Summary Review

Date	April 14, 2023
From	Heather Fitter, M.D. Paul R. Lee, M.D., Ph.D.
Subject	Summary Review
NDA #	205394
Applicant	IntelGenx Corp
Date of Submission	October 17, 2022
PDUFA Goal Date	April 17, 2023
Proposed Proprietary Name	RizaFilm
Established or Proper Name	Rizatriptan
Dosage Form(s)	10 mg oral film
Route of Administration	Oral
Recommended Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults and in pediatric patients 12 to 17 years of age weighing 40 kg or more
Recommended Proposed Dosing Regimen(s)	10 mg single dose
Recommendation on Regulatory Action	*Approval*

1. Introduction/Background

A 505(b)(2) application was originally submitted by RedHill BioPharm (with IntelGenx acting as the US agent) for RizaFilm (in previous submissions referred to as Rizaport), an immediate-release oral film formulation of rizatriptan for the acute treatment of migraine on March 26, 2013. A Complete Response Letter (CRL) 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 first 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 CRL.

IntelGenx Corp submitted a second Complete Response (CR) to the CRL which resulted in another Complete Response action due to the multiple CMC deficiencies including deficiencies noted at the manufacturing sites. This second CR also included a comparative BA study of Rizaport to Maxalt-MLT which demonstrated bioequivalence for the rizatriptan 10-mg oral film to the listed drug, Maxalt-MLT 10-mg ODT. (b) (4)

[redacted] In the second CRL, the Division advised that the applicant should develop a [redacted] dosage strength of its product to support dosing for pediatric patients 6 through 11 years of age.

The applicant submitted a third complete response submission (a Class 2 resubmission) for this NDA. The applicant proposed 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 proposed to use Maxalt-MLT oral disintegrating tablet at as the listed drug. This application only included the 10-mg formulation, [redacted] A Complete Response action was taken on this submission due to multiple CMC issues including a "withhold recommendation" made during both the second and the third review cycle.

During the last review cycle, multiple CMC deficiencies were identified, in addition to a manufacturing facility recommendation of "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.

This is the fourth complete response submission for this application. The applicant is seeking approval for a rizatriptan oral film formulation. This submission includes findings derived from a 10 mg formulation and therefore only supports 10 mg dosing.

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

Chemistry, Manufacturing, and Controls (CMC):

- Drug Product/Labeling primary reviewer was Dr. Eric Bow, and the secondary reviewer was Dr. Martha Heimann.
- Drug Substance primary reviewer was Dr. Zhixing Shan, and the secondary reviewer was Dr. Gaetan Ladouceur.
- The Manufacturing primary reviewers were Drs Qin Liang and Erin Kim and the secondary reviewers were Drs. Cassandra Abellard, and Lane Christensen.
- The application technical lead was Dr. Martha Heimann.

2. Nonclinical Pharmacology/Toxicology

N/A

3. Office of Product Quality (OPQ)

The proposed product submitted for review in this application is an oral film containing 10 mg of rizatriptan. The applicant cross references two Type II Drug Master Files for the drug substance [redacted] Drug Master File (DMF) [redacted] was reviewed six times by the Agency, and this last time OPQ concluded that the DMF is adequate. The applicant provides a description of the general properties of rizatriptan benzoate drug substance and also refers to the DMF providing information for the specification, potential impurities, analytical methods, batch analyses, and stability. There are no concerns of potential genotoxic impurities

and [redacted] in the drug substance. Based on the stability data in this DMF, the drug substance is stable for at least [redacted] months when stored in [redacted]. The Holder sets a retest data of [redacted] months for the drug substance, which OPQ considers to be adequate.

DMF [redacted] has been reviewed 8 times by the Agency and the last review concluded that the DMF is adequate. Based on the information submitted there are no concerns of potential genotoxicity for the drug substance. The applicant refers to the DMF and provides information for the specification, analytical methods, batch analyses, and stability. OPQ concludes that the information is adequate.

The structure of rizatriptan benzoate was investigated and confirmed by the substance manufacturer using multiple techniques. The applicant has provided adequate information for the impurities in the drug substance and the corresponding control strategies. Based on this information, there are no concerns of potential genotoxic impurities and [redacted] for the drug substance, rizatriptan benzoate.

One primary issue from the previous review cycle was the inadequate control strategy for a [redacted] The applicant is also qualifying another drug substance manufacturer, [redacted] in addition to [redacted] Three batches of drug product manufactured with [redacted] drug substance and one batch with [redacted] drug substance. Certificates of analysis are provided for each batch, with all tested parameters meeting the acceptance criteria. Stability data for the three [redacted] API batches is provided, with [redacted] No trends or out-of-spec results were noted, with the [redacted] impurity remaining within the stability specification of not more than (NMT) [redacted]%. The analytical method for impurities has been adequately revalidated to enable detection of the [redacted] impurity at levels well below the release specification of NMT [redacted]%. The proposed product is adequate based on the control strategies, release, and stability results of the registration batches.

