complete response letter (CRL) related to the qualitative and quantitative composition of the product, and controls for noncompendial excipients. Manufacturing changes were made since the CRL was issued and include a site change from a contract facility to an IntelGenx facility located in Canada, change (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.

Dr. Heimann notes in her summary review that there are multiple deficiencies in product quality. The list of deficiencies is described below copied from the CMC Executive Summary:

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

13. During recent inspections of the (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.

The Office of Product Quality review team recommends a Complete Response action for this NDA because from a quality perspective, the application does not include adequate information to ensure that the applicant can consistently manufacture a product that is suitable

for use to treat the intended patients. In addition, as noted above, the overall manufacturing inspection recommendation is "Withhold" due to deficiencies at two manufacturing facilities.

4. Clinical Pharmacology

Dr. Priya Brunsdon reviewed the submission, and the team recommends approval on a clinical pharmacolology perspective. This recommendation is based on the bioequivalence demonstrated for the rizatriptan 10-mg oral film to the listed drug, Maxalt-MLT 10-mg ODT.

(b) (4)

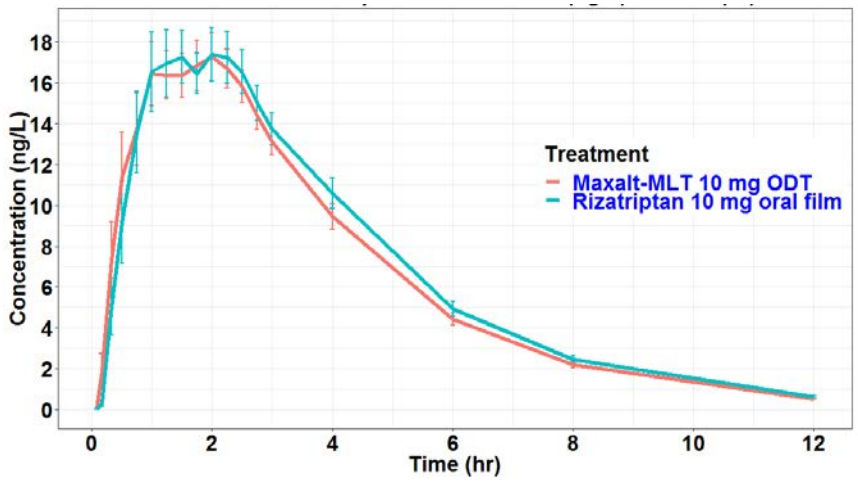
The applicant conducted a pivotal relative bioavailability study (Study 2259), which was a three-way crossover study in healthy subjects with rizatriptan 10-mg oral film, Maxalt-MLT 10-mg ODT, and Maxalt-Lingua 10-mg Oro-dispersible tablets. Maxalt-Lingua is the European reference product, and was not considered in Dr. Brunsdon's review. For the comparison of rizatriptan 10-mg oral film with Maxalt-MLT 10-mg ODT, the ratio (test/reference) of the geometric means of C_{max}, AUC_{last}, and AUC_{0-inf} were 1.02, 1.04, and 1.05, respectively. The 90% confidence intervals of the geometric mean ratios were within 0.8 to 1.25. The rate and extent of absorption of rizatriptan 10-mg oral film and Maxalt-MLT ODT were within the acceptable boundaries for bioequivalence (Table 1).

Table 1: Statistical Comparison of Plasma Rizatriptan PK Parameters: Rizatriptan 10-mg oral film vs Maxalt-MLT 10-mg ODT (source: Table 1 of Dr. Priya's review)

	Geometric Means			
Pharmacokinetic Parameters	**Treatment A Rizatriptan 10 mg oral film (test, N =26)**	**Treatment B Maxalt®-MLT 10 mg ODT (reference, N = 26)**	**Geometric Mean Ratio (%)**	**90% Confidence Interval**
C_{max} (ng/mL)	22.72	22.19	102.37	93.85 – 111.67
AUC_{0-t} (ng*hr/mL)	80.91	77.46	104.46	99.30 – 109.90
AUC_{0-inf} (ng*hr/mL)	82.88	79.01	104.90	99.82 – 110.23

Rizatriptan 10-mg oral film and Maxalt-MLT ODT both achieved maximum concentrations at a median of 1.4 hours and had mean elimination half-lives of approximately 2 hours (Figure 1).

