CLINICAL REVIEW

Application Type	NDA, 505(b)(2) resubmission
Application Number(s)	205394
Priority or Standard	Standard
Submit Date(s)	09/29/2018
Received Date(s)	09/29/2018
PDUFA Goal Date	03/29/2019
Division/Office	Division of Neurology Products/Office of New Drugs
Reviewer Name(s)	Laura Jawidzik, MD
Review Completion Date	12/27/2018
Established/Proper Name	Rizatriptan
(Proposed) Trade Name	Rizaport
Applicant	IntelGenx Corporation
Dosage Form(s)	Oral film
Applicant Proposed Dosing Regimen(s)	Single dose of 10mg
Applicant Proposed Indication(s)/Population(s)	Treatment of acute migraine in adults and pediatric patients age 12 and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acute migraine in adults and pediatric patients age 12 and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Rizaport, also known as rizatriptan oral film, is a serotonin receptor agonist belonging to the class of drugs known as triptans. Rizaport is an immediate release oral film formulation. Rizatriptan is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients age 6 and older.

Rizatriptan is an approved product that comes in several formulations including a tablet and an orally dissolving tablet. Rizatriptan is also available in generic form as a tablet and an orally dissolving tablet. Both generic dosage forms are available in 5mg and 10mg strengths. The applicant previously submitted a 505(b)(2) application for this new formulation of rizatriptan. The prior application for Rizaport received a complete response in 2014 because of numerous deficiencies from the Chemistry, Manufacturing, and Controls (CMC) discipline. Previously the (b) (4) The applicant (b) (4) is seeking approval of only the 10mg dose.

The listed drug is Merck's product, Maxalt-MLT under NDA 020865. Maxalt-MLT is approved for acute treatment of migraine in adults and pediatric patients age 6 and older. The adult recommended dosage of Maxalt-MLT is 5mg or 10mg as a single dose with repeat doses separated by at least 2 hours. Maximum recommended dose in 24 hours is 30mg. In pediatric patients, 5mg single doses are recommended in patients less than 40kg, and 10mg single doses in patients weighing 40kg or more. For business reasons, Merck is no longer marketing the 5mg dose of Maxalt and Maxalt-MLT although the 5mg dose continues to be available in a generic. The 5mg dose is considered a safe and effective dose of rizatriptan.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505(b)(2) application which utilized a bioequivalence study to bridge the efficacy and safety of the product to Maxalt. The Office of Clinical Pharmacology has reviewed the results of the pivotal bioequivalence study and concluded that Rizaport is bioequivalent to Maxalt.

1.3. Benefit-Risk Assessment

The overall risk benefit assessment of Rizaport is acceptable. Rizatriptan has been marketed in the United States for adult migraine patients since 1998 and has a well-characterized safety profile. No new adverse events were discovered in the course of the development program for Rizaport that would affect the risk benefit assessment.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a very common, chronic neurological disease with a broad spectrum of frequency and severity. Migraine can be a serious and, at times, disabling condition that can impact the quality of patients' lives.

Migraine is a disease characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last from 4 to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.

2.2. Analysis of Current Treatment Options

There are many FDA-approved therapies for the treatment of acute migraine, and many others that are used off-label. In 2015, the American Headache Society (AHS) published a guideline on the treatment of acute migraine therapies (Marmura et al. 2015).

The guideline lists the following drugs as having Level A evidence (established as effective): acetaminophen, acetylsalicylic acid, diclofenac, ibuprofen, naproxen, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, dihydroergotamine (intranasal and pulmonary inhaler), and butorphanol. The following combination products are considered to have Level A evidence as well: sumatriptan/naproxen, and acetaminophen/acetylsalicylic acid/caffeine.

The following drugs and combination products are considered by this guideline to have Level B evidence (probably effective): chlorpromazine, droperidol, metoclopramide, prochlorperazine, flurbiprofen, keoprofen, ketorolac, IV magnesium, isometheptene, dihydroergotamine (SC, IV, IM); ergotamine/caffeine; tramadol/acetaminophen; and codeine/acetaminophen.

The following drugs and combination products are considered by this guideline to have Level C evidence (possibly effective): valproate (IV), phenazone, codeine, ergotamine, butorphanol (IM), meperidine, methadone, tramadol, dexamethasone, lidocaine (intranasal); butalbital/acetaminophen/caffeine, and butalbital/acetaminophen/caffeine/codeine.

3. Regulatory Background

The IND number associated with Rizaport is 110753. The IND was never formally opened with a clinical study. A pre-investigational new drug (IND) meeting was held for rizatriptan oral film on February 23, 2011. This meeting addressed the applicant's plans for establishing bioequivalence to Maxalt-MLT and CMC related issues.

