CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214621Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 8, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 214621
Product Name and Strength:	Orgovyx (relugolix) tablets, 120 mg
Applicant/Sponsor Name:	Myovant Sciences GmbH
OSE RCM #:	2020-834-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 7, 2020 for Orgovyx. Division of Oncology 1 (DO1) requested that we review the revised container labels and carton labeling for relugolix (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Gao, T. Label and Labeling Review for relugolix (NDA 214621). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 July 28. RCM No.: 2020-834.

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/s/

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ASHLEIGH V LOWERY
12/08/2020 10:22:33 AM

Clinical Inspection Summary

Date	September 25, 2020
From	Yang-min (Max) Ning, M.D., Ph.D. Karen Bleich, M.D. Kassa Ayalew, M.D., M.P.H. GCPAB/OSI/CDER/FDA
To	Sundeep Agrawal, M.D. Daniel Suzman, M.D. Rashida Redd, RPM DO1/OOD/CDER/FDA
NDA #	214621
Applicant	Myovant Sciences GmbH
Drug	Relugolix tablets
New Molecular Entity	Yes
Therapeutic Classification	Gonadotropin-releasing hormone (GnRH) receptor antagonist
Proposed Indication	Treatment of men with prostate cancer (b) (4)
Consultation Request Date	May 21, 2020
Inspection Summary Goal Date	September 30, 2020
Action Goal Date	December 20, 2020
PDUFA Date	December 20, 2020

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

The clinical data of a Phase 3 study [MVT-601-3201] were submitted to the Agency in support of a New Drug Application (NDA) for use of relugolix in men with prostate cancer (b) (4) Three participating investigators [Dr. Curtis Dunshee (Site 2001), Dr. Lawrence Gervasi (Site 2071), and Dr. Lawrence Karsh (Site 2004)] and the study sponsor [Myovant Sciences GmbH] were selected for clinical inspections.

The inspections of the three clinical investigators found that the submitted data by the Applicant to FDA were verifiable with source data. For Drs. Dunshee and Gervasi, there were no objectionable regulatory deficiencies identified. For Dr. Karsh, regulatory violations were identified, including potential underreporting of adverse events for several subjects [e.g., Subjects (b) (6) This was communicated to the DO1 Review Team and an information inquiry was conveyed by the Team to the Applicant. A re-examination of source data was performed by the Applicant, leading to an updated safety data and analysis submitted for the site in August 2020 [see detailed

information in Section III of this summary]. With the feedback from the Review Team and our review, no reinspection of Dr. Karsh was requested or conducted during the current review cycle.

Although regulatory violations were found at Dr. Karsh's site, including underreporting of adverse events for several subjects, Study MVT-601-3201 appears to have been adequately conducted based on the results of these inspections and the follow-up reports received from the Applicant. The clinical data generated from the three clinical investigators appear to be acceptable in support of this NDA.

II. BACKGROUND

Relugolix is a new, orally-administered GnRH receptor antagonist. The Applicant for this NDA submitted clinical data from a Phase 3 study [MVT-601-3201] of relugolix and proposed an indication for use in men with prostate cancer (b) (4) .

Study MVT-601-3201 was titled "A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men with Advanced Prostate Cancer." The parallel treatment was a 3-month depot of leuprolide, an approved GnRH receptor agonist administered intramuscularly or subcutaneously.

The primary objective of this study was to evaluate the ability of relugolix to achieve and maintain serum testosterone suppression to castrate levels of < 50 ng/dL in men with advanced prostate cancer that required at least one year of continuous ADT. The primary endpoint was the sustained castration rate, defined as the cumulative probability of serum testosterone suppression to <50 ng/dL from Week 5 Day 1 [Day 29] through Week 49 Day 1 [Day 337] of the study.

Key eligibility criteria of the study included: 1) advanced prostate cancer that in opinion of the investigator, necessitated ADT for the disease management; 2) a serum testosterone level of ≥150 ng/dL at study entry; 3) no prior treatment with a GnRH analog or systemic chemotherapy for prostate cancer. Eligible subjects were to be randomly assigned (2:1) to receive relugolix orally once daily or leuprolide depot every three months for a total of 48 weeks. During the study, radiotherapy and/or chemotherapy in combination with study treatment were to be allowed.