Figure 1: Mean (+/-SE) Rizatriptan Plasma Concentration for Rizatriptan 10 mg oral film and Maxalt-MLT 10 mg ODT (N=26)- Study 2259 (source: Figure 1 of Dr. Priya's review)



A request for clinical and bioanalytical site inspections for Study 2259 was submitted to the Office of Study Integrity and Surveillance (OSIS) and they recommended accepting data without an on-site inspection.

5. Clinical Microbiology

N/A

6. Clinical/Statistical- Efficacy

No efficacy evaluations were included in this application.

7. Safety

Dr. Laura Jawidzik conducted the clinical safety review, which included safety data from the single bioavailability study (Study 2259).

This study was a single-dose, randomized, open-label, three-way crossover, three-period, three-sequence comparative bioavailability study. The three treatments were either Rizaport 10-mg oral film, Maxalt-MLT 10-mg orally disintegrating tablets (U.S. listed drug) or Maxalt Lingua 10-mg oro-dispersible tablet (European listed drug).

Safety was evaluated through assessment of adverse events, laboratory evaluations, vital signs, and ECGs. In addition, all subjects had their buccal cavity visually inspected 10 minutes and 1 hour after administration of the oral film for mucosal irritation.

Dr. Jawidzik reports that there were no deaths, or SAEs and that one patient dropped out of the study due to an adverse event listed as vessel puncture site pain. The most common AE for

subjects receiving Rizaport was headache, reported in 2 subjects. AEs experienced by only one subject each were the following: dizziness, fatigue, nausea, and neck pain. All AEs were reported as mild. No buccal mucosal irritation was reported for any subject. No significant laboratory abnormalities or vital sign abnormalities were identified in the safety database provided for this application. Dr. Jawidzik concludes that no new safety signals were identified.

8. Other Relevant Regulatory Issues

Division of Medical Error Prevention and Analysis (DMEPA)
Dr. Briana Rider conducted a review of the proposed labels and labeling for Rizaport (rizatriptan) oral (b) (4) film to evaluate whether there were areas of vulnerability that could lead to medication errors. She identified multiple areas in the label and labeling that were vulnerable to medication error and provided recommendations to the Division. Since labeling negotiations were not conducted with the applicant in this cycle, these revisions were not discussed with the applicant. Refer to Dr. Rider's review for details on her recommendations.

Dr. Rider concluded that the proposed proprietary name requested by the applicant for their product, Rizaport, could result in medication errors due to confusion with another product under review. Therefore, whether the proposed name is deemed acceptable ultimately would depend on which product is approved first. The applicant submitted an alternate proprietary name for review March 13, 2019, but due to the short timeline before the due date of this application, the proposed new name was not reviewed during this cycle.

9. Pediatrics

This application does trigger PREA due to a new dosage form. At the time of submission of the original application, PeRC agreed with the Division to grant a partial waiver in pediatric patients age 0-5 years, because studies were impossible or highly impracticable. Since the pediatric information of the listed drug, at that time, was protected by pediatric exclusivity, pediatric studies in patients age 6-17 years were required for this product. The applicant's plan was to leverage Maxalt's pediatric data after the expiration of the pediatric exclusivity (2015) to satisfy their PREA requirements. (b) (4)

PeRC agreed with the Division that (b) (4) the applicant will need to address this population by developing a (b) (4) dose for patients weighing < 40 kg, if they choose to submit a complete response to this application.

10. Labeling

There were no labeling negotiations during this review cycle. The identified CMC deficiencies preclude discussion of labeling changes and/or postmarketing requirements.

11. Recommendations/Risk-Benefit Assessment

I recommend a complete response action for this application due to the multiple CMC deficiencies and the deficiencies noted at the manufacturing sites.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HEATHER D FITTER
03/28/2019 03:03:07 PM

ERIC P BASTINGS
03/28/2019 03:41:25 PM
I concur, and will issue a CR letter.

