CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205394Orig1s000

OTHER ACTION LETTERS

U.S. FOOD & DRUG ADMINISTRATION

NDA 205394

COMPLETE RESPONSE

IntelGenx Corp.
Attention: Ross C. D'Emanuele
50 South Sixth Street, Suite 1500
Minneapolis, MN 55402-1498

Dear Dr. D'Emanuele:

Please refer to your new drug application (NDA) dated March 26, 2013, received March 27, 2013, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for RizaFilm (rizatriptan) oral film 10 mg.

We acknowledge receipt of your amendment dated September 26, 2019, which constituted a complete response to our March 28, 2019, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1) With respect to the manufacturing process:

2) With respect to drug product stability:

We acknowledge the out of specification (OOS) investigations submitted in response to the September 26, 2019, action letter. However, due to the manufacturing process deficiencies described in Item 1 above, we have determined that stability data obtained from testing of the existing exhibit batches cannot be used as primary data for establishment of product shelf life. Therefore, we recommend the following:

a) Submit 12 months of long-term stability data for exhibit batches manufactured as recommended in Comment 1. Stability testing should be performed using fully validated methods and the suitability of analytical equipment should be verified prior to use. The product shelf life assigned will be based on review of this stability data.

b) If you intend to use the 2017 or 2018 batch stability results as supportive data, provide the raw HPLC data for all corrected analytical results. Additionally, regarding INV-2019-017, in order to support disqualification of the OOS stability results obtained using (b) (4) for analysis of this product, further investigation is needed to identify the root cause.

FACILITY INSPECTIONS

3) During a recent inspection of the (b) (4) drug substance manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations 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 facility.

4) During the recent inspections of IntelGenx Corp. (FEI 3005721224) for oral film products, our field investigator observed objectionable conditions at the drug product manufacturing facility. In addition, during the review of the submission dated 09/26/2019, we are recommending manufacture of new exhibit batches tested in accordance with cGMPs. Please note that that this information will be reviewed by the Agency during the review of the application and a follow up Pre approval inspection may be needed to verify that the facility has taken necessary corrective actions to ensure oral film product quality.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

If you resubmit this application, include draft carton and container labeling revised as follows:

General Comments (Container labels and Carton Labeling)

- The usual dose statement can be improved to ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information labeling. We recommend you revise the usual dose statement: (b) (4) (b) (4) to read “Recommended Dosage: See prescribing information.”
- The current temperature statements do not contain the temperature scale designation (i.e., “°C” or “°F”) after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. Ensure that the degree symbol and temperature scale follow each numeric value denoting temperature ranges to increase clarity. For example, revise “59° - 77°F (15° - 25°C)” to read “59°F to 77°F (15°C to 25°C)”.

Container Labels

- As currently presented, the format for the expiration date is “YYYY MM.” However, it is unclear whether the month (that is, MM) will be displayed using numerical (for example, 06) or alphabetical (for example, JU) characters. Therefore, we were not able to assess the appropriateness of the proposed expiration date format from a medication safety perspective. Please clarify whether you propose to use only numerical characters for the expiration date, or whether you propose to use alphabetical characters for the month. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day, if space permits. FDA recommends that the expiration date appear in YYYY-MM-DD format if only

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

Carton Labeling

- It is unclear what information will be contained within the "Serialization Area." Therefore, we are unable to assess the acceptability of the information. Please clarify the specific information you intend to display in the "Serialization Area."
- As currently presented, there is no product identifier on the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
- We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
- We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the carton labeling. The lot number and expiration date are required per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively. Ensure that the lot number and expiration date are present on the carton labeling in accordance with 21 CFR 10(i)(1) and 21 CFR 211.137.
- We note the statement [redacted (b) (4)] which could lead to confusion. Consider relocating this statement to the back panel, deleting the statement altogether, or address this concern by other means.

PROPRIETARY NAME

Please refer to correspondence dated, January 29, 2020, which addresses the proposed proprietary name, RizaFilm. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

You should develop a [redacted (b) (4)] dosage strength of your product to support dosing and administration in pediatric patients age 6 through 11 years.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we

may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Alina Salvatore, Regulatory Project Manager, at 240-402-0379.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

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/

NICHOLAS A KOZAUER
03/24/2020 10:24:20 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205-394

COMPLETE RESPONSE

IntelGenx Corp.
Attention: Ross C. D'Emanuele
50 South Sixth Street, Suite 1500
Minneapolis, MN 55402-1498

Dear Dr. Emanuele:

Please refer to your New Drug Application (NDA) dated March 26, 2013, received March 27, 2013, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rizaport (rizatriptan) oral film (b) (4) 10 mg.

We acknowledge receipt of your amendment dated October 1, 2018, which constituted a complete response to our January 21, 2014, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

(b) (4)

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PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

If you resubmit this application, include draft carton and container labeling revised as follows:

A. Container Labels

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or

YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. The immediate container label lacks a barcode. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual pouch as required per 21CFR 201.25(c)(2).
3. The layout of the strength is not consistent with our current guidance for the presentation of the proprietary name, established name, dosage form, and strength for drug products.[a] Relocate the strength statement to follow the established name on the principal display panel as this is the customary placement of the strength statement, and therefore the location most familiar to users. See example below:

RIZAPORT
(rizatriptan)
oral (b) (4) film
10 mg

4. We note the container label lacks instruction on how to use the film, which poses risk of wrong technique administration errors. We recommend adding a statement such as "How to use: Use dry hands. Place film on tongue. Keep in place until film dissolves." or any other relevant statements should be added to the container label to minimize the risk of wrong technique administration errors.

B. Carton Labeling

1. The net quantity statement (i.e., 18 Films, 12 Films, 6 Films) competes in prominence with the proprietary name, established name, and product strength and takes away from important product information.[a] Decrease the prominence of the net quantity statement (i.e., 18 Films, 12 Films, 6 Films).

C. References

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 336-342). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

During recent inspections of the [redacted] (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.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Product Quality

1. Provide the full report for the elemental impurities risk assessment summarized in section 3.2.P.5.6 Justification of Specification. We note that this assessment was provided in the previous 3.2.P.2 Pharmaceutical Development document submitted October 31, 2017, which has been removed from the submission, but does not appear in the current version of this document submitted October 1, 2018.

[redacted] (b) (4)

8. We request that you upload the original method validation reports for the assay and dissolution methods (ITG-17-0002, ITG-17-0004, resp.) into eCTD format.

9. In section 3.2.P.8.3, the long-term results for assay and impurities at approximately 2 months appear to be missing for the four batches manufactured at IntelGenx in 2018. Provide this data, if available, and update the application accordingly.

Clinical

You should develop (b) (4) dosage strength of your product to support dosing and administration in pediatric patients age 6 through 11 years.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/

ERIC P BASTINGS
03/28/2019 03:42:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205-394

COMPLETE RESPONSE

RedHill Biopharma Ltd.
Reza Fathi, Ph.D.
Senior VP Research and Development
88 North Franklin Turnpike
Hohokus, NJ 07423

Dear Dr. Fathi:

Please refer to your New Drug Application (NDA) dated March 27, 2013, received April 3, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rizaport (rizatriptan) oral film.

We acknowledge receipt of your amendments dated July 10, 2013, October 10, 2013, October 30, 2013, November 22, 2013, and December 5, 2013.

We also acknowledge receipt of your amendment dated January 15, 2014, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Process Description Deficiencies:

(b) (4)

(b) (4)

Formulation Deficiencies:

(b) (4)

Deficiencies Regarding Impurities:

(b) (4)

12. Provide information pertaining to the characterization of impurities in the drug product (section P.5.5)

Drug Product Specification Deficiencies:

13. Update the drug product specifications to include tests and acceptance criteria for physical characteristics of the film (e.g., flexibility, tensile strength, acceptable level of bubbles, etc) or provide justification, supported by data, for not monitoring these parameters in the finished product.
14. The proposed acceptance criterion for the disintegration is overly broad. Tighten the specification for disintegration to a limit that is justified by data and patient requirements.

(b) (4)

17. The acceptance criterion for the dissolution in the drug product specification was revised to Q (b) (4)% in 15 minutes. Update the drug product release and stability specifications to reflect this change and provide dissolution data for the last time point on the stability samples with this method.

Container Closure Deficiencies:

18. Provide a 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.
19. Provide a description of any secondary packaging used for the drug product.

Stability Deficiencies:

20. Revise the post approval stability commitment to provide for placement of the first three commercial batches of each strength on stability under long-term and accelerated conditions.
21. Your application lacks photostability data for the drug product. Provide photostability on at least one batch of the drug product as per ICH Q1A(R2) and Q1B, or a justification for the exclusion of this data.
22. Provide 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 (See comment 17 above).

Environmental Impact Assessment:

23. Amend your application to request a categorical exclusion from preparing an environmental impact consideration, citing the specific citation under 21 CFR 25.31.

LABELING

We reserve full comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Please submit draft carton and container labels and labeling revised as follows:

1. General Comments for Labels and Labeling
   a. (b) (4) The (b) (4) text against the (b) (4) background for the 10 mg strength is difficult to read. Change the background colors or change the colored text for better contrast and to improve readability.
   b. Revise the active ingredient from (b) (4) to "Rizatriptan".
   c. Relocate the strength to beneath the dosage form for customary placement.

2. Pouch Labels
   a. It is unclear where the pouch should be folded before tearing open at the notch. Add a dotted line to show where it should be folded. Revise the statement (b) (4) to read similar to "To open: Fold on the dotted line and tear open at the notch." for clarity. In addition, the dotted line and instructions for opening the pouch should appear on the principal display panel instead (b) (4) In

order to accommodate this information, relocate the net quantity to the lower third of the principal display panel, away from the strength.

b. Add the statement "Keep product in pouch until ready to use." to the back panel, similar to the carton labeling, to help maintain the integrity of the product.

3. Carton Labels

a. Revise statements in all upper case to sentence case to improve readability.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

505(b)(2) REGULATORY PATHWAY

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.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ERIC P BASTINGS
01/31/2014