CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214621Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214621
PDUFA Goal Date	December 20, 2020
OSE RCM #	2020-833, 2020-835
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Acting Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	December 7, 2020
Subject	Evaluation of Need for a REMS
Established Name	relugolix
Trade Name	Orgovyx
Name of Applicant	Myovant Sciences GmbH
Therapeutic Class	gonadotropin releasing hormone (GnRH) receptor antagonist
Formulation(s)	120 mg tablet
Dosing Regimen	relugolix loading dose of 360 mg orally on the first day of treatment, followed by 120 mg orally once daily.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Orgovyx (relugolix) is necessary to ensure the benefits outweigh its risks. Myovant Sciences GmbH submitted a New Drug Application (NDA) 214621 for relugolix with the proposed indication for the treatment of adult patients with advanced prostate cancer. The serious risks associated with relugolix include QT/QTc interval prolongation, embryo-fetal toxicity, and laboratory testing. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 1 (DO1) agree that a REMS is not necessary to ensure the benefits of relugolix outweigh its risks. The efficacy of relugolix was supported by the HERO trial, in which relugolix achieved and maintained serum testosterone suppression to castrate levels (< 50 ng/dL) from Day 29 through 48 weeks (Day 337) of treatment. The serious risks associated with relugolix of QT/QTc interval prolongation, embryo-fetal toxicity, and laboratory testing will be communicated in the warnings and precautions section of the label. The likely prescribers will be medical oncologists and urologists who specialize in the treatment of prostate cancer who should have experience prescribing a gonadotropin releasing hormone (GnRH) receptor antagonist.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Orgovyx (relugolix) is necessary to ensure the benefits outweigh its risks. Myovant Sciences GmbH submitted a New Drug Application (NDA) 214621 for relugolix with the proposed indication for the treatment of adult patients with advanced prostate cancer.[1] This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Orgovyx (relugolix), a NME, is a gonadotropin releasing hormone (GnRH) receptor antagonist, proposed for the treatment of adult patients with advanced prostate cancer. Relugolix is supplied as a 120 mg tablet. The proposed dosing regimen is a loading dose of 360 mg orally on the first day of treatment, followed by 120 mg orally once daily.[b] Relugolix is currently approved in Japan.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for relugolix NDA 214621 relevant to this review:

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 04/20/2020: NDA 214621 submission for the treatment of adult patients with advanced prostate cancer received
- 07/30/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for relugolix

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Prostate cancer is a common cause of cancer in men in the United States.[2,3] Guidelines for advanced prostate cancer from the American Urological Association (AUA), American Society of Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) define advanced prostate cancer by disease states including biochemical recurrence without metastatic disease after exhaustion of local treatment options, metastatic hormone-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, and metastatic castration-resistant prostate cancer.[3] The estimated number of new cases and the estimated number of deaths of prostate cancer in the United States is 191,930 and 33,330, respectively.[2,c] The five year relative survival of localized, regional and distant prostate cancer is 100%, 100%, and 30.2%, respectively.[4] Furthermore, the median overall survival of metastatic castration-resistant prostate cancer is approximately 3 years.[5,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Androgen deprivation therapy is a foundational therapy for patients with advanced prostate cancer.[6] Androgen deprivation therapy includes orchiectomy or treatment with GnRH agonists or GnRH antagonists.[3,7] Guidelines for advanced prostate cancer from the AUA, ASTRO, and SUO include androgen deprivation therapy in treatment regimens for metastatic hormone-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, and metastatic castration-resistant prostate cancer.[3] The GnRH agonists leuprolide acetate, goserelin acetate, histrelin acetate, and triptorelin pamoate do not have a boxed warning in their respective labels or have required a REMS for approval.[8,9,10,11,12] Degarelix (Firmagon), a GnRH receptor antagonist, was approved by the FDA in 2008 for the treatment of patients with advanced prostate cancer.[13] The serious risks associated with degarelix include hypersensitivity reactions, QT interval prolongation, laboratory testing, and embryo-fetal toxicity. Degarelix does not have a boxed warning in its label a REMS was not required for approval.

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

4 Benefit Assessment

The pivotal trial NCT 03085095 (HERO) supporting this application for efficacy and safety consisted of a Phase 3 randomized, open label trial which evaluated relugolix in men with advanced prostate cancer.[1,14] Patients in this study required at least 1 year of androgen deprivation therapy and patients had biochemical or clinical relapse following local primary intervention, newly diagnosed castration-sensitive metastatic disease, or advanced localized disease. In HERO, 934 patients were randomized to relugolix loading dose of 360 mg orally on the first day, followed by 120 mg orally once daily (N=622) or leuprolide acetate 22.5 mg (or 11.25 mg in Japan and Taiwan) subcutaneously every 3 months (N=308). The primary efficacy endpoint was medical castration rate defined as achieving and maintaining serum testosterone suppression to castrate levels (< 50 ng/dL) by Day 29 through 48 weeks of treatment. The relugolix group and leuprolide acetate group had medical castration rates of 96.7% (95% CI 94.9% to 97.9%) and 88.8% (95% CI 84.6% to 91.8%). The FDA clinical reviewer concluded that the HERO trial met the primary endpoint, with relugolix achieving and maintaining serum testosterone suppression to castrate levels (< 50 ng/dL) from Day 29 through 48 weeks (Day 337) of treatment.[15,e]

5 Risk Assessment & Safe-Use Conditions

The safety of relugolix was evaluated in NCT 03085095 (HERO).[1,14,f] In the safety population from this clinical trial, 622 patients received relugolix and 308 patients received leuprolide acetate. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 22/622 (3.5%) in the relugolix group and 1/308 (0.3%) in the leuprolide acetate group.[14] Common adverse reactions reported with relugolix included hot flush, increased glucose, increased triglycerides, musculoskeletal pain, decreased hemoglobin, increased alanine aminotransferase, fatigue, increased aspartate aminotransferase, constipation, and diarrhea.

