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APPLICATION NUMBER:

212306Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td>June 21, 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>selinexor</td>
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<td>Trade Name</td>
<td>Xpovio</td>
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<td>Name of Applicant</td>
<td>Karyopharm Therapeutics Inc.</td>
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<td>Therapeutic Class</td>
<td>exportin 1 (XPO1) inhibitor</td>
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<td>Formulation(s)</td>
<td>20 mg tablet</td>
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<td>Dosing Regimen</td>
<td>80 mg orally on days 1 and 3 of each week in combination with dexamethasone 20 mg orally on days 1 and 3 of each week</td>
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Xpovio (selinexor) is necessary to ensure the benefits outweigh its risks. Karyopharm Therapeutics Inc. submitted a New Drug Application (NDA) 212306 for selinexor with the proposed indication in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody. Upon further review the proposed indication was revised to the treatment of adult patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The serious risks associated with selinexor include thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, neurological toxicity, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application, but proposed a monitoring and education plan for adverse events.

DRISK and Division of Hematology Products (DHP) agree that a REMS is not necessary to ensure the benefits of selinexor outweigh its risks. The efficacy of selinexor in patients with RRMM was supported by the STORM trial in a subgroup of patients that were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. The serious risk associated with selinexor will be addressed in the warnings and precautions section of the label. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with selinexor.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xpovio (selinexor) is necessary to ensure the benefits outweigh its risks. Karyopharm Therapeutics Inc. submitted a New Drug Application (NDA) 212306 for selinexor with the proposed indication in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody. Upon further review the proposed indication was revised to the treatment of adult patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The application is under review in the Division of Hematology Products. The applicant did not submit a proposed REMS or risk management plan with this application but proposed a monitoring and education plan for adverse events.

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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.
2 Background

2.1 PRODUCT INFORMATION
Xpovio (selinexor), a NME, is a first in class exportin 1 (XPO1) inhibitor proposed in combination with
dexamethasone for the treatment of adult patients with RRMM who have received at least four prior
therapies and whose disease is refractory to at least two proteasome inhibitors, at least two
immunomodulatory agents, and an anti-CD38 monoclonal antibody. Selinexor is supplied as a 20 mg
tablet. The proposed dosing regimen is 80 mg orally on days 1 and 3 of each week. The recommended
starting dose of dexamethasone is 20 mg orally on days 1 and 3 of each week. Selinexor is not currently
approved in any jurisdiction. It was designated an orphan drug. If approved, the indication will be
approved under accelerated approval based on response rate.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for selinexor NDA 212306 relevant to this review:

- 01/05/2015: Orphan drug designation granted
- 08/06/2018: NDA 212306 submission for in combination with dexamethasone for the treatment
  of adult patients with RRMM who have received at least three prior therapies and whose
disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory
agent, and an anti-CD38 monoclonal antibody received
- 11/20/2018: 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 selinexor. However, the review team
expressed concern about whether a single arm trial would demonstrate that selinexor and
dexamethasone provides an advantage over available therapies and about the toxicity of this
regimen.
- 02/26/2019: Oncologic Drugs Advisory Committee Meeting was convened to discuss whether
  the approval of selinexor be delayed until results of the randomized Phase 3 trial Boston are
  available. The AC voted 8 in favor/ 5 against delaying approval of selinexor.
- 03/14/2019: Major amendment acknowledgment letter sent to the applicant; PDUFA goal date
  extended by 3 months. The proposed indication was revised to penta-refractory multiple
  myeloma.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Multiple myeloma is a neoplasm due to malignant plasma cells that proliferate in the bone marrow. Signs of multiple myeloma include hypercalcemia, renal insufficiency, anemia, osteopenia, and

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b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug
osteolytic bone lesions. The estimated number of new cases of multiple myeloma in the United States in 2018 is 30,770.\textsuperscript{4,c} However, multiple myeloma is currently not curable, with most patients relapsing after treatment. In a retrospective multicenter study, the median overall survival for patients with relapsed multiple myeloma (received at least three lines of therapy, refractory to an immunomodulatory drug and a proteasome inhibitor, and exposed to an alkylating agent) was 13 months.\textsuperscript{5,d}