A Type B pre-NDA meeting was held on November 7, 2012. This meeting primarily focused on CMC related issues, and the applicant's plan for submitting a 505(b)(2) application. The Division informed the applicant that the product triggers PREA because it is a new dosage form. The applicant was instructed to provide a plan for addressing each pediatric age group (age 0 to 6 years, 6 to 11 years, and 12 to 17 years). Merck received Hatch-Waxman Exclusivity for Maxalt for studies in pediatric patients age 6-17 that was due to expire in 2015. The applicant was advised to take this information in consideration when planning the timeline for PREA required studies.

The applicant submitted a 505(b)(2) NDA on March 26, 2013. The application was filed with a goal date of February 3, 2014. The filing letter outlined several CMC-related potential review issues and alerted the applicant that a Pediatric Plan was required. Per the filing letter, "We note that you have not fully addressed how you plan to fulfill this requirement. While we acknowledge the rationale behind your requested deferral of pediatric studies, this proposal is inadequate at this time. As noted above, a Pediatric Plan outlining your planned pediatric studies is a required component of your application. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this application."

On July 9, 2013, the sponsor submitted a waiver request to the NDA for pediatric studies with a very minimal outline of a Pediatric Plan and the intent to leverage Maxalt's data after the expiration of pediatric exclusivity in 2015.

PeRC meeting recommendations from December 4, 2013 stated the following: "Once exclusivity has expired for Maxalt, the sponsor may satisfy their PREA requirement by submitting reference to the full pediatric labeling for Maxalt."

A Complete Response (CR) was issued January 31, 2014. It was understood that the PREA requirements could be fulfilled once the pediatric exclusivity for Maxalt expired.

Following the CR, a Type A End-of-Review meeting was held on March 12, 2014, to discuss the deficiencies. The applicant responded to the original CR in February 2014; however, an Acknowledge Incomplete Response letter was issued on April 10, 2014, as the applicant did not fully address all aspects of the CR. Another End-of-Review meeting was held August 7, 2014, where the primary discussion was related to CMC issues.

The applicant submitted another incomplete response in October 2017 and in November 2017 another Acknowledge Incomplete Response letter was issued to the applicant. In that letter, the Division recommended to the applicant to conduct another relative BA study using the final proposed to-be-marketed drug product as the overall CMC changes were substantial changes that could potentially impact in vivo performance. The Division also recommended the applicant request a Type C meeting specifically to address CMC-related issues. The CMC Type C meeting was held March 22, 2018, via teleconference.

The current resubmission was received September 29, 2018 (eCTD sequence 0005). The sponsor submitted a comparative bioavailability study of Rizaport to Maxalt-MLT. The sponsor submitted (b) (4) .

Reviewer's comment: The sponsor's request (b) (4) *is not justified. The sponsor will need to address this population to satisfy PREA requirements in the pediatric population. The sponsor will need to develop* (b) (4) *dose for patients weighing under 40kg.*

4. Sources of Clinical Data and Review Strategy

The sponsor has submitted a single clinical study with the application, study BPSI 2259. The study will be reviewed for safety. No efficacy studies were submitted.

5. Review of Relevant Individual Trials Used to Support Safety

Study BSPI 2259

Title

A Single-Dose, Randomized, Open-Label, Three-Way Crossover, Pivotal Comparative Bioavailability Study of Rizatriptan 10mg Oral Films, Maxalt-MLT 10mg Orally Disintegrating Tablets, and Maxalt Lingua 10mg Oro-Dispersible Tablets in Healthy Male and Female Volunteers under Fasting Conditions

Overview and Objective

To assess the comparative bioavailability of Rizaport 10mg oral film, Maxalt-MLT 10mg orally disintegrating tablets, and Maxalt Lingua 10mg oro-dispersible tablets. To assess the safety and tolerability of Rizaport in healthy, non-smoking male and female volunteers under fasting conditions.

Trial Design

This was a single dose, randomized, open-label, three-way crossover, three-period, three-sequence, three-treatment, comparative bioavailability study. The drug administrations were separated by a wash-out of three calendar days.

Subjects were randomized equally into one of the following three sequences:

	Period 1	Period 2	Period 3
Sequence 1	A	B	C
Sequence 2	B	C	A
Sequence 3	C	A	B

A: Rizaport 10mg oral film
B: Maxalt-MLT 10mg orally disintegrating tablets (U.S. reference product)
C: Maxalt Lingua 10mg oro-dispersible tablet (European reference product)

Safety was evaluated through assessment of adverse events, laboratory evaluations, vital signs, and ECGs.