For the primary efficacy assessment, blood specimens were to be collected at the protocol-prespecified timepoints [e.g. Weeks 0, 1, 3, 5, 9, and then every 4 weeks until Week 49 of the study] and submitted to a central laboratory for determination of serum total testosterone levels. Study treatment and other protocol-required assessments continued for the 48-week study period until intolerable toxicity, failure to maintain testosterone suppression to castrate levels, consent withdrawal, noncompliance, or occurrence of other events for discontinuation as prespecified in the study protocol.

From April 18, 2017 through December 10, 2019 (database lock date for analysis in the current submission), the study enrolled a total of 934 subjects from 155 study sites in 20 countries. Twenty-four percent of subjects were from the United States. Of the enrolled, 624 subjects were randomized to the relugolix arm and 310 to the leuprolide arm. All randomized subjects who received at least one dose of study treatment were included in the efficacy and safety analyses. Note that two subjects in each arm who did not receive study treatment after randomization were excluded from the reported analyses per the statistical plan which used a modified intent-to-treat population. As of the database lock date, the study was ongoing.

The Review Division DO1 and OSI selected three participating clinical investigators in this study, including Dr. Curtis Dunshee (Site 2001), Dr. Lawrence Gervasi (Site 2071), and Dr. Lawrence Karsh (Site 2004), and the study sponsor for clinical inspections. These three investigators had a high enrollment of subjects into the relugolix arm and were associated with a high castration rate relative to other study sites. The study sponsor was selected given no history of inspection by FDA and the new molecular entity application for relugolix.

III. RESULTS by STUDY SITE

1. **Dr. Curtis Dunshee, Site 2001**
   2260 West Orange Grove Road
   Tucson, AZ 85741

Dr. Dunshee was inspected on June 22-26, 2020 as a data audit for Study MVT-601-3201. This was the first FDA inspection of this investigator. The investigator site enrolled 15 subjects into the study, with 11 subjects allocated to the relugolix arm and 4 to the leuprolide arm. As of the data cutoff date of December 10, 2019, Subject (b) (6) in the relugolix arm was discontinued from study treatment due to adverse event [Grade 3 gastric bleeding] and Subject (b) (6) in the leuprolide arm was discontinued at the investigator's discretion. The 13 remaining subjects completed study treatment per the protocol. Note that after completion of study treatment, Subject (b) (6) in the relugolix arm died from myocardial infarction and Subject (b) (6) in the leuprolide arm died from metastatic prostate cancer.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, eligibility criteria, randomization allocation and treatment administered, protocol-required assessments and documentation (e.g., blood sampling dates, times, and submissions to the central laboratory), adverse events and reporting, investigational product accountability and disposition, and protocol deviations. Regulatory documents and study procedures were also reviewed, including the Institutional Review Board (IRB) approvals for the study and continuing reviews, FDA 1572 forms, Financial Disclosure forms, training records, data collection and reporting to the sponsor, study monitoring logs, access to the electronic systems used for the study, and record

retention.

The inspection identified no regulatory deficiencies. The Applicant's submitted efficacy and safety data listings were verifiable with source records at the site, with no discrepancies noted. There was no evidence of underreporting of adverse events. At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued to the investigator.

2. Dr. Lawrence Gervasi, Site 2071
6900 Pearl Road, 2nd Floor
Middleburg Heights, OH 44130

Dr. Gervasi was inspected on June 22-30, 2020 as a data audit for Study MVT-601-3201. For the investigator, this was the initial inspection by FDA. The site enrolled 25 subjects, with 18 assigned to the relugolix arm and 7 to the leuprolide arm. As of the data lock date, 23 subjects completed the study. Two subjects in the relugolix arm were discontinued from study treatment due to adverse event [acute cardiac failure for Subject (b) (6)] and consent withdrawal [Subject (b) (6)], respectively.