Another issue that led to issuance of a complete response with the last cycle was related to deficiencies following inspection of the manufacturing facility. During this review cycle, it was determined that the drug substance manufacturing facility [redacted] (FEI: [redacted] is in compliance and was found to be acceptable in the most recent inspection. The newly proposed drug substance manufacturer [redacted] (FEI [redacted] is acceptable based on file review. The drug product manufacturing site IntelGenx Corp. is recommended for PAI. The PAI conducted on 3/20-24/2023 was classified Voluntary Action Indicated (VAI). The facility is acceptable.

OPQ recommends an Approval action for this supplement.

4. Clinical Pharmacology

N/A

5. Clinical Microbiology

N/A

6. Clinical/Statistical- Efficacy

N/A

7. Safety

N/A

8. Other Relevant Regulatory Issues

Division of Medical Error Prevention and Analysis (DMEPA)
Dr. Beverly Weitzman conducted the primary review of the proposed labels and labeling for rizatriptan oral film to evaluate whether there were areas of vulnerability that could lead to medication errors. Dr. Stephanie DeGraw was the Team Leader.

DMEPA completed a review of the labels and labeling for this application on January 10, 2014. However, since the application received a CRL on January 31, 2014, the recommendations for the (b) (4) 10 mg strength container labels and carton labeling were sent to the applicant as part of the CRL. The CRL noted that the FDA reserved comment on the proposed labeling (i.e., PI and PPI) until the application is otherwise adequate. Therefore, the recommendations for the PI and PPI were not communicated to the applicant.

In response to the CRL issued on January 31, 2014, the applicant submitted NDA 205394 as a Class 2 resubmission on October 1, 2018. Under the Class 2 resubmission, the applicant submitted 10 mg strength (b) (4) container label and carton labeling which were revised in response to the recommendations sent to the applicant in the CRL dated January 31, 2014. DMEPA completed a review of the labels and labeling on December 11, 2018, however, the application received a second CRL on March 28, 2019, and again, DMEPA's recommendations for the container label and carton labeling were sent to the applicant as part of the CRL. DMEPA's recommendations for the PI were not communicated to the applicant at that time.

In response to the CRL issued on March 28, 2019, the applicant submitted a Class 2 resubmission under NDA 205394 on September 26, 2019. Under this Class 2 resubmission, the applicant submitted container label and carton labeling which were revised in response to the recommendations sent to the applicant in the March 28, 2019, CRL. DMEPA completed a review of the label and labeling on December 23, 2019. The application received a third CRL

on March 24, 2020, and DMEPA's recommendations for the container label and carton labeling were sent to the applicant as part of the CRL. DMEPA's recommendations for the PI were not communicated to the applicant at that time.

Subsequently, the applicant submitted NDA 205394 as a Class 2 resubmission on October 17, 2022. Under the Class 2 resubmission, the applicant submitted container label and carton labeling which were revised in response to the recommendations sent to the applicant in the March 24, 2020, CR letter and as well as PI and PPI labeling for the current supplemental application under review.

DMEPA concludes that the final agreed-upon prescribing information and carton and container labeling are acceptable.

Dr. Weitzman concluded that the proposed proprietary name requested by the applicant for their product, RizaFilm, was conditionally acceptable.

9. Pediatrics

This application does trigger the Pediatric Research Equity Act (PREA) due to a new dosage form. At the time of submission of the original application, the Pediatric Review Committee (PeRC) agreed with the Division to grant a partial waiver in pediatric patients 0-5 years old, 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 6-17 years old 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 the applicant's PREA requirements. (b) (4)

The second resubmission, received September 2018, included only the 10 mg strength. The submission was discussed with the PeRC in February 2019, and they agreed that if an approval action is taken a PREA PMR should be issued for the development of a (b) (4) strength to support use in patients 6 through 11 years of age. The third resubmission also included no information on (b) (4) In the CRL issued in response to this third submission, the applicant was informed that they should develop a (b) (4) formulation appropriate for patients 6 through 11 years of age.

The current resubmission only includes the 10-mg formulation, and therefore, is insufficient to satisfy the PREA requirements based on the plan outlined in the original application. We will issue the following PREA PMR to the applicant:

Develop an age-appropriate dose strength of RizaFilm for administration to pediatric patients 6 through 11 years of age.

10. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

The indication statement includes reference to pediatric age as well as weight because the Listed Drug, Maxalt, specifies dosing of either 5 mg to children that weigh less than 40 kg or 10 mg to children that weigh equal to or over 40 kg. Since the indication for this supplement is limited to children 12 through 17 years of age (b) (4) the reference to a weight cutoff of 40 kg or over was included in the indication statement.

11. Recommendations/Risk-Benefit Assessment

RizaFilm oral film meets bioequivalence criteria with Maxalt-MLT 10 mg ODT, which the Division has previously determined to be safe and effective for the treatment of migraine with or without aura in adults and children 12 years of age and older. Overall, the risk/benefit assessment is acceptable and similar to that of previously approved triptan products. An Approval action will be taken for this application.

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
04/14/2023 01:37:58 PM

PAUL R LEE
04/14/2023 01:57:18 PM