Cross-Discipline Team Leader Review

Date	1/31/2014
From	Angela Yuxin Men., MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205394 Original NDA
Applicant	RedHill BioPharm
Date of Submission	3/27/2013 (Agency received on 4/3/2013)
PDUFA Goal Date	2/3/2014
Proprietary/ Established (USAN) Name	Rizaport (rizatriptan oral film)
Dosage forms / Strength	(b) (4) 10 mg films
Proposed Indication(s)	Migraine with or without aura
Recommended:	Complete Response

1. Introduction

Rizatriptan is a selective 5-HT1B/1D receptor agonist, which is the active pharmaceutical ingredient in Maxalt® tablets and Maxalt-MLT® orally disintegrating tablets (ODT). Both of them were approved to treat migraine with or without aura. The newly developed immediate-release oral film formulation of rizatriptan (Rizaport) for the treatment of migraine attacks in adults has similar (b) (4) route of administration and medication directions/instructions to that of Maxalt-MLT .

In this submission, the applicant conducted one pivotal bioequivalence (BE) study entitled. "Single Dose Cross-Over 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" demonstrating that 10-mg oral film is bioequivalent to Maxalt-MLT® 10-mg ODT. The Applicant requested (b) (4) There was no efficacy trial conducted for rizatriptan oral film.

The following are the key primary reviewers for the Rizaport NDA:

- Clinical: Nushin Todd, M.D., Ph.D. (Team Leader: Nicholas Kozauer, M.D.)
- Clinical Pharmacology: Xinning Yang, Ph.D. (Team Leader: Angela Yuxin Men, M.D., Ph.D.)
- CMC: Sherita D Mclamore, Ph.D. (Branch Chief: Olen M Stephens, Ph.D.)
- Biopharmaceutics: John Duan, Ph.D. (Team Leader: Angelica Dorantes, Ph.D.)
- Office of Scientific Investigations: Arindam Dasgupta, Ph.D., (Branch Chef: Sam H. Haidar, R.Ph., Ph.D.)
- Office of Manufacturing and Product Quality: Vibhakar Shah, Ph.D.
  Senior Policy Advisor

- DMEPA: Jacqueline Sheppard, PharmD, Julie Neshiewat, PharmD, BCPS (reviewer and acting team leader)
- Project Manager: Lana Chen, Pharm.D

2. Regulatory Background

The sponsor is seeking approval of Rizaport (rizatriptan oral film) for the treatment of migraine with or without aura via 505(b)(2) of the Food, Drug and Cosmetic Act using Maxalt-MLT® (NDA20865) as reference listed drug (RLD). Maxalt-MLT® was originally approved by the FDA for the treatment of acute migraine in adults on June 29, 1998, and is commercially available as 5 mg and 10 mg orally disintegrating tablets.

Development of Rizaport was conducted under IND 110,753. During the product development period, two meetings with the Division were requested by the applicant:

- Pre-IND teleconference (February 23, 2011)
- Pre-NDA teleconference (November 7, 2012)

The clinical program that forms the basis of its approval consists of one bioequivalence study conducted in 26 healthy male and female volunteers, which compared the rate and extent of absorption of rizatriptan under fasting conditions for Maxalt-MLT® and Rizaport.

The sponsor proposed to use Rizaport in adults only as the safety and efficacy information for pediatrics is protected under pediatric exclusivity.

On January 30, 2013, the review team receive the comments from Dr. Beth Duvall, an associate director for Regulatory Affairs CDER/Office of New Drugs regarding 505(b)(2) regulatory pathway. Although this application is cleared for action from a 505(b)(2) perspective, it can only be CRd due to the deficiency noted below which should be included in your CR letter as written:

An applicant filing a certification under 505(b)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50(i)(1)(i)(A)(4) (i.e., a paragraph IV certification) must provide notice of such certification to each owner of the patent that is the subject to the certification or the representative designated by the patent owner to receive the notice. The contact information for the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office (PTO). See 21 CFR 314.52(a)(1). You are proposing to rely on NDA 20865 as the listed drug. The only unexpired patent is Patent No. 5,457,895. According to the PTO's website, it appears that this patent has been assigned to Catalent USA Woodstock, Inc., Catalent USA Packaging, LLC, Catalent Pharma Solutions, Inc., Catalent USA Paintball, Inc., and Catalent Pharma Solutions, LLC. http://assignments.uspto.gov/assignments/q?db=pat&qt=pat&reel=&frame=&pat=5457895&pub=&asnr=&asnri=&asne=&asnei=&asns Based on our records, you have not provided notice to the appropriate entities. This is a deficiency that must be addressed before FDA can approve your application.