The inspection involved a comprehensive review of all subject source records and examined the Applicant's submitted data listings for the site. The reviewed records included the IRB's approvals, informed consent forms, subject eligibility, enrollment log, protocol-required assessments and submissions of blood samples to the central laboratory, concomitant medications, adverse events and serious adverse events, sponsor correspondence, study monitoring log, study drug accountability and storage, and other pertinent regulatory documentation (e.g., FDA 1572s, financial disclosures) and record retention.

The inspection identified no objectionable conditions and a Form FDA 483 was not issued to the investigator. The submitted data from the site matched what was found in the source records. No discrepancies or unreported adverse events were identified.

3. Dr. Lawrence Karsh, Site 2004
2777 Mile High Stadium Circle
Denver, CO 80211

Dr. Karsh was inspected from June 22, 2020 through July 16, 2020 for Study MVT-601-3201. For the investigator, this was the third FDA inspection. The first inspection, conducted in April-May 2009, identified several regulatory deficiencies, for which a Form FDA 483 was issued. The final compliance classification was Voluntary Action Indicated. The second inspection was conducted in June 2014, with No Action Indicated as the final compliance classification.

The investigator site enrolled 16 subjects for Study MVT-601-3201, with 11 assigned to the relugolix arm and 5 to the leuprolide arm. As of the data cutoff date, 15 subjects were found to have competed study treatment. One subject (Subject (b) (6)) in the leuprolide arm was terminated early due to a protocol violation identified after randomization and study

treatment initiation (see additional information below).

The current inspection audited source records for the enrolled subjects and compared them with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, medical history, subject eligibility, randomization allocation, study treatment administration and/or discontinuation, primary endpoint assessments, adverse events, serious adverse events, and protocol deviations. Regulatory documents and procedures for the study were also reviewed, including the IRB's correspondences and approvals, financial disclosure forms, training records, monitoring reports, correspondences between the sponsor and the clinical site, drug accountability, and study record retention at the site.

The inspection reported three Inspectional Observations in a Form FDA 483 issued to the investigator. These observations and related key supporting evidence are summarized below:

1) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. For example, there was no evidence of requests for and/or reviews of all medical records to completely assess and document adverse events for several subjects [Subjects (b) (6), (b) (6) in the relugolix arm and Subject (b) (6) in the leuprolide arm] who received study treatment in combination with chemotherapy and/or radiotherapy outside the site during their study participation; informed consent forms for 8 subjects showed no documentation of a witness involved;

2) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. A few subjects who did not meet the eligibility criteria or who did not fully complete all eligibility assessments were enrolled in the study. For example, Subject (b) (6) who had a QTc of 472 msec was enrolled and treated with leuprolide;

3) Failure to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug. Subject (b) (6) in the relugolix arm who had an alanine aminotransferase (ALT) level of 134 U/L (reference range 6-43 U/L) on 3/20/2019 [at Week 49] was reported to the sponsor on 5/16/2019, 8 weeks after the finding. Section 7.5. [Adverse Events of Clinical Interest (AECI) Reporting] of the study protocol required any increase in ALT $\geq$ 3x ULN be reported to the sponsor within 24 hours.

Dr. Karsh provided his written response, dated July 30, 2020, to the Form FDA 483. He acknowledged the Observations and provided his explanations and his corrective and prevention action (CAPA) plans to ensure compliance moving forward. The plans entail a newly completed "Process Improvements" and a series of trainings (GCP Refresh, Data Management, etc.) at the site. The "Process Improvements" includes detailed information on the following 5 items:

a) Institute a more rigorous and robust quality control program
b) Standardize and revise guidelines for the collection research data
c) Standardization of source documents
d) Update and revise SOPs.
e) Re-organization the Research Department roles