Table 1 Study Schedule of Events

Procedure/Activity	Time points				
	Screening	Period 1	Period 2	Period 3	Post-Study
Study ICF	X				
Medical History	X				
BMI	X				
ECG	X	X[h]	X[h]	X[h]	X
Vital Signs (BP, HR, RR and temperature)	X				X
Physical Exam	X				X
Laboratory Testing	X				X
Drugs of Abuse	X	X[a]	X[a]	X[a]	
Breath Alcohol Test	X	X[a]	X[a]	X[a]	
Urine Cotinine	X	X[a]	X[a]	X[a]	
Pregnancy Test[#]	X	X[a]	X[a]	X[a]	
Inclusion/Exclusion Assessment	X				
Vital Signs (BP & HR)		X[b]	X[b]	X[b]	
Restrictions Compliance Check		X[c]	X[c]	X[c]	
Study Drug Administration		X	X	X	
PK Blood Sampling		X[d]	X[d]	X[d]	
Adverse Event Reporting		X[e]	X[e]	X[e]	X
Meals		X[f]	X[f]	X[f]	
Visual Inspection of the buccal cavity		X[g]	X[g]	X[g]	

[#]- Serum pregnancy at screening and Urine pregnancy at check-in.
[a]- At check-in only.
[b]- Vital signs measurements (BP and HR) were obtained at pre-dose and at 2, 4 and 12 hours after dosing in each study period.
[c]- Confirmed at check-in and each ambulatory blood draw, if applicable.
[d]- PK sampling - Pre-dose (0) and at 0.083, 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8 and 12 hours after dosing in each study period.
[e]- Pre-dose conditions at Period 1 check-in and confirmed at each check-in and each ambulatory blood draw, if applicable.
[f]- Meals were served at check-in and approximately at 4.5 and 9.5 hours after dosing.
[g]- At 10 minutes and 1 hour after dosing in each study period.
[h]- At approximately 2.5 hours after dosing in each study period.

This table is taken from the study report body from BPSI 2259

Findings

Initially 30 subjects were randomized with 10 subjects in each sequence. Two subjects were dismissed from sequence 1 and two subjects did not complete sequence 3.

Table 2 Demographics of the Subjects Completing the Study

	Age (years)	Height		Weight		BMI	Race/Ethnicity	
		(cm)	(in)	(kg)	(lb)			
Mean	31	169.6	66.8	73.3	161.7	25.5	**White**	4
+/- SD	5	9.3	3.7	10.1	22.2	2.8	**Black**	12
Median	33	170.4	67.1	72.6	160.1	25.4	**Asian**	5
							Native	0
Range	19-40	146.3-183.6	57.6-72.3	56.7-97.5	125.0-214.9	20.7-29.7	**Hispanic/ Latino**	5

Sponsor's table from the report body for study BPSI-2259

6. Review of Safety

In study BSPI 2259, 26 subjects were exposed to single doses of Rizaport oral film.

6.1. Safety Results

6.1.1. Deaths

None.

6.1.2. Serious Adverse Events

None.

6.1.3. Dropouts and/or Discontinuations Due to Adverse Effects

One subject withdrew due to an adverse event listed as vessel puncture site pain.

6.1.4. Significant Adverse Events

None.

6.1.5. Treatment Emergent Adverse Events and Adverse Reactions

For each subject, the buccal cavity was visually inspected 10 minutes and 1 hour after administration of the oral film for full disappearance of the soluble film and any mucosal irritation. No mucosal irritation was reported for any subject. For subjects receiving Rizaport, the most common AE was headache in 2 subjects. AEs experienced by only one subject each

were the following: headache, dizziness, fatigue, nausea, and neck pain. All AEs were reported as mild.

Reviewer's comment: No new safety signals were identified. No changes to the labeling will be recommended.

6.1.6. Laboratory Findings

Prior to each study period, each subject underwent laboratory testing including hematology, chemistry, and urinalysis. There were no AEs related to laboratory findings.

6.1.7. Vital Signs

During the study there were several subjects who had AEs related to vital sign measurements. One subject experienced bradycardia, and two experienced an irregular heart rate. None of these subjects were in the Rizaport treatment group (Group A).

6.1.8. Electrocardiograms (ECGs)

An ECG was recorded at approximately 2.5 hours after dosing during the study for each of the three study periods. No clinically significant on-study ECG assessments were reported during this study.

7. Labeling Recommendations

7.1. Prescription Drug Labeling

This is a 505(b)(2) application. The applicant is relying on the findings of safety and efficacy of Maxalt-MLT (NDA 020865). The label will be consistent with the prescribing information for FDA-approved label for Maxalt-MLT except for the pediatric prescribing information and other information pertaining to the 5mg dose. The sponsor has only developed a 10mg dose but has not developed a 5mg dose.

7.2 Nonprescription Drug Labeling

N/A

8. Postmarketing Requirements and Commitments

The sponsor will be issued a PMR for the fulfillment of the PREA requirements for pediatric patients age 6 through 11. The sponsor can fulfill the PREA requirements with the existing pediatric labeling from Maxalt, but they will need to develop an appropriate pediatric formulation.

9. Appendices

9.1. References

N/A

9.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BPSI 2259

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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/

LAURA A JAWIDZIK
03/27/2019 03:09:54 PM

HEATHER D FITTER
07/07/2019 07:32:56 AM