3. CMC

From a Chemistry, Manufacturing, and Controls (CMC) perspective, numerous deficiencies were identified in process description, formulation, specification, container closure, stability, and impurities (shown in the Table below).

	Deficiencies
Process Description	(b) (4)
Formulations	
Impurities	
	- No information pertaining to the characterization of impurities in the drug product
Drug Product Specification	- No tests and acceptance criteria for physical characteristics of the film (e.g., flexibility, tensile strength, acceptable level of bubbles, etc) - No acceptable acceptance criterion for the disintegration, which is overly broad. (b) (4) - No updated drug product release and stability specifications to reflect the change on the acceptance criterion for the dissolution, which was revised to Q= (b) (4)% in 15 minutes.
Container Closure	- No 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. - No description of any secondary packaging used for the drug product.
Stability	- No placement of the first three commercial batches (b) (4) on stability under long-term and accelerated conditions in post approval stability commitment. - No photo-stability data for the drug product. Provide - No 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:	- No categorical exclusion from preparing an environmental impact considerations, citing the specific citation under 21 CFR 25.31.

A complete response is recommended from a CMC perspective for NDA 205394 due to the deficiencies related to the manufacture and control of the drug product as outlined in the above Table.

On January 31, 2014, Dr. Vibhakar Shah, a Senior Policy Advisor from Office of Manufacturing and Product Quality, emailed the team that the (b) (4) drug substance manufacture facility inspection in (b) (4) was closed and a FDA 483 was issued to the sponsor. The field investigators conveyed significant deficiencies to the representative of the facility. Satisfactory resolution of these significant deficiencies is required before this application may be approved.

4. Nonclinical Pharmacology/Toxicology

There is no updated information as the information in these fields remaining unchanged from those in the approved NDA.

5. Biopharmaceutics

Dr. John Duan from ONDQA evaluated the proposed dissolution methodology and its acceptance criteria. He concluded that, based on the acceptability of the composition of the formulation and dissolution profile similarity data, (b) (4) In addition, after multiple communications between the FDA and the Applicant, an agreement was reached regarding the dissolution method and acceptance criterion for product release.

USP Apparatus 5: 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

ONDQA-Biopharmaceutics 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.

6. Clinical Pharmacology

Dr. Xinning Yang reviewed the submission and the team concluded that NDA 205-394 is acceptable from an OCP perspective.

The applicant conducted a single center, randomized, single dose (10 mg), laboratory-blinded, 2- period, 2-sequence, crossover study (RZA-P9-688) in 26 healthy subjects. The geometric mean ratio of Cmax, AUC_T and AUC∞ were around 1 and their 90% CI fell into 80-125% range. The test formulation (rizatriptan 10 mg oral film) is bioequivalent to the reference formulation (Maxalt-MLT® 10 mg orally disintegrating tablet) under fasting conditions (Table and Figures 1 and 2 below).

Table. Comparison of Results with Standards for Bioequivalence – Rizatriptan

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	20.0	19.845	20.308	97.72	88.57	107.82
AUC_T	8.8	73.868	72.870	101.37	97.07	105.86
AUC_∞	8.0	78.744	78.713	100.04	95.94	104.31

Figure 1. Plasma Concentrations of Rizatriptan versus Time Profiles. Left Panel: Test, oral film; Right Panel: Reference, Maxalt® ODT. (x-axis: time after dosing (hours), y-axis: rizatriptan concentration (ng/ml) expressed as mean ± SD).