In study HERO, 7 deaths were due to a TEAE in the relugolix group and 9 deaths were due to a TEAE in the leuprolide acetate group.[14] In the relugolix group, deaths were due to myocardial infarction, acute myocardial infarction, metastatic non-small cell lung cancer, prostate cancer, metastatic prostate cancer, metastatic small cell lung cancer, and acute kidney injury.

The serious risks[g] associated with relugolix of QT/QTc interval prolongation, embryo-fetal toxicity, and laboratory testing are summarized in the sections below.

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[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.1 QT/QTc Interval Prolongation

QT/QTc interval prolongation has been reported with androgen deprivation therapy. In the HERO trial, an adverse event of QTc interval prolongation occurred in 2.1% of the relugolix group and 1.9% of the leuprolide acetate group.[6] If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 Embryo-Fetal Toxicity

Relugolix may cause fetal harm based on animal studies and the mechanism of action of the drug. The safety and efficacy of relugolix has not been established in females. The proposed label recommends in males with a female partner of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 Laboratory Testing

Section 5 of the proposed labeling indicates that treatment with relugolix suppresses the pituitary gonadal system and diagnostic tests of the pituitary gonadotropic and gonadal functions may be affected. The proposed label recommends monitoring the therapeutic effect of relugolix by serum prostate specific antigen (PSA) and if PSA increases to measure serum concentrations of testosterone.

6 Expected Postmarket Use

If approved, relugolix will primarily be used in both inpatient and outpatient settings. The likely prescribers will be medical oncologists and urologists who specialize in the treatment of prostate cancer.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for relugolix beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of relugolix on the basis of the efficacy and safety information currently available. Relugolix is an oral GnRH receptor antagonist and is an additional treatment option for patients with advanced prostate cancer. The efficacy of relugolix was supported by the HERO trial, in which relugolix achieved and maintained serum testosterone suppression to castrate levels (< 50 ng/dL) from Day 29 through 48 weeks (Day 337) of treatment. The serious risks associated with relugolix of QT/QTc interval prolongation, embryo-fetal toxicity, and effects on laboratory testing will be communicated in the warnings and precautions section of the label.

Prostate cancer is a common cause of cancer in men in the United States. The estimated number of new cases and the estimated number of deaths of prostate cancer in the United States is 191,930 and 33,330, respectively. The median overall survival of metastatic castration-resistant prostate cancer is approximately 3 years. The likely prescribers will be medical oncologists and urologists who specialize in the treatment of prostate cancer who should have experience prescribing GnRH receptor antagonist. If approved, based on the efficacy and risks associated with relugolix for the treatment of adult patients with advanced prostate cancer, the DRM and DO1 agree that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for relugolix to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Proposed prescribing information for relugolix as currently edited by FDA, Accessed November 3, 2020.

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

[3] Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline 2020. https://www.auanet.org/guidelines/advanced-prostate-cancer (accessed 2020 October 22).

[4] Cancer Stat Facts: Prostate Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/prost.html (accessed 2020 October 22).

[5] Esther J, Maughan BL, Anderson N, Agarwal N, Hahn AW. Management of nonmetastatic castration-resistant prostate cancer: recent advances and future direction. Curr Treat Options Oncol. 2019;20(2):14.

[6] Myovant Sciences GmbH. Relugolix. Module 2.5. Clinical Overview. April 20, 2020.

[7] Nguyen C, Lairson DR, Swartz MD, Du XL. Risks of Major Long-Term Side Effects Associated with Androgen-Deprivation Therapy in Men with Prostate Cancer. Pharmacotherapy. 2018;38(10):999-1009.

[8] Lupron Depot (leuprolide acetate for depot suspension) package insert. North Chicago, IL: AbbVie Inc., 2019 March.

[9] Eligard (leuprolide acetate) package insert. Fort Collins, CO: Tolmar Pharmaceuticals, Inc., 2019 April.

[10] Zoladex (goserelin acetate implant) package insert. Lake Forest, IL: TerSera Therapeutics LLC, 2019 February.

[11] Vantas (histrelin acetate) package insert. Malvern, PA: Endo Pharmaceuticals Solutions Inc., 2019 February.

[12] Trelstar (triptorelin pamoate) package insert. Wayne, PA: Verity Pharmaceuticals, Inc., 2020 May.

[13] Firmagon (degarelix) package insert. Parsippany, NJ: Ferring Pharmaceuticals Inc., 2020 February.

[14] Agrawal S, Hadadi M, Zhang L, Fiero M, Suzman D. Division of Oncology 1 (DO1). Relugolix. Mid-Cycle Meeting, clinical and statistics reviewer slides. July 23, 2020.

[15] Relugolix NDA 214621 multi-disciplinary review and evaluation draft. Accessed November 9, 2020.

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