### 3.2 Description of Current Treatment Options

Treatment options for previously treated multiple myeloma include systemic treatment, stem cell transplant, and enrollment in a clinical trial.\textsuperscript{2} The selection of therapy depends on factors including tumor features, host features, and prior history and available treatment options.\textsuperscript{6} Current guidelines from the National Comprehensive Cancer Network (NCCN) for multiple myeloma list a number of regimens in the "Preferred Regimens" and "Other Recommended Regimens" section for previously treated multiple myeloma. Drug listed in these regimens that are FDA approved for the treatment of RRMM include bortezomib, lenalidomide, carfilzomib, daratumumab, elotuzumab, ixazomib, doxorubicin hydrochloride liposome injection, pomalidomide, and panobinostat.\textsuperscript{7,8,9,10,11,12,13,14,15,16} Lenalidomide, pomalidomide, and panobinostat have a REMS and a boxed warning while doxorubicin hydrochloride liposome injection has a boxed warning. Lenalidomide has a REMS with elements to assure safe use (ETASU) to prevent the risk of embryo-fetal exposure and to inform about the serious risks and safe use conditions and also a boxed warning for hematologic toxicity and venous and arterial thromboembolism. Pomalidomide has a REMS with ETASU to prevent the risk of embryo-fetal exposure and to inform about the serious risks and safe use conditions and also a boxed warning for venous and arterial thromboembolism. In addition, panobinostat has a communication plan REMS and boxed warning to inform health care providers about the risks of severe diarrhea and cardiac toxicities. Doxorubicin hydrochloride liposome injection has a boxed warning for cardiomyopathy and infusion related reactions.

### 4 Benefit Assessment

The pivotal trial NCT 02336815 (KCP-330-012, STORM) supporting this application for efficacy and safety consisted of a Phase 2b multicenter open-label single arm trial. STORM Part 1 included patients with quad-exposed, double class-refractory or penta-exposed, triple class refractory multiple myeloma (N=79) and STORM Part 2 included patients with penta-exposed, triple class refractory multiple myeloma (N=123).\textsuperscript{17} STORM Part 2 evaluated the combination of selinexor 80 mg orally twice weekly with dexamethasone 20 mg orally twice weekly in patients with RRMM. In STORM Part 2 122 patients

\textsuperscript{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.

\textsuperscript{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.
received at least 3 prior therapies and were refractory to glucocorticoids, to their most recent multiple myeloma regimen, to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody. In the STORM Part 2 study, there was a patient with multiple myeloma who were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. The primary endpoint was overall response rate (ORR) in patient's refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. The selinexor and dexamethasone treatment group had an ORR of 25.3% (95% CI 16.4% to 36%) with a median duration of response of 3.8 months. The FDA clinical reviewer concluded that the trial supported the efficacy of selinexor in patients with RRMM who have received at least four prior therapies and whose disease is refractory or intolerant to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

5 Risk Assessment & Safe-Use Conditions

The safety of selinexor was evaluated in NCT 02336815 (KCP-330-012, STORM). In the safety population from this clinical trial, 202 patients received selinexor and dexamethasone. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 54/202 (26.7%) of the selinexor and dexamethasone group. In STORM part 2, dose modifications due to a TEAE occurred in 109/123 (88.6%) of patients and the median duration of treatment with selinexor 80 mg twice weekly with dexamethasone 20 mg twice weekly was 3.5 weeks. Furthermore, 202/202 (100%) of patients experienced a TEAE. Common TEAE reported with selinexor included thrombocytopenia, nausea, fatigue, anemia, decreased appetite, weight decreased, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

Nineteen deaths were reported in STORM Part 1, with 9 deaths due to disease progression, 8 deaths due to a TEAE, and 2 deaths with insufficient information. The causes of death due to a TEAE included dyspnea, influenza, cardiorespiratory arrest (N=2), subdural hematoma, multiple organ dysfunction syndrome, ascites and plasma cell leukemia, and respiratory failure. Twenty-three deaths were reported in STORM Part 2, with 13 deaths due to disease progression and 10 deaths due to a TEAE. The causes of death due to a TEAE included pneumonia (N=2), sepsis (N=2), subdural hematoma, cardiac disorder, fungal sepsis, multiple organ dysfunction syndrome, respiratory arrest, and septic shock.

The serious risk associated with selinexor which include thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, neurological toxicity, and embryo-fetal toxicity are

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\(^a\) 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.

\(^b\) 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.

\(^c\) 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.
summarized in the sections below. If approved, these risks will be communicated in the warnings and precautions section of the label. DHP has determined that none of these serious risks require a boxed warning. Monitoring and dose modifications for selinexor will be addressed in section 2 of the proposed label.

5.1 **Thrombocytopenia**

A TEAE of thrombocytopenia occurred in 149/202 (74%) of patients who received selinexor and dexamethasone, with Grade 3 or greater thrombocytopenia reported in 124/202 (61%) of patients. Fatal hemorrhage was reported in < 1% of patients.

5.2 **Neutropenia**

A TEAE of neutropenia occurred in 68/202 (33.7%) of patients who received selinexor and dexamethasone, with Grade 3 or greater neutropenia reported in 43/202 (21.3%) of patients. The proposed label contains recommendations for the supportive care of neutropenia including treatment with granulocyte colony-stimulating factor.

5.3 **Gastrointestinal Toxicity**

Treatment emergent adverse events of nausea, vomiting, and diarrhea occurred in 146/202 (72.3%), 82/202 (40.6%), and 89/202 (44.1%) of patients who received selinexor and dexamethasone, respectively. In addition, Grade 3 or greater nausea, vomiting, and diarrhea were reported in 18/202 (8.9%), 7/202 (3.5%), and 13/202 (6.4%) of patients, respectively. The proposed label contains recommendations for the supportive care of nausea and vomiting including 5-HT3 antagonist and/or other anti-nausea medications prior to and during treatment with selinexor and IV fluids and electrolyte replacement in patients at risk of dehydration. The proposed label also contains recommendations for supportive care of diarrhea including antidiarrheal medications and IV fluids in patients at risk of dehydration.

Treatment emergent adverse events of anorexia and weight loss occurred in 53% and 47% of patients who received selinexor and dexamethasone, respectively. In addition, Grade 3 anorexia and weight loss were reported in 5% and 1% of patients, respectively. The proposed label contains recommendation for the management of anorexia and weight loss including appetite stimulants and nutritional support.

5.4 **Hyponatremia**

A TEAE of hyponatremia occurred in 78/202 (38.6%) of patients, with Grade 3 or greater hyponatremia reported in 44/202 (21.8%) of patients who received selinexor and dexamethasone. The proposed label contains recommendations for the management of hyponatremia including adequate sodium intake, IV saline, and/or salt tablets.

5.5 **Infections**

Infections including upper respiratory tract infections, pneumonia, and sepsis have been reported in patients receiving selinexor and dexamethasone. Treatment emergent adverse events of upper respiratory tract infections and pneumonia occurred in 42/202 (21%) and 26/202 (13%) of patients,
respectively. Grade 3 or greater upper respiratory tract infections and pneumonia were reported in 6/202 (3%) and 18/202 (9%) of patients, respectively. A TEAE of sepsis occurred in 13/202 (6.4%) of patients, with Grade 3 or greater sepsis reported in 6% of patients, respectively.

5.6 NEUROLOGICAL TOXICITY

Neurological toxicity including dizziness, syncope, depressed level of consciousness, and mental status changes have been reported in patients who received selinexor and dexamethasone. Neurological toxicity occurred in 30% of patients, with Grade 3 and 4 toxicity reported in 9% of patients. The proposed label contains recommendations for the management of neurological toxicity including optimizing hydration status and hemoglobin level and avoiding concomitant medications that may cause dizziness or mental status changes.

5.7 EMBRYO-FETAL TOXICITY

Selinexor may cause fetal harm based on animal studies and the mechanism of action of the drug. No clinical data is available with selinexor in pregnancy in humans. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting selinexor and that effective contraception be used during treatment and for at least one week after the last dose. In addition, in males with a female partner of reproductive potential it is recommended that effective contraception be used during treatment and for at least one week after the last dose.

6 Expected Postmarket Use

If approved, selinexor will primarily be used in both inpatient and outpatient settings. The likely prescribers will be hematologists and oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for selinexor beyond routine pharmacovigilance and labeling but proposed a monitoring and education plan for adverse events.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of selinexor on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on response rate. Selinexor is a first in class XPO1 inhibitor and may be an additional treatment option for patients with penta-refractory multiple myeloma. The efficacy of selinexor in RRMM was supported by the STORM trial in a subgroup of patients that were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.

The serious risk associated with selinexor which include thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, neurological toxicity, and embryo-fetal toxicity will be addressed in the warnings and precautions section of the label. However, selinexor and dexamethasone is associated with significant toxicity. In the STORM study, 100% of patients experienced a TEAE. In
STORM Part 2, dose modifications due to a TEAE occurred in 88.6% of patients and the median duration of treatment with doses of selinexor 80 mg twice weekly with dexamethasone 20 mg twice weekly was 3.5 weeks. Furthermore, careful monitoring and management of hyponatremia is necessary as Grade 3 or greater hyponatremia was reported in 21.8% of patients.

Multiple myeloma is a neoplasm due to malignant plasma cells. The estimated number of new cases of multiple myeloma in the United States in 2018 was 30,770. Multiple myeloma is currently not curable and most patients relapse after treatment. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with selinexor. Based on the efficacy and risk associated with selinexor for treatment of adult patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody, 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 selinexor 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 selinexor as currently edited by FDA, Accessed 6/19/2019.


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/s/

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