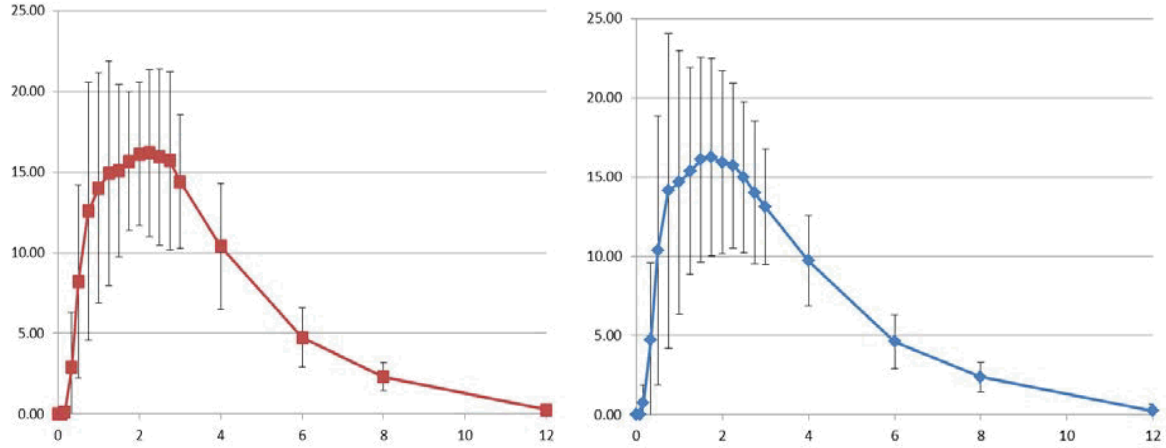
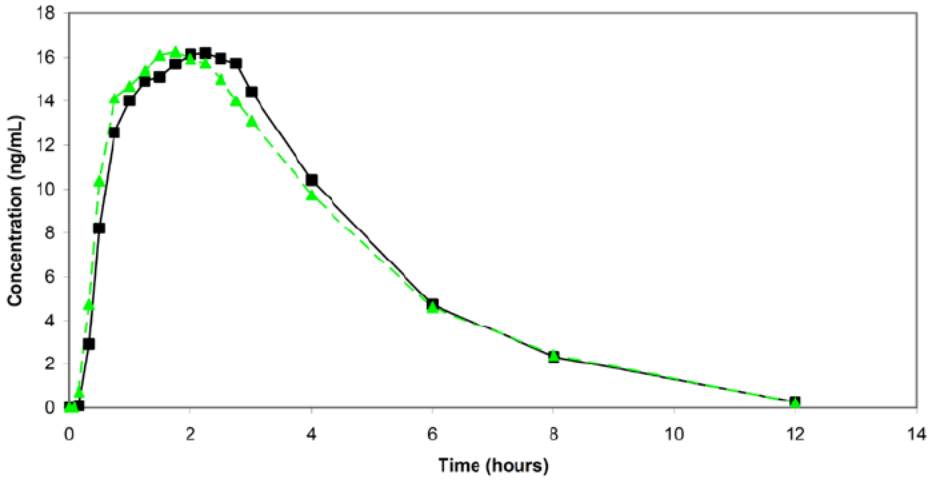


Figure 2. Mean Plasma Concentrations of Rizatriptan versus Time Profiles (Reference: green triangles; Test: black squares)



No food-effect study was conducted per the agreement reached between the Agency and the applicant due to several fold reasons:

- Per the labeling, the administration of Maxalt® (tablet) with food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. There is no restriction on the status of food intake for either Maxalt® or Maxalt-MLT®.
- According to the Food-effect Guidance, important food effects on bioavailability are least likely to occur with many rapidly dissolving, immediate-release drug products containing BCS Class I drugs, because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution. Although rizatriptan has not been granted the designation of BCS Class I drug, per the labeling of Maxalt® and Maxalt-MLT®, rizatriptan benzoate has a BCS classification as Class 1 (high solubility, high permeability) according to the FDA Guidance1 for BCS.Therefore, no significant food effect on the total exposure (AUC) is expected for rizatriptan oral film, as what has been observed for Maxalt®.
- The Food-effect guidance also states that, for rapidly dissolving formulations of BCS Class I drug substances, food can affect Cmax and Tmax by delaying gastric emptying and prolonging intestinal transit time. However, the food effect on these measures is expected to be similar for test and reference products in BE studies.

Therefore, no clinically significant food effect is expected for the rizatriptan oral film product. A fasted BE study alone is considered sufficient for this submission.

[redacted] (b) (4)

Dr. Arindam Dasgupta conducted site inspection for the BE study, RZA-P9-688. The clinical and analytical portions of the study were audited at [redacted] (b) (4) OSI recommends that data for clinical and analytical portions of study RZA-P9-688 are acceptable for further agency review.

7. Efficacy

There is no clinical efficacy trial conducted.

8. Safety

As noted above, this approval is based upon a demonstration of PK equivalency of rizatriptan oral film to the RLD, Maxalt-MLT®. Such equivalency should apply to both issues of safety as well as efficacy conclusion. The safety of this drug is therefore largely based upon the safety of the referenced label drug, Maxalt-MLT®.

Although there is no specific efficacy/safety study conducted, safety data were collected from the Rizaport Clinical Pharmacology study from a total of 26 healthy male and female volunteers enrolled in Study RZA-P9-688. Dr. Nushin examined the safety data and concluded that no new or unexpected adverse events were detected in the single bioequivalence study that formed the basis of the NDA. There are no identified significant deficiencies in the NDA safety submission. The applicant submitted all necessary summaries and supporting data. There were no notable inconsistencies between the data sources. The routine clinical safety testing was appropriate and capable of identifying major safety signals of rizatriptan oral film.

In summary, from a clinical perspective, the overall risk to benefit assessment of Rizaport is acceptable and there are no safety issues impeding the approval of the proposed product. However, numerous deficiencies from the CMC justify a Complete Response. It is therefore recommended that a Complete Response be issued to the applicant.

9. Advisory Committee Meeting

None

10. Pediatrics

Per the current labeling, the efficacy and safety of MAXALT in the acute treatment of migraine in patients aged 6 to 17 years was established in an adequate and well-controlled study. Maxalt® tablets and Maxalt-MLT® have dosing information in 6 to 17 Years pediatric population. 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. The efficacy and safety of treatment with more than one dose of MAXALT within 24 hours in pediatric patients 6 to 17 years of age have not been established. Safety and effectiveness in pediatric patients under 6 years of age have not been established.

NDA 205394 Rizatriptan oral film triggers PREA because it is a new dosage form. PeRC meeting was held on December 4, 2013. The PeRC agreed with the Division to grant a partial waiver in pediatric patients 0 to 5 years because studies impossible or highly impractical. This

was also granted for RLD. Meanwhile, the required pediatric studies for the RLD (Maxalt) have been completed and labeling is present for Maxalt. Currently, this information is protected because of pediatric exclusivity. Therefore, this information cannot appear in Rizatriptan labeling until the pediatric exclusivity has expired and administratively studies for this product must be deferred to satisfy PREA requirements. Once exclusivity has expired for Maxalt, the sponsor may satisfy their PREA requirement by submitting reference to the full pediatric labeling for Maxalt.

11. Labeling

DMEPA found the proprietary name, Rizaport (rizatriptan oral film), acceptable from both a promotional and safety perspective.

Dr. Julie Neshiewat evaluated the proposed labels and labeling for Rizatriptan Oral Films, NDA205394, for areas of vulnerability that could lead to medication errors. In addition, DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Maxalt-MLT medication error cases.

DMEPA concludes that the proposed labels and labeling can be improved and made a number of comments on the container label, carton labeling, pouch labels, Prescribing Information, Patient Package Insert, and Patient Information Leaflet, which to be conveyed to the sponsor.

No labeling negotiation during this review cycle. The identified CMC deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments. Please refer to the Discipline Review letter issued on December 12, 2013 for details.

12. Recommended Regulatory Action

The Sponsor's submission has numerous deficiencies from CMC, manufacturing inspections and 505(b)(2) review committee. This application does not provide adequate information for regulatory approval of Rizaport (rizatriptan oral film).

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

/s/

YUXIN MEN
01/31/2014