CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	217677
PDUFA Goal Date	November 27, 2023
OSE TTT #	2022-3190
Reviewer Name	Bob Pratt, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	October 27, 2023
Subject	Evaluation of Need for a REMS
Established Name	Nirogacestat
Trade Name	Osgiveo
Name of Applicant	SpringWorks Therapeutics, Inc.
Therapeutic Class	Gamma secretase inhibitor
Formulation(s)	50 mg tablets
Dosing Regimen	150 mg taken orally twice daily until disease progression or unacceptable toxicity

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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 Osgiveo (nirogacestat) is necessary to ensure the benefits outweigh its risks. SpringWorks Therapeutics, Inc. submitted a New Drug Application (NDA) 217677 for nirogacestat, an inhibitor of the Notch cell-surface receptor. The proposed indication is the treatment of adults with desmoid tumors. The serious risks associated with nirogacestat include diarrhea, ovarian toxicity, hepatotoxicity, non-melanoma skin cancers, electrolyte abnormalities, and embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan.

DRM and the Division of Oncology 3 (DO3) agree that a REMS is not necessary to ensure the benefits of nirogacestat outweigh its risks. The efficacy of nirogacestat was supported by Study NIR-DT-301, in which patients treated with nirogacestat had significant improvements ($p < 0.001$) in progression-free survival and objective response rate compared with placebo. At the time of this review, DO3 is recommending regular approval for adult patients with progressing desmoid tumors who require systemic treatment. The serious risks associated with nirogacestat will be communicated in the Warnings and Precautions section of the label. The likely prescribers will be medical oncologists who should have experience monitoring for and managing the serious risks associated with nirogacestat.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Osgiveo (nirogacestat) is necessary to ensure the benefits outweigh its risks. SpringWorks Therapeutics, Inc. submitted a New Drug Application (NDA) 217677 for nirogacestat, an inhibitor of the Notch cell-surface receptor. The proposed indication is for the treatment of adults with desmoid tumors. This application is under review in the Division of Oncology 3 (DO3). The Applicant did not submit a proposed REMS or risk management plan.

2 Background

2.1 PRODUCT INFORMATION

Osgiveo (nirogacestat), an NME, is an inhibitor of the Notch cell-surface receptor.[b] Interaction of Notch with its ligands on adjacent cells initiates a biochemical cascade that causes the intracellular domain of Notch to move from the membrane to the nucleus to alter gene expression through transcriptional regulation.[1] Nirogacestat inhibits the Notch pathway by inhibiting gamma secretase, which prevents cleavage of the Notch intracellular domain and its movement to the nucleus. Although the mechanism of action of nirogacestat in desmoid tumors is not fully understood, dysregulation of Notch can play a role in activating pathways that contribute to tumor growth.[2]

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

[b] The name 'notch' originates from an observation that noted the formation of notches at the wing margin of the Drosophila fruit fly caused by partial loss of function in what was later named the Notch gene [Mohr O., Character changes caused by mutation of an entire region of a chromosome in Drosophila. Genetics. 1919; 4:275-282].

Nirogacestat is proposed for the treatment of adults with desmoid tumors. Nirogacestat is supplied as 50 mg tablets and the proposed dosing regimen is 150 mg (three tablets) taken orally twice daily until disease progression or unacceptable toxicity.[c] Nirogacestat is not currently approved in any jurisdiction. Nirogacestat was designated as an orphan product and received fast track and breakthrough therapy designations.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for nirogacestat NDA 214801 relevant to this review:

- 6/7/2018: Orphan product designation granted for the treatment of desmoid tumor.
- 11/1/2018: Fast Track designation granted for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis.
- 8/28/2019: Breakthrough Therapy designation granted the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis.
- 12/27/2022: Final submission of NDA 217677 received for real-time oncology review for the treatment of adult patients with desmoid tumors.
- 4/11/2023: The Mid-Cycle Communication meeting was held between the Agency and the Applicant via videoconference. Although there was no discussion of REMS during the meeting, the Mid-Cycle Communication Meeting Agenda stated that there currently is no need for a REMS.
- 6/6/2023: The Agency issued a Review Extension-Major Amendment letter related to the following issues: data errors in the submission that affected pharmacokinetic and other analyses; incomplete information to assess patient-reported outcomes; the Applicant's submission of updated laboratory datasets; and other data discrepancies. The user fee goal date was extended three months to November 27, 2023.
- 9/27/2023: The Late-Cycle meeting was held between the Agency and the Applicant via videoconference. There was no discussion of REMS during the meeting. The Late-Cycle Background Package noted that no issues related to risk management have been identified to date.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Desmoid tumors, or aggressive fibromatosis, are rare, soft-tissue tumors with an estimated incidence of two to four per million persons per year in the general population.[3,d] Individuals between the ages of 15 and 60 years are most commonly affected. Of note, desmoid tumors affect between 10 to 20 percent of patients with familial adenomatous polyposis (FAP). The prognosis of patients with desmoids varies according to the extent of disease. Desmoids can develop at virtually any body site, but the main

