Office of Clinical Pharmacology Review

NDA Number:	205394
Link to EDR	\\CDSESUB1\evsprod\NDA205394\0005
Submission Type:	Original NDA (505(b)(2)), Class 2 Resubmission
Associated IND:	110753
Applicant:	IntelGenX Corp.
Submission Date:	9/28/2018
Brand Name:	TBD. See Proprietary Name Review 12/10/2018
Generic Name	Rizatriptan
Dosage Form:	Oral film
Dosage Strength:	10 mg
Proposed Indication:	Acute treatment of migraine with or without aura in adults
Proposed Dose:	10 mg single dose. Maximum dose of 30 mg in a 24 hour period. Separate doses by at least 2 hours.
OCP Division:	DCP1
Primary Reviewer:	Priya Brunsdon, Pharm.D
Team Leader:	Sreedharan Sabarinath, Ph.D

Contents

1. Executive Summary

IntelGenX Corp. submitted a Class 2 resubmission of a New Drug Application (NDA) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 10 mg rizatriptan (b) (4) oral film. This submission relies on the findings of safety and efficacy of Maxalt®-MLT 10 mg oral disintegrating tablet (ODT) (NDA 020865), approved on 6/29/1998, as the listed drug for the indication of treatment of migraine with and without aura in adults.[1] Maxalt®-MLT ODT is approved as single doses of 5 mg or 10 mg with a maximum daily dose of 30 mg in a 24 hour period. The currently approved label requires a dose adjustment to 5 mg for pediatric patients age 6 to 17 years that are <40 kg and adult patients or pediatric patients ≥40 kg taking propranolol. The Applicant is seeking approval for the 10 mg dose level only. (b) (4) .

This application relies on the results from a pivotal relative bioavailability study (Study 2259), a three-way crossover study conducted 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 will not be analyzed in this review. Study 2259 demonstrated bioequivalence between rizatriptan 10 mg oral film and Maxalt®-MLT 10 mg ODT based on C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

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. See Bioequivalence Establishment Inspection Report Review (1/14/2019) for details.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval of rizatriptan 10 mg oral film for the acute treatment of migraine with or without aura in adults. This recommendation is based on the bioequivalence demonstrated for rizatriptan 10 mg oral film to the listed drug, Maxalt®-MLT 10 mg ODT. (b) (4)

2. Background and Regulatory History

Rizatriptan is a 5HT-1B/1D receptor agonist that was approved for the treatment of acute migraine in adults in 1998. It is metabolized primarily by oxidative deamination via monoamine oxidase-A (MAO-A) to the inactive indole acetic acid (IAA) metabolite. It is primarily excreted

[1] MAXALT-MLT™ (rizatriptan benzoate) USPI: { https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20864lbl.pdf}

in the urine as its major metabolite, indole acetic acid (IAA) (51% of dose) and unchanged rizatriptan (14%). The plasma half-life of rizatriptan is approximately 2-3 hours.

Prior to the submission of this NDA on September 28, 2018, the investigational drug was studied under IND 110753. The Applicant submitted an NDA on March 27, 2013 and received a Complete Response on January 31, 2014 due to deficiencies in product quality and facility inspections. The current submission is a Class 2 Resubmission. Other notable regulatory meetings include a pre-IND meeting (2/23/2011, IND 100753) at which time the Agency agreed that no food effect study was required given the rapidly dissolving nature of the dosage forms and because the Maxalt®-MLT label states no significant food effects on C_{max} or AUC.

The pivotal study 2259 is the only study conducted and was determined to be adequate to support this application.

3. Summary of Pivotal Relative Bioavailability Study

Study Title: A Single-Dose, Randomized, Open-Label, Three-Way, Crossover, Pivotal, Comparative Bioavailability Study of Rizatriptan 10 mg Oral Films (IntelGenx Corp.), Maxalt®- MLT 10 mg Orally Disintegrating Tablets (Merck & Co., Inc., USA) and Maxalt®-Lingua 10 mg Oro-dispersible Tablets (MSD Sharp & Dohme,GmbH) in Healthy Male and Female Volunteers under Fasting Conditions.

Methodology:
This was an open-label, randomized, three-way crossover study conducted in healthy adult volunteers under fasting conditions to assess the relative bioavailability, safety and tolerability of a single dose of rizatriptan 10 mg oral film. All doses were administered by study staff members. Subjects remained confined to the clinical facility from 10 hours prior to drug administration until after the 12-hour blood sample collection.

Blood Sampling for PK: Blood samples were collected pre-dose (0 hours), 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.25, 2.75, 3, 4, 6, 8, and 12 hours post-dose. The washout period was at least 3 days (>24 half-lives) between each period and was sufficient to ensure the elimination of the rizatriptan dose and avoid carry-over effects.

Number of Subjects Enrolled and Randomized:
Thirty healthy adults were enrolled and randomized. Twenty-six subjects completed the study. Two subjects were dismissed due to non-compliance (use of restricted items), one subject withdrew due to catheter-site pain (from blood collection), and one subject voluntarily withdrew.

Main Criteria for Inclusion:
Healthy, non-smoking adults 18 – 45 years old, with body weight greater than or equal to 55 kg for males and 50 kg for women.

Test and Reference Products:
Treatment A: Rizatriptan 10 mg Oral Films (test product)
Treatment B: Maxalt®-MLT 10 mg Orally Disintegrating Tablets
Treatment C: Maxalt®-Lingua 10 mg Oro-dispersible Tablets

Subjects were randomized to 1 of 3 sequences: A-B-C, B-C-A or C-A-B

Criteria for BE Assessment:
Bioequivalence between the test treatment and the reference treatment was concluded if the 90% confidence interval of the geometric mean ratio (test/reference) of C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ values were within 0.80 to 1.25.

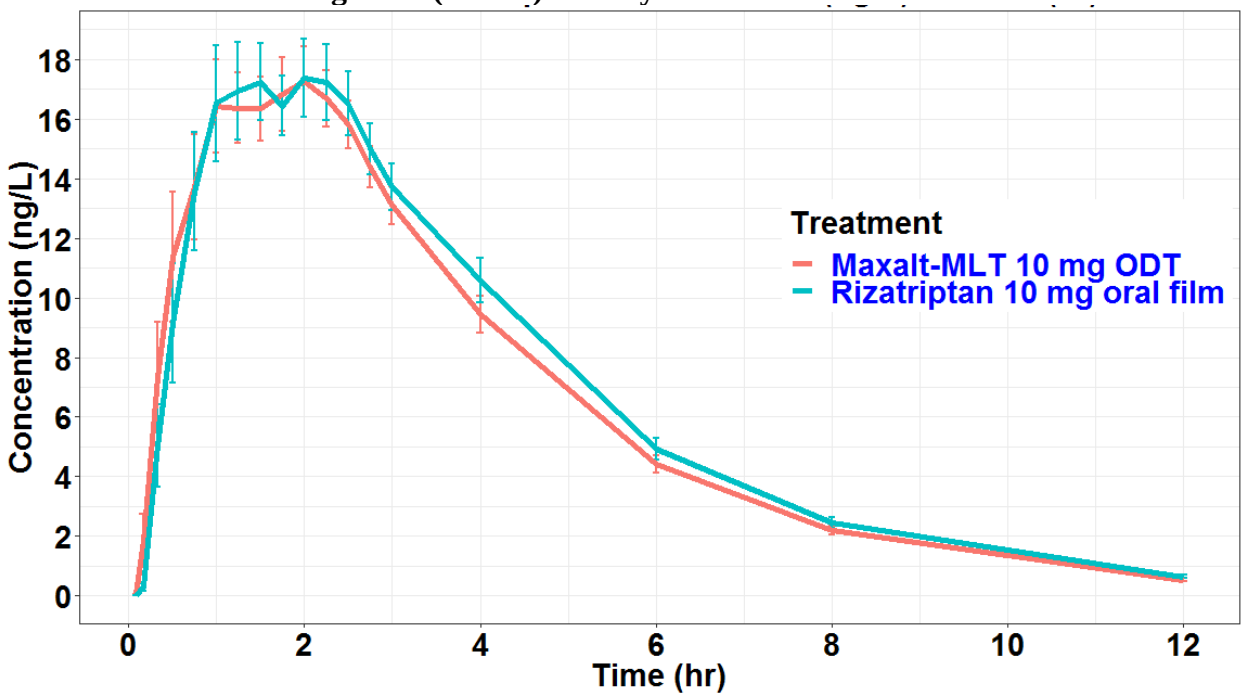
Results:
For the comparison of rizatriptan 10 mg oral film with Maxalt®-MLT 10 mg ODT, the ratio (test/reference) of the geometric means of C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ were 1.02, 1.04, and 1.05, respectively. The 90% confidence intervals of the geomatric mean ratios were within 0.8 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 (the listed drug)

	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
$AUC_{0\text{-}t}$ (ng*hr/mL)	80.91	77.46	104.46	99.30 – 109.90
$AUC_{0\text{-}inf}$ (ng*hr/mL)	82.88	79.01	104.90	99.82 – 110.23

(Source: Clinical Study Report 2259 page 67, Link \\cdsesub1\evsprod\nda205394\0005\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\bpsi-2259\bpsi-2259-report-body.pdf)

Figure 1. Mean (±SE) Rizatriptan Plasma Concentration for Rizatriptan 10 mg oral film and Maxalt®-MLT 10 mg ODT (N = 26) – Study 2259



(Source: Study 2259 Dataset PC, \\cdsesub1\evsprod\nda205394\0005\m5\datasets\bpsi-2259\tabulations\send\pc.xpt)

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.

Conclusion:

The pivotal study (Study 2259) demonstrated bioequivalence with Maxalt®-MLT 10 mg ODT based on C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. All labeling pertaining to intrinsic and extrinsic factors will be same as in the label for the listed drug (Maxalt®-MLT ODT).

4. Bioanalytical Method Validation

For the determination of rizatriptan concentrations in human K_2EDTA plasma over the range of 0.15 to 75.00 ng/mL, the Applicant used a validated High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry detection (LC-MS/MS). This method was developed and validated by [redacted] (b) (4) The method validation for the determination of rizatriptan in human plasma as well as the in-study analytical run acceptance criteria and sample analysis results were in compliance with the standards established by the FDA Bioanalytical Method Validation Guidance (2018) and was acceptable. The validation parameters are summarized in **Table 2**.

Table 2. Bioanalytical Method Validation Summary

Parameter	**Value**
Analyte	Rizatriptan
Internal standard (IS)	Rizatriptan-d_6
Limit of quantitation (ng/mL)	0.15 to 75.00 ng/mL
Average recovery of drug (%)	72.7
Average recovery of IS (%)	74.5
Standard curve concentrations (ng/mL)	0.15, 0.30, 0.75, 1.20, 3.75, 15.00, 45.00, 67.50, 75.00
QC concentrations (ng/mL)	LLQC: 0.15, QC1: 4.5, QC2: 37.50, QC3: 60.00
QC Intraday precision range (%)	1.2 – 9.8
QC Intraday accuracy range (%)	97.8 – 101.1
QC Inter-day precision range (%)	3.5 – 8.1
QC Inter-day accuracy range (%)	100.6 – 104.9
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24 hours at room temperature
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Rizatriptan: 75 days at -70°C ± 10°C Internal Standard: 50 days at -20°C ± 5°C
Processed stability (hrs) (equivalent to post-preparative stability)	2 hours at room temperature 97 hours at 5°C
Freeze-thaw stability (cycles)	4 cycles (frozen at -70°C, thawed at RT) (LQC, HQC and DQC) 4 cycles (frozen at -20°C, thawed at RT) (LQC, HQC and DQC)
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	75 days at -70°C ± 10°C

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/

PRIYA BRUNSDON
03/15/2019 08:51:49 AM

SREEDHARAN N SABARINATH
03/15/2019 09:02:05 AM