APPLICATION NUMBER:

212099Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td>July 19, 2019</td>
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<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
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<td>Established Name</td>
<td>darolutamide</td>
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<td>Trade Name</td>
<td>Nubeqa</td>
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<tr>
<td>Name of Applicant</td>
<td>Bayer HealthCare Pharmaceuticals Inc.</td>
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<td>Therapeutic Class</td>
<td>androgen receptor inhibitor</td>
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<td>Formulation(s)</td>
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<td>Dosing Regimen</td>
<td>600 mg orally twice daily</td>
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Nubeqa (darolutamide) is necessary to ensure the benefits outweigh its risks. Bayer HealthCare Pharmaceuticals Inc. submitted a New Drug Application (NDA) 212099 for darolutamide with the proposed indication for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC). The serious risk associated with darolutamide is embryo-fetal toxicity. The applicant did not submit a REMS with this application or risk management plan with this application.

DRISK and the Division of Oncology Products 1 (DOP1) agree that a REMS is not necessary to ensure the benefits of darolutamide outweigh its risks. The efficacy of darolutamide in nmCRPC was supported by the ARAMIS trial in which darolutamide had a statistically significant improvement in median metastasis-free survival when compared to placebo. The serious risk associated with darolutamide of embryo-fetal toxicity will be addressed in the warnings and precautions section of the label. The approved androgen receptor inhibitors enzalutamide and apalutamide also do not have a boxed warning in their respective labels or have required a REMS for approval.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nubeqa (darolutamide) is necessary to ensure the benefits outweigh its risks. Bayer HealthCare Pharmaceuticals Inc. submitted a New Drug Application (NDA) 212099 for darolutamide with the proposed indication for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC). This application is under review in the Division of Oncology Products 1 (DOP1). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION
Nubeqa (darolutamide), a NME, is an androgen receptor inhibitor, proposed for the treatment of patients with nmCRPC. Darolutamide is supplied as a 300 mg tablet. The proposed dosing regimen is 600 mg orally twice daily. Patients should also receive a gonadotropin-releasing hormone analog with darolutamide or have had a bilateral orchiectomy. Darolutamide is not currently approved in any jurisdiction. Darolutamide was granted fast track designation.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for darolutamide NDA 212099 relevant to this review:

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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.
3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Nonmetastatic castration-resistant prostate cancer, as defined by the FDA Guidance for Industry in 2018, is defined by increasing levels of prostate-specific antigen (PSA) even with castrate levels of testosterone and no evidence of distant metastatic disease. Patients with localized prostate cancer may have biochemical recurrence after definitive radiation or surgical therapy. Even after local salvage therapy and androgen deprivation therapy, patients may have increasing PSA levels. The estimated number of new cases of prostate cancer in the United States is 174,650. In addition, the estimated incidence of nmCRPC in the United States is 50,000 to 60,000 cases per year. In a natural history study in patients with nmCRPC and increasing PSA levels even with androgen deprivation therapy (placebo group from a zoledronic acid trial), bone metastasis were observed in 33% of patients at 2 years. The median overall survival of metastatic castration-resistant prostate cancer is approximately 3 years.

3.2 Description of Current Treatment Options
In patients with no distant metastasis (M0) castration-resistant prostate cancer, current guidelines for prostate cancer from the National Comprehensive Cancer Network (NCCN) recommend continued androgen deprivation therapy and list treatment regimens based on PSA doubling time (PSADT). In patients with a PSADT > 10 months, observation or other secondary hormone therapy is recommended. In patients with a PSADT ≤ 10 months, apalutamide, enzalutamide, or other secondary hormone therapy is recommended. Enzalutamide, an androgen receptor inhibitor, was approved by the FDA in 2012 for the treatment of patients with metastatic castration-resistant prostate cancer and in 2018 for the treatment of patients with nmCRPC. The serious risks associated with enzalutamide include seizure, posterior reversible encephalopathy syndrome, hypersensitivity, ischemic heart disease, falls and fractures, and embryo-fetal toxicity. Apalutamide, an androgen receptor inhibitor, was approved by the FDA in 2018 for the treatment of patients with nmCRPC. The serious risks associated with apalutamide include falls and fractures and seizure. Apalutamide is contraindicated in pregnancy. Neither androgen receptor inhibitor has a boxed warning in their respective labels or have required a REMS for approval.

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

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 02200614 (ARAMIS) supporting this application for efficacy and safety consisted of a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial which evaluated darolutamide in patients with nmCRPC with a PSADT of ≤ 10 months. Patients in this study received a gonadotropin-releasing hormone analog or had bilateral orchiectomy. In ARAMIS, 1509 patients were randomized to darolutamide 600 mg orally twice daily (N=955) or placebo (N=554). The primary efficacy endpoint was metastasis-free survival (MFS). The darolutamide group and placebo group had median MFS of 40.4 months and 18.4 months, respectively (HR 0.41, 95% CI 0.34 to 0.5, p<0.0001). The FDA clinical reviewer concluded that the ARAMIS trial found that in patients with nmCRPC the darolutamide arm had a statistically significant and clinically meaningful improvement in median MFS when compared to placebo.

5 Risk Assessment & Safe-Use Conditions

The safety of darolutamide was evaluated in NCT 02200614 (ARAMIS). In the safety population from this clinical trial, 954 patients received darolutamide and 554 patients received placebo. Discontinuation due to an adverse event occurred in 85/954 (8.9%) in the darolutamide group and 48/554 (8.7%) in the placebo group. Common adverse reactions reported with darolutamide included fatigue, pain in extremity, rash, decreased neutrophil count, increased aspartate aminotransferase, and increased bilirubin.

One hundred thirty-seven deaths were reported in ARAMIS, with 80 deaths in the darolutamide group (8.4% of patients) and 57 deaths in the placebo group (10.3% of patients). In the darolutamide group, 14 deaths occurred on study treatment, 23 deaths occurred up to 30 days after the last dose, and 43 deaths occurred greater than 30 days after the last dose. In the placebo group, 7 deaths occurred on study treatment, 11 deaths occurred up to 30 days after the last dose, and 39 deaths occurred greater than 30 days after the last dose. One death in the darolutamide group due to intestinal perforation was thought to be related to study drug per investigators.

The serious risk associated with darolutamide of embryo-fetal toxicity is summarized in the section below. This serious risk is also listed in the enzalutamide and apalutamide labels.

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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.

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.

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 **Embryo-Fetal Toxicity**
Darolutamide may cause fetal harm and loss of pregnancy based on the mechanism of action of the drug. Animal embryo-fetal development toxicology studies were not conducted on darolutamide and no clinical data is available with darolutamide in pregnancy in humans. The proposed label recommends in males with a female partner of reproductive potential to use effective contraception during treatment and for at least one week after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 **Expected Postmarket Use**
If approved, darolutamide 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 darolutamide beyond routine pharmacovigilance and labeling.

8 **Discussion of Need for a REMS**
The FDA clinical reviewer recommends approval of darolutamide on the basis of the efficacy and safety information currently available. Darolutamide is an androgen receptor inhibitor and is an additional treatment option for patients with nmCRPC. The efficacy of darolutamide in nmCRPC was supported by the ARAMIS trial in which darolutamide had a statistically significant improvement in median MFS when compared to placebo. The serious risk associated with darolutamide of embryo-fetal toxicity will be addressed in the warnings and precautions section of the label.

Nonmetastatic castration-resistant prostate cancer is defined by increasing levels of PSA even with castrate levels of testosterone and no evidence of distant metastatic disease. The estimated incidence of nmCRPC in the United States is 50,000 to 60,000 cases per year. Patients with nmCRPC may develop metastatic disease. The likely prescribers will be medical oncologists and urologists who specialize in the treatment of prostate cancer who should have experience prescribing androgen receptor inhibitors. Based on the efficacy and risk associated with darolutamide for the treatment of patients with nmCRPC, this reviewer’s recommendation is 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 darolutamide to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK 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 darolutamide as currently edited by FDA, Accessed 7/9/19.

2 Refer to Guidance for Industry Nonmetastatic, Castration-Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials for more information (https://www.fda.gov/media/117792/download)


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/s/

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Concur