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*
[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

anatomic sites include the trunk and extremities, abdominal wall, and intra-abdominal tumors. In patients with FAP, intra-abdominal (bowel and mesenteric area) desmoids predominate.[3] Although they do not metastasize, desmoid tumors can be locally aggressive and invasive, leading to substantial morbidity, and rarely death. Compression of vital structures by desmoid tumors can result in severe pain, functional impairment, nerve damage, and bowel obstruction or perforation.[4,e]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Management of desmoid tumors is challenging because of their variable presentation and an unpredictable disease course. Because of locally aggressive behavior and a tendency to relapse with disease that is more aggressive, multimodality treatment is often required and best delivered by a multidisciplinary team specializing in sarcoma treatment. No therapies are currently approved, and existing management guidelines vary depending on tumor location, symptoms, and disease progression. Treatment approaches can incorporate periods of active surveillance as well as interventions including cytotoxic chemotherapy, tyrosine kinase inhibitors, hormonal therapy, ablation therapy, or radiation therapy.[5] Surgery has become a less frequent option owing to high morbidity as well as recurrence rates of 50 to 88% after surgery.[3,4]

4 Benefit Assessment

The pivotal trial supporting the efficacy and safety of the application consisted of a Phase 3, multicenter, double-blind, placebo-controlled study (NIR-DT-301 [NCT03785964]) that randomized 142 patients with progressing desmoid tumors not amenable to surgery. Patients were randomized 1:1 to receive 150 mg nirogacestat or placebo twice daily continuously in 28-day cycles until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) determined radiographically using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by blinded independent central review (BICR). The definition of PFS also included clinical progression as assessed by the investigator and confirmed by independent review. Clinical progression was defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from trial treatment and initiation of emergent treatment. Objective response rate (ORR) was a secondary efficacy endpoint also assessed by BICR. The nirogacestat treatment group had a statistically significant improvement in PFS over placebo, with a 71% reduction in the risk of disease progression or death (HR=0.29 [95% C.I., 0.15, 0.55]; $p < 0.001$), where the median was not reached (NR [95% C.I., NE[f], NE]) compared to placebo (15.1 months (95% C.I., 8.4, NE]). In addition, the ORR was statistically significantly higher ($p < 0.001$) in the nirogacestat group (41% [95% C.I., 29.8, 53.8]) versus the placebo group (8% [95% C.I., 3.1, 17.3]).[g] At this time, the draft integrated review concludes that nirogacestat 150 mg twice daily demonstrated a clinically meaningful and statistically significant

[e] 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.*
[f] NE = not estimable
[g] 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.*

improvement in PFS with a statistically significant and durable ORR, for the treatment of progressing desmoid tumors in patients who require systemic treatment.[6]

5 Risk Assessment & Safe-Use Conditions

The safety population for this risk assessment is based on the 141 patients who received at least one dose of nirogacestat (N=69) or placebo (N=72) in Study NIR-DT-301.[h]

The serious risks associated with nirogacestat, which include diarrhea, ovarian toxicity, hepatotoxicity, non-melanoma skin cancers, electrolyte abnormalities, and embryo-fetal toxicity are summarized in the adverse events of special interest section below.

5.1 Serious and Severe Adverse Events

At least one serious adverse event (SAE) was experienced by 14 (20%) patients in the nirogacestat group and 8 (11%) patients in the placebo group.[7] The only MedDRA Preferred Term reported as an SAE by more than one patient in the nirogacestat group was premature menopause (n=3).[8]

Severe (Grade 3 or higher) adverse events occurred in 38 (55%) patients in the nirogacestat group and 12 (17%) patients in the placebo group.[7] The most frequently reported severe events (event count ≥ 3) by Preferred Term in the nirogacestat group were diarrhea (n=11, 16%), rash (n=4, 6%), and stomatitis (n=3, 4%). One patient in the nirogacestat group died due to multi-organ failure more than 30 days after discontinuing study treatment in the setting of aggressive tumor progression and a new diagnosis of spindle cell sarcoma. In addition, one adverse event leading to death occurred in a patient in the placebo group who experienced sepsis.[8]

5.2 Adverse Events of Special Interest

5.2.1 Diarrhea

In Study NIR-DT-301, diarrhea occurred in 84% of patients in the nirogacestat group and 35% of the placebo group. Most nirogacestat-associated events were Grade 1/2 and could be medically managed. Sixteen percent (16%) of events were Grade 3. Thirty-eight percent (38%) of patients with diarrhea in the nirogacestat group and 40% patients in the placebo group had ongoing, unresolved diarrhea at the time of data cutoff. The proposed label includes a Warning and Precaution for diarrhea and recommends monitoring patients and to manage using antidiarrheal medications. Dose modifications are recommended for patients with persisting diarrhea of Grade 3/4 severity despite maximal medical treatment.[2]

5.2.2 Ovarian Toxicity

Although the Applicant reported that ovarian toxicity occurred in 75% of women of child-bearing potential taking nirogacestat, the clinical review team was unable to adequately characterize the risk due to limitations to interpretability of the data.[7,9] These limitations included the Applicant's incomplete assessment of all premenopausal patients, the lack of documented menstrual histories, no standardization of hormonal assays and missing data, and the lack of standardized case definitions, among other issues.

[h] 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.*

The proposed label includes a Warning and Precaution for ovarian toxicity that states female reproductive function and fertility may be impaired in patients being treated with nirogacestat, and to advise patients on the potential risks for ovarian toxicity, and to monitor patients for changes in menstrual cycle regularity and/or the development of symptoms of estrogen deficiency.[2]

5.2.3 Hepatotoxicity

ALT or AST elevations occurred in 30% and 33% of patients who received nirogacestat in the clinical study, and Grade 3 ALT or AST elevations occurred in 6% and 3% of patients, respectively. There were no cases of Hy's Law or drug induced liver injury. The proposed label includes a Warning and Precaution for hepatotoxicity and to monitor liver function tests regularly and modify the dose as recommended.[2]

5.2.4 Non-melanoma Skin Cancers

There were three adverse events of cutaneous malignancies in patients who received nirogacestat in the clinical study. Cutaneous squamous cell carcinoma occurred in 2 patients (2.9%) and basal cell carcinoma (BCC) occurred in one patient (1.4%). No patients in the placebo group developed a cutaneous malignancy. The proposed label includes a Warning and Precaution for non-melanoma skin cancers and to perform dermatologic examinations at baseline and routinely during treatment.[2]

5.2.5 Electrolyte Abnormalities

In the clinical study, 65% of patients in the nirogacestat group experienced decreased phosphate and 22% experienced decreased potassium. Grade 3 decreased potassium occurred in 1.4% of patients who received nirogacestat. The proposed label includes a Warning and Precaution that electrolyte abnormalities can occur in patients treated with nirogacestat and to monitor phosphate and potassium levels regularly and supplement as necessary.[2]

5.2.6 Embryo-Fetal Toxicity

Nirogacestat can cause fetal harm based on animal studies and the mechanism of action of the drug. The proposed label states to advise pregnant women of the potential risk to the fetus and to advise female patients of reproductive potential as well as males with female partners of reproductive potential to use effective contraception during and after treatment with nirogacestat. This risk will be communicated in the Warnings and Precautions section of the label.[2]

6 Expected Postmarket Use

If approved, nirogacestat will likely be used in both inpatient and outpatient settings. The likely prescribers will be medical oncologists who specialize in sarcoma treatment.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a proposed REMS or risk management plan and proposed that the risks will be managed by the product labeling.

8 Discussion of Need for a REMS

The FDA review team recommends regular approval of nirogacestat based on the efficacy and safety information currently available. Desmoid tumors are rare tumors that can be locally aggressive and invasive, leading to substantial morbidity and rarely death. Compression of vital structures by desmoid tumors can result in severe pain, functional impairment, nerve damage, and bowel obstruction or perforation. There currently are no approved treatments for the disease. Nirogacestat is a gamma secretase inhibitor that blocks proteolytic activation of the Notch receptor. When dysregulated, Notch can activate pathways that contribute to tumor growth.

The efficacy of nirogacestat for the treatment of desmoid tumors is supported by Study NIR-DR-301, in which patients treated with nirogacestat had a 71% reduction in the risk of disease progression or death compared with placebo. The ORR was statistically significantly higher ($p < 0.001$) in the nirogacestat group (41%) versus the placebo group (8%). The serious risks associated with nirogacestat of diarrhea, ovarian toxicity, hepatotoxicity, non-melanoma skin cancers, electrolyte abnormalities, and embryo-fetal toxicity will be communicated in the Warnings and Precautions section of the label. The risk of ovarian toxicity was not well-characterized in the BLA. Therefore, the Agency is proposing a postmarketing requirement that evaluates options for characterization of the risk of ovarian toxicity.[10]

The likely prescribers will be medical oncologists who should have experience monitoring for and managing the serious risks associated with nirogacestat. Based on the efficacy and safety information currently available for the treatment of adult patients with progressing desmoid tumors who require systemic treatment, DRM and DO3 agree that a REMS for nirogacestat is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the review team's evaluation of the data at present, the benefit-risk profile supports approval. Therefore, a REMS is not necessary for nirogacestat to ensure the benefits outweigh the risks. At the time of this DRM 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

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/s/

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