APPLICATION NUMBER:

213756Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<tr>
<td>PDUFA Goal Date</td>
<td>April 22, 2020</td>
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<td>OSE RCM #</td>
<td>2019-1636 and 1638</td>
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<tr>
<td>Reviewer Name</td>
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<td>Review Completion Date</td>
<td>February 25, 2020</td>
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<tr>
<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td>Established Name</td>
<td>Selumetinib</td>
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<td>Trade Name</td>
<td>Koselugo</td>
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<tr>
<td>Name of Applicant</td>
<td>AstraZeneca Pharmaceuticals LP</td>
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<tr>
<td>Therapeutic Class</td>
<td>A kinase inhibitor</td>
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<td>Formulation(s)</td>
<td>10 mg and 25 mg capsules</td>
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<td>Dosing Regimen</td>
<td>25 mg/m² taken orally twice daily, every 12 hours.</td>
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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 Koselugo (selumetinib) is necessary to ensure the benefits outweigh its risks. AstraZeneca Pharmaceuticals LP (AstraZeneca) submitted a New Drug Application (NDA) 213756 for selumetinib with the proposed indication for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN). The serious risks associated with selumetinib include left ventricular dysfunction, ocular toxicity, gastrointestinal toxicity, skin toxicity and increased creatinine phosphokinase. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Oncology 2 (DO2) have determined that a REMS is not needed to ensure the benefits of selumetinib outweigh its risks. At this time, there are no products approved for the treatment of NF1 with symptomatic, inoperable PN. The primary treatment option for NF1 with PN is surgical debulking. Complete surgical resection is often not feasible, and even when it is, the tumors often recur. There remains a clear medical need to develop an effective and safe therapy to treat NF1 with PN. In the clinical trial, selumitinib demonstrated 44% of partial response with duration of response of ≥12 month in 59% of these responders. The trial also provided evidence of improvement in clinical outcomes. If selumetinib is approved, the risks of left ventricular dysfunction, and the risks of ocular, gastrointestinal and skin toxicity as well as the risk for increased creatinine phosphokinase will be communicated in labeling in Section 5 Warnings and Precautions, recommendations on the management of these risks in Section 2 Dosage and Administration.

1 Introduction
This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Koselugo (selumetinib) is necessary to ensure the benefits outweigh its risks. AstraZeneca submitted a New Drug Application (NDA) 213756 for selumetinib with the proposed indication for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN). This application is under review in the Division of Oncology 2 (DO2). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION
Selumetinib, a new molecular entity (NME), a kinase inhibitor, proposed for the treatment of pediatric patients 2 years of age and older with NF1 and symptomatic, inoperable PN. Selumetinib is a mitogen-activated protein kinase 1 and 2 (MEK 1/2) inhibitor. MEK 1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Both MEK and ERK are critical components of the Reticular Activating System (RAS)-regulated RAF-MEK-ERK pathway, which is often activated in different

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

Reference ID: 4566010
types of cancers. Selumetinib is available as 10 mg and 25 mg capsules. The recommended dose is 25 mg/m² taken orally twice daily, every 12 hours until disease progression or unacceptable toxicity occurs. Selumetinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 213756 relevant to this review:

- 02/14/2018: Orphan designation for the treatment of NF1 granted.
- 03/29/2019: Breakthrough therapy designation for the treatment of NF1 granted.
- 07/03/2019: Rolling review granted.
- 09/13/2019: Last portion of rolling review received.
- 01/27/2020: 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 selumetinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Neurofibromatosis (NF) is a rare genetic disorder of the nervous system which causes tumors to form on the nerves anywhere in the body at any time. This progressive disease affects all races, all ethnic groups and both sexes equally. NF is one of the most common genetic disorders in the United States (US). There are three genetically distinct forms: NF1, NF2, and Schwannomatosis. NF1 affects about 1 in 2600 - 3000 individuals.¹ It is estimated that more than 80,000 cases in the United States (US).² NF1 is the most common type among these.³ The condition is usually recognized in early childhood. About one-half of the cases are familial. The remainder are the result of sporadic mutations. NF1 is a multisystem disorder that involves non-malignant features and cancer predisposition features. Non-malignant features include pigmentary, skeletal, cardiac, neurocognitive, cutaneous neurofibromas, and plexiform neurofibromas. Cancer predisposition features include optic glioma, malignant peripheral nerve sheath tumors (MPNSTs), Gastrointestinal stromal tumors (GISTs), pheochromocytomas, breast cancer, leukemia, and brain tumors.² Although NF1 is highly variable in its expression, most affected children follow patterns of growth and development within the normal range. The typical order of clinical manifestations is skin pigmentation (so-called café-au-lait macules), axillary and/or inguinal freckling, Lisch nodules, and neurofibromas.¹ Some features of NF1 can be present at birth, but most expressions emerge with age.

Patients with NF1 develop both benign and malignant tumors. In 20-50% of these patients, tumors develop on the nerve sheaths called plexiform neurofibromas (PNs). PNs are locally invasive tumors that

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¹ Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
may be located deep inside the body or may have both superficial and deep components. Deeper PNs can grow into a complex mass consisting of a network of enlarged nerves. PNs can cause debilitating complications, including pain, disfigurement, and functional limitations. It is a major cause of morbidity and mortality. PNs may compress the vital structures (e.g., airway), or spinal cord and may transform into malignant peripheral nerve sheath tumors (MPNSTs).

People with NF1 may experience many other complications, such as learning difficulties, visual impairment, twisting and curvature of the spine, high blood pressure, and epilepsy. NF1 also increases a person’s risk of developing other cancers, including malignant brain tumors, MPNSTs, and leukemia. Symptoms begin during early childhood, with varying degrees of severity, and can reduce life expectancy by up to 15 years.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There is no one overall treatment for NF1, nor are there any agents specifically approved for patients with NF1 at the current time. The goals of longitudinal care for patients with NF1 are early detection and symptomatic treatment of complications as they occur. The Genetics Committee of the American Academy of Pediatrics have published diagnostic and health supervision guidelines for children with NF1. Regular annual visits with pediatricians, and pediatric medical subspecialists should include physical examination, a formal ophthalmologic examination, assessment for precocious puberty, developmental assessment, review of school progress, and monitoring of PNs.

The primary treatment option for NF1 associated PN is surgical debulking. Complete surgical resection of PNs is rarely possible, often is limited to debulking of a specific area of a large lesion. And tumors may grow again after surgical resection. There is no systemic treatment for NF1 associated PN.

4 Benefit Assessment

An open-label, multicenter, single arm trial, SPRINT phase II Stratum 1 (NCT 01362803) evaluated the efficacy of selumetinib. Eligible patients were required to have NF1 with inoperable PN, defined as a PN that could not be completely removed without risk for substantial morbidity due to encasement of, or close to vital structures, invasiveness, or high vascularity of the PN. Another requirement was patient had significant morbidity related to the target PN. Morbidities that were observed in >20% of patients included disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction. Patients received selumetinib 25 mg/m² orally twice daily until disease progression or unacceptable toxicity.

Objective Response Rate (ORR) was used to measure the major efficacy outcome. ORR was defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as ≥20% reduction in PN volume confirmed at a subsequent tumor assessment within 3-6 months) based on National Cancer Institute (NCI) central review. The target PN

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
defined as the PN that caused relevant symptoms or complications (PN-related morbidities), was
evaluated for response rate using centrally read volumetric magnetic resonance imaging (MRI) analysis
per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. Tumor response
was evaluated at baseline, every 4 cycles for 2 years, and then every 6 cycles. Duration of Response
(DoR) was an additional efficacy outcome measure.5

Fifty pediatric patients received selumetinib. The median age was 10.2 years (range 3.5-17.4 years), 60%
were male, 84% were white, 8% were black, and 2% were Asian. Efficacy resultsd is shown in Table 1,
which demonstrated ORR was 44%. The median time to onset of response was 11 months.5

Table 1  Efficacy Results from SPRINT Phase II Stratum 1 by Independent Central Review

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
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<tr>
<td>Overall Response Rate, n (%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(30, 59)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>0</td>
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<tr>
<td>Confirmed Partial Response, n (%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Duration of Response ≥ 12 months, n (%)</td>
<td>13 (59%)</td>
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</table>

5 Risk Assessmente & Safe-Use Conditions

The safety of selumetinib was evaluated in SPRINT Phase II Stratum 1. This trial enrolled pediatric
patients aged 3-18 years with NF1 and inoperable PN that was causing significant morbidity. Exclusion
criteria were abnormal left ventricular ejection fraction (LVEF), uncontrolled hