CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205394Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

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.

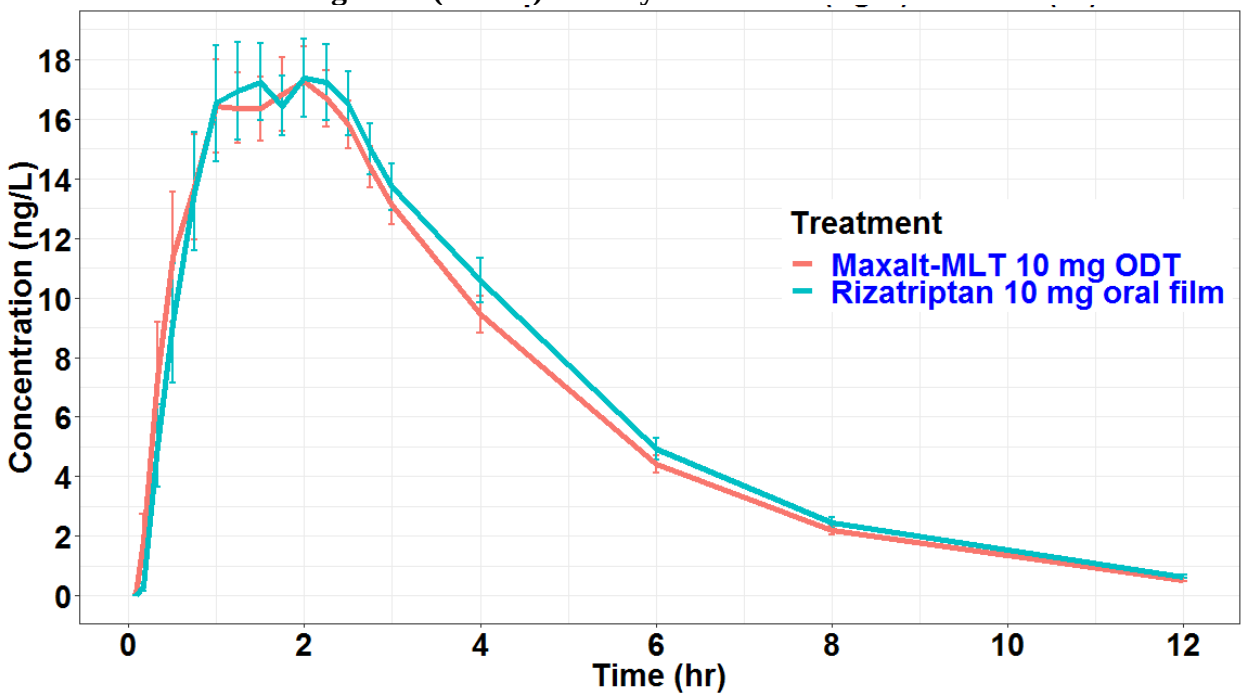
Results:
For the comparison of rizatriptan 10 mg oral film with Maxalt®-MLT 10 mg ODT, the ratio (test/reference) of the geometric means of C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ were 1.02, 1.04, and 1.05, respectively. The 90% confidence intervals of the geomatric mean ratios were within 0.8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

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/s/

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

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

Clinical Pharmacology Review

PRODUCT (Generic Name):	Rizatriptan benzoate
PRODUCT (Brand Name):	Rizaport
NDA:	205,394
DOSAGE FORM:	Oral film
DOSAGE STRENGTHS:	(b) (4) 10 mg
INDICATION:	Migraine with or without aura
SUBMISSION DATE:	3/26/2013
SPONSOR:	RedHill BioPharm
CP REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

Rizatriptan is a selective 5-$HT_{1B/1D}$ receptor agonist. It is currently marketed as the active pharmaceutical ingredient in Maxalt® (rizatriptan benzoate) tablets and Maxalt-MLT® (rizatriptan benzoate) orally disintegrating tablets (ODT), both of which were approved in 1998 to treat migraine with or without aura Both formulations are available in 5 mg and 10 mg dosage units for oral administration. Dosing regimen is one tablet upon acute migraine attack with re-dosing separated by at least two hours and up to 30 mg a day.

The applicant seeks the approval of immediate-release oral film formulation of rizatriptan for the treatment of migraine attacks in adults with similar (b) (4) route of administration and medication directions/instructions to that of Maxalt-MLT®. Per the applicant, this drug product will improve compliance and therefore efficacy, since its size and packaging system makes it easier for patients to carry with them at all time.

The applicant submitted the NDA via 505(b)(2) pathway referring to the NDA 20-865 for Maxalt-MLT®. The applicant conducted one 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"*(Protocol No RZA-P9-688, randomized, lab-blinded, 2-period, 2-

sequence), demonstrating that 10-mg oral film is bioequivalent to Maxalt-MLT® 10-mg ODT. There was no efficacy trial conducted for rizatriptan oral film.

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

* units are ng/mL for C_{max} and ng·hr/mL for AUCt and AUC_{inf}.

The applicant intents to market (b) (4) the 10-mg (b) (4)

No food-effect study was conducted. This has been discussed during the pre-IND meeting for IND 110,753. The Agency agreed with the sponsor's proposal of only conducting a fasted BE study based on the following considerations: if food has not affected the bioavailability of the active drug in the conventional oral dosage, similar lack of food effect may be expected with an ODT, if BE has been established between the conventional oral dosage and the ODT. In this case, no food effect study is necessary. Similar logic may be extended to the oral film formulation. 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®. Therefore, no clinically significant food effect is expected for the rizatriptan oral film product.

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 (high solubility and high permeability 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 is completely absorbed following oral administration, indicating that rizatriptan is a highly permeable drug. The labeling also states that rizatriptan benzoate is soluble in water at about 42 mg/mL (expressed as free base) at 25°C. This suggests that rizatriptan has good aqueous solubility. *In vitro* dissolution studies showed that both rizatriptan oral film and Maxalt®-ODT dissolved rapidly, with more than 85% amount of drug dissolved in 15 minutes (refer to Biopharmaceutical review by Dr. John Duan). 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 C_{max} and T_{max} 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, a fasted BE study alone is considered sufficient for this submission.

In conclusion, the information submitted under NDA 205-394 has been reviewed and found to be acceptable from the Clinical Pharmacology's perspective.

Xinning Yang, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D. Ph.D._____

Study RZA-P9-688: Single Dose Crossover Comparative Bioavailability Study of Rizatriptan 10 mg Immediate Release Oral Film and Maxalt-MLT® 10 mg Orally Disintegrating Tablets in Fasting State in Healthy Male and Female Volunteers (Study Period: Apr 22, 2012 – May 9, 2012)

<table>
<tr><td>Objective</td><td>To evaluate and compare the relative bioavailability and therefore the bioequivalence of a Rizatriptan Immediate Release Oral Film versus Rizatriptan Orally Disintegrating tablet (ODT) after a single oral dose administration under fasting conditions as well as to assess the safety of Rizatriptan Immediate Release Oral Film.</td></tr>
<tr><td>Study Design</td><td>The study was a single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design in healthy subjects. The following investigational products were to be administered under fasting conditions:
Test: 1 x Rizatriptan 10 mg Immediate Release Oral Film
Reference: 1 x Maxalt-MLT® 10 mg ODT
<table>
<tr><th></th><th>Period 1</th><th>Period 2</th></tr>
<tr><td>Sequence 1 (n= 13)</td><td>Test</td><td>Reference</td></tr>
<tr><td>Sequence 2 (n= 13)</td><td>Reference</td><td>Test</td></tr>
</table>
The wash-out period was 7 days.

Subjects were asked to place the orally dispersible tablet/film directly on their tongue and to close their mouth. Subjects had to let the tablet/film completely dissolve in their mouth and then swallow their saliva. The subjects should have avoided rubbing the film with their tongue until it was completely dissolved. Time of complete dissolution was to be noted. No water was to be provided with the administration of the drug. The tablet/film must not have been swallowed whole and must not have been chewed or broken.

(Reviewer's note: This is consistent with the instruction in Patient Information for Maxalt-MLT®, which states 'Peel open the blister pack with dry hands and place the MAXALT-MLT orally disintegrating tablet on your tongue. The tablet will dissolve and be swallowed with your saliva. No liquid is needed to take the orally disintegrating tablet'.)</td></tr>
<tr><td>Study Population</td><td>Of the 26 healthy males (14) and females (12) who were included in the study, 24 subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1 and day 8. The age ranged from 22 to 40 years with a mean of 32 years. Twenty-three subjects were white and 3 subjects were black. The body weight ranged from 55.2 to 95.6 kg with a mean of 72.8 kg.</td></tr>
<tr><td>Pharmacokinetic Assessments</td><td>Blood samples were collected prior to and 0.08, 0.17, 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 drug administration.