Regarding the above-listed Observation 1, Dr. Karsh stated that the site was not in compliance with the established process of an audit review of subject's study documents and that he implemented a series of trainings, including Standard Operating Procedures for "Roles and Responsibilities of the Research Staff", "Preparing and Managing Source Documents", "Informed Consent Process", and "Revised Quality Control (QC) Checks for Drug Studies". In response to the above Observation 2, Dr. Karsh reported that he informed the sponsor's medical monitor upon discovery of the error in the enrollment of Subject (b) (6). This subject was terminated from the study and reported as a protocol deviation. For a few subjects who did not complete all the required eligibility assessments but were randomized, he stated that these subjects did not receive study treatment until all the procedures were completed. To prevent this from reoccurrence, the "Process Improvements" has been implemented. With respect to the above Observation 3, the delayed reporting of the AECI was related to a change in Study Coordinator who was not aware of the reporting requirement. Dr. Karsh stated that he did follow the subject's hepatic test abnormality until it returned to a normal level and that additional trainings of research staff were performed in October 2019, including "Transition of Study Checklist", "Implementation of QC Checklist", and "Roles and Responsibilities of the Research staff". Following the current FDA inspection, an additional training "Following the Protocol" was carried out on adding non-typical requirements to the study specific visit.

Besides the above observations, the inspection found that the enrolled subjects received study treatment per their treatment allocation. Blood samples for testosterone were collected according to the protocol and submitted to the central laboratory for analysis. The submitted data listings were verifiable with the reviewed source records. Of note, Subject (b) (6) had a reported testosterone level of 52.81 ng/mL at Week 5 of the study.

<u>Reviewer's Comments</u>: The above regulatory violations and related findings were conveyed to the DO1 Review Team upon feedback from the inspection on July 23, 2020. Of the listed findings, the reported failure to obtain and/or review relevant medical records for the subjects who received study treatment in combination with chemotherapy and/or radiotherapy during the study is suggestive of underreporting of adverse events and thus may affect the risk-benefit assessment of the investigational product relugolix.

Although the clinical investigator failed obtain and/or review relevant medical records for the subjects who received study treatment in combination with chemotherapy and/or radiotherapy during the study, which is a regulatory violation, the Applicant provided additional information as listed below to address the concerns related to potential underreporting of safety data.

Upon discussion with the DO1 Review Team, information requests were conveyed on July

27, 2020 to the Applicant to: 1) provide an updated list of adverse events from the site and an analysis of the impact of the unreported adverse events on the overall safety profile; 2) identify whether there are additional study sites with evidence of underreporting of adverse events based on your monitoring of the study.

On August 21, 2020, the Review Team received the Applicant's response. According to the response, the Applicant sent a new Clinical Research Associate (CRA) to re-examine the safety data at the site, including comparison of medical history, physical examinations, and adverse events in the study database with source data and any other reports related to radiotherapy notes and/or chemotherapy notes. The CRA confirmed most of the unreported adverse events for subjects listed in the Form FDA 483 and identified an additional 22 unreported adverse events, including fatigue, nasopharyngitis, alopecia, asthenia, dysuria, nausea, and other. Together with the originally reported 125 adverse events from the site, the sponsor provided an updated summary list of adverse events and reported that the rate of adverse events of grade 3-4 or events which led to study treatment withdrawal or interruption remained unchanged between the original and updated safety data for the site. Regarding whether there are additional study sites with evidence of underreporting of adverse events, the sponsor reviewed the monitoring reports from sites with adverse events reported for <80% of subjects, sites with performance improvement plans, and sites with subjects who received docetaxel or radiotherapy at outside clinics while on study. The sponsor found no evidence of additional sites with underreporting of adverse events. The reviewer and DO1 Review Team considered the Applicant's response to be acceptable.

The investigator's CAPA plans appear to be reasonable.

4. **Sponsor: Myovant Sciences GmbH**
   2000 Sierra Point Pky 9th Floor
   Brisbane, CA 94005

The sponsor was inspected from June 23 through June 30, 2020 to evaluate its conduct and management of Study MVT-601-3201. This was the first inspection of the sponsor.

The inspection reviewed the sponsor's history, organizational chart, clinical operations organizational chart for the study, key individuals and their responsibilities, contract research organizations (CRO) involved in the study and related agreements and responsibilities, operating procedures and records, selection and monitoring of participating investigators and related agreements and financial disclosures, site initiation visits, monitoring plans and reports, adverse event reporting, protocol violations, and data collection and management.

The inspection found no objectionable regulatory violations, with no Form FDA-483 issued to the sponsor at the conclusion of the inspection. For the study, a total of 934 subjects were verified to have enrolled and randomized as of the database lock date. All study site records were checked and found to contain the required regulatory documentation. Examination of monitoring records for 10 randomly selected sites found no deficiencies. Overall, the reported inspectional findings demonstrate adequate oversight of Study MVT-601-3201 by the sponsor.

Reviewer's Comments: *The sponsor inspection did not identify the monitoring issue related to the underreporting of adverse events at Dr. Karsh's site. This may be secondary to the random selection of a limited number of sites for monitoring records. The sponsor inspection had no access to source records at study sites.*

{See appended electronic signature page}

Yang-min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

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cc:

Review Division /Division Director
Review Division /Project Manager
Review Division /Clinical Team Lead
Review Division/Medical Officer
OSI/DCCE/GCPAB Reviewer
OSI/Office Director
OSI/DCCE/Division Director
OSI/DCCE/GCPAB Branch Chief
OSI/DCCE/GCPAB Team Lead
OSI/GCP Program Analyst
OSI/Database PM

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 25, 2020

To: Rashida Redd, Regulatory Project Manager
Division of Oncology 1 (DO1)

William Pierce, PharmD, Associate Director for Labeling, Office of Oncologic Diseases

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (relugolix) tablets for oral use

NDA: 214621

In response to DO1's consult request dated May 6, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for relugolix tablets for oral use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DO1 on September 11, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed PPI will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on April 20, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer, PharmD at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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LYNN M PANHOLZER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 25, 2020
To:	Rashida Redd, BA Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (relugolix)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214621
Applicant:	Myovant Sciences GmbH

1 INTRODUCTION

On April 20, 2020, Myovant Sciences GmbH submitted for the Agency's review an original New Drug Application (NDA) 214621 for TRADENAME (relugolix). The proposed indication for TRADENAME (relugolix) is for the treatment of patients with advanced prostate cancer.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on May 6, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (relugolix) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (relugolix) PPI received on April 20, 2020, and received by DMPP and OPDP on September 11, 2020.
- Draft TRADENAME (relugolix) Prescribing Information (PI) received on April 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 11, 2020

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the font size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 28, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 214621
Product Name, Dosage Form, and Strength:	(b) (4) (relugolix) tablets, 120 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Myovant Sciences GmbH
FDA Received Date:	April 20, 2020 and July 9, 2020
OSE RCM #:	2020-834
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the review process for (b) (4) (relugolix) tablets, the Division of Oncology 1 (DO1) requested that we review the proposed (b) (4) prescribing information, patient information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed (b) (4) container labels, carton labeling, PI, and patient information and determined that they may be improved to ensure safe product use.

4 CONCLUSION & RECOMMENDATIONS

The proposed (b) (4) container labels, carton labeling, PI, and patient information may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

a. If the intended meaning of the statement "[redacted (b) (4)]" is to dispense to patients in original container, we recommend revising this statement to state "Dispense to patients in original container only" for clarity.

B. Patient Information

1. Consider delete the statement "[redacted (b) (4)]" in the sentence "After that, take one RELUGOLIX tablet once da[redacted (b) (4)] since this appears to be leading advice that is not supported by the recommended dosage.

4.2 RECOMMENDATIONS FOR MYOVANT SCIENCES GMBH

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. We request that you submit the NDC numbers for the container labels and carton labeling. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

2. Ensure that the expiration date is present as required per 21 CFR 211.137. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date 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 forward slash to separate the portions of the expiration date. See *Draft Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

3. Ensure that the lot number is present as required per 21 CFR 201.10(i)(1) and clearly differentiated from the expiration date.

B. Container Label: Commercial Bottle and Professional Sample Bottle

1. The established name for drug products should include the finished dosage form. If space does not permit the finished dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient. Therefore, revise the principal display panel so that it reads:

   (b) (4)
   (relugolix)
   tablets

   120 mg

   30 tablets

   Ensure there is sufficient white space between the dosage form (tablets), strength (120 mg), and net quantity (30 tablets) to improve readability.

2. Revise the statement "(b) (4)" to read, "Recommended Dosage: See Prescribing Information."

C. Container Label: 7-day Commercial Starter Package

We included an image of the blister card below with each panel labeled as "PDP", "Side Panel A", "Side Panel B", and "Side Panel C" to provide clarity for our recommendations below.

1. On the principal display panel (PDP), The established name for drug products should include the finished dosage form. If space does not permit the finished dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient. Therefore, revise the principal display panel so that it reads:

   (b) (4) OR (b) (4) (relugolix) tablets

2. On the PDP, revise the strength statement "[redacted]" to state "120 mg per tablet"] to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.
3. On Side Panel B, revise the statement "[redacted]." to "Day 1: Take 3 tablets at same time." We recommend this to instruct the patients to take the 3 tablets at same time for their day 1 dose.
4. On Side Panel B, revise the statement "[redacted]." to "Take 1 tablet once daily for each of the remaining days." We recommend this to instruct the patients to take the 1 tablet once daily for their day 2 to day 7 doses.
5. On Side Panel B, consider revise the statement [redacted]." to "To remove the tablet, push down on the tablet and break it through the back side."
6. On Side Panel C, revise the statement "[redacted]" to read, "Recommended Dosage: See Prescribing Information." and relocate this statement to Side Panel A and immediately above the statement "Each tablet contains 120 mg of relugolix." because users may not read the back of the blister card and overlook this important information (Side Panel C).
7. On Side Panel C, relocate the storage statement to Side Panel A and immediately above the statement "Keep out of reach of children. [redacted] because users may not read the back of the blister card and overlook this important information (Side Panel C).

D. Container Label: 7-day [redacted]

1. See recommendations C1 to C7 above.
2. Starter packs are not considered to be drug samples by the Agency. [redacted] on the PDP. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-

documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

E. Carton Labeling: 7-Day Commercial Starter Package

1. See recommendations C1 to C2 above.
2. On the PDP, revise the statement "[redacted (b) (4)] to read, "Recommended Dosage: See Prescribing Information."

F. Carton Labeling: 7-day Professional Sample

1. See recommendations C1 to C2 above.
2. On the PDP, revise the statement [redacted (b) (4)] to read, "Recommended Dosage: See Prescribing Information."
3. Starter packs are not considered to be drug samples by the Agency. [redacted (b) (4)] the PDP. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for (b) (4) received on July 9, 2020 from Myovant Sciences GmbH.

Table 2. Relevant Product Information for (b) (4)	
Initial Approval Date	N/A
Active Ingredient	relugolix
Indication	treatment of patients with advanced prostate cancer.
Route of Administration	oral
Dosage Form	tablets
Strength	120 mg
Dose and Frequency	Initiate treatment of RELUGOLIX with a single loading dose of 360 mg (three 120-mg tablets) and continue treatment with a 120-mg dose taken once daily at approximately the same time each day.
How Supplied	Bottle of 30 tablets, enclosed with a child-resistant induction seal cap. Blister card of 9 tablets, in a single fold-over blister card with foil film and lidding.
Storage	Store at 15°C to 30°C (59°F to 86°F).
Container Closure	Bottle: 75cc, high density polyethylene (HDPE) bottle with desiccant and a (b) (4) child-resistant induction seal cap Blister pack: Aluminum (b) (4) in a single fold-over blister card (blister card)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Myovant Sciences GmbH.

- Container label received on April 20, 2020
- Professional Sample Blistercards received on April 20, 2020
- Professional Sample Carton Labeling received on April 20, 2020
- Prescribing Information and Patient Information (Image not shown) received on July 9, 2020, available from \\cdsesub1\evsprod\nda214621\0018\m1\us\pc-draft-uspi-review-updated-redline.docx.

G.2 Label and Labeling Images

Container label: bottle

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

TINGTING N GAO
07/28/2020 01:09:26 PM

ASHLEIGH V LOWERY
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