The PK parameters, C_{max}, T_{max}, AUC_t, AUC_{inf}, $AUC_{t/inf}$, k_{el} and $t_{1/2, el}$, were estimated using non-compartmental approach.

Statistical analysis was based on a parametric random ANOVA model of the PK parameters; two-sided 90% confidence interval of the ratio of geometric means for the C_{max}, AUC_t and AUC_{inf} based on natural log-transformed data; T_{max} based on a non-parametric approach.
ANOVA model:
- fixed factors: sequence, period, treatment
- random factor: subject (nested within sequence)</td></tr>
</table>

Bioanalytical Method	The bioanalytical assay was validated.

Analyte	Rizatriptan (ng/ml)
Method	LC-MS/MS
Internal Standard	Rizatriptan-D_6
LLOQ	0.5
Calibration Range	0.5, 1, 2.5, 7.5, 12.5, 20, 35, 42, 50
QC	1.5, 9, 13, 37.5
Accuracy (%Actual)	94.9 – 103.1%
Precision (%CV)	2.4 – 5.3%

Safety	Clinical laboratory tests, vital signs, ECGs, and adverse event (AE) reporting

Results

The clinical and analytical sites of the study were inspected during the period of (b) (4) by Office of Regulatory Affairs (ORA) investigator George C. Amedro and Office of Scientific Inspection (OSI) scientist Arindam Dasgupta. The data for clinical and analytical portions of this study were determined acceptable for Agency's review (please refer to the memo documented in DARRTS on September 26, 2013 for details).

Twenty-four subjects were analyzed and included in the PK and statistical analysis. Subject (b) (6) was withdrawn immediately after dosing of period 2 following Sponsor decision onsite at the time of the event (during dissolution of the study medication, a portion of the subject's saliva dropped to the floor (~ 0.5 mL)). This subject received both formulations under study, but was removed from the PK and statistical analysis; his samples were not assayed. Subject (b) (6) was withdrawn before dosing of period 2 due to a positive cocaine test and received only one single oral dose of the Test; he was removed from the PK/statistical analysis and his samples were not assayed.

The PK parameters and profiles of rizatriptan after administration of either Maxalt ODT® (reference) or applicant's oral film product (test) were shown as below.

Table 1. Summary of Main Study Results – Rizatriptan

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	20.672	28.6	21.140	27.5
ln (C_{max})	2.9880	9.9	3.0110	9.9
T_{max} (hours) $^{\$}$	1.63	47.0	1.63	55.3
AUC_T (ng·h/mL)	75.784	23.6	74.362	21.0
ln (AUC_T)	4.3023	5.4	4.2887	4.8
AUC_∞ (ng·h/mL)	80.571	21.3	80.289	18.8
ln (AUC_∞)	4.3683	4.8	4.3694	4.2
$AUC_{T/\infty}$ (%)	95.83	2.3	94.83	2.7
K_{el} (hours^{-1})	0.3859	13.9	0.3703	12.9
$T_{½el}$ (hours)	1.83	14.2	1.90	12.3

$^{\$}$ For T_{max}, the median is presented

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).

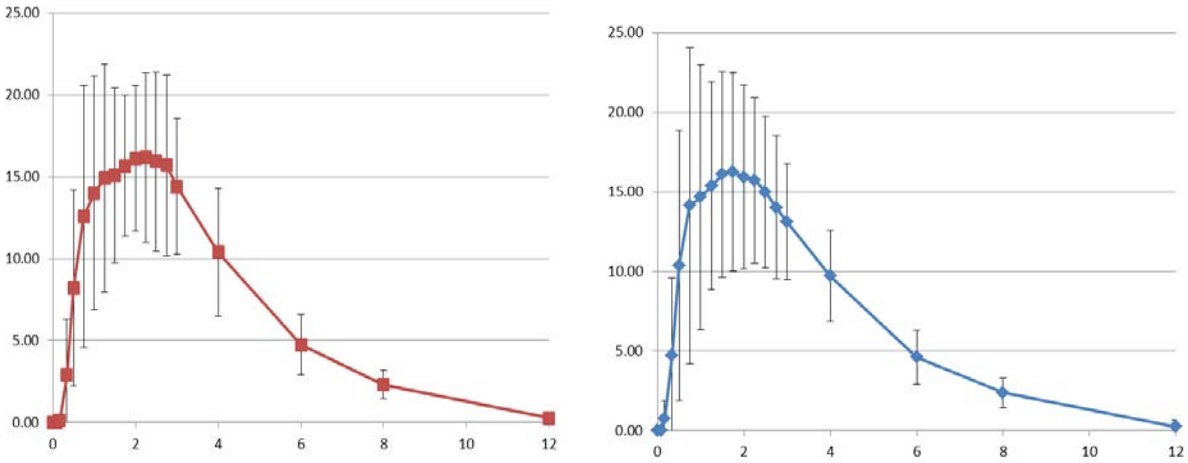
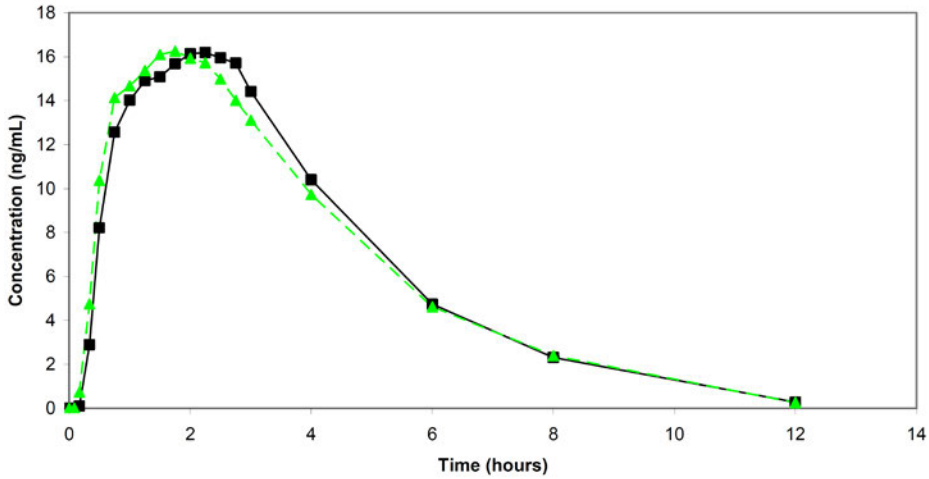


Figure 2. Mean Plasma Concentrations of Rizatriptan versus Time Profiles (Reference: green triangles; Test: black squares)



The terminal phases of rizatriptan could not be adequately estimated for the subject (b) (6) after administration of the test product and subject #017 after receiving the reference product. Therefore, the parameters AUC_{inf}, $AUCT_{t/inf}$, K_{el}, $t_{1/2,el}$ were not calculated. The number of subjects included in the statistical analysis of these parameters was 22.

The 90% confidence intervals (CIs) of the geometric mean ratio of rizatriptan (test/reference) C_{max}, AUCt, and AUC_{inf} fell within the 80%-125% range. The T_{max} of rizatriptan achieved after administration of the applicant's oral film product was similar to the T_{max} from Maxalt ODT® (median (range): 1.63 (0.5 – 4.0) hours for both). The findings were confirmed by the reviewer's independent analysis based on the PK concentration data. Overall, these results demonstrated that the applicant's oral film product is bioequivalence to the Maxalt ODT® product.

Table 2. 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

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

Safety Results	Both formulations tested were generally safe and well tolerated by the subjects included in this study. Three (11.5%) of the 26 subjects experienced a total of 4 adverse events. Two subjects (7.7%) reported 2 adverse events (1 System Organ Class and 1 Preferred Term) after the administration of the test product and 2 subjects (8.0%) reported 2 adverse events (2 different System Organ Classes and 2 different Preferred Terms) after the administration of the reference product. The severity of adverse events ranged from mild to moderate. No severe adverse events were observed. No mucosal irritation was reported for any subject. No adverse events required the use of medications following dosing. No subject was withdrawn from the study for safety reasons.
Conclusions	The test formulation (rizatriptan 10 mg oral film) is bioequivalent to the reference formulation (Maxalt-MLT® 10 mg orally disintegrating tablet) under fasting conditions.

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/s/

XINNING YANG
01/09/2014

YUXIN MEN
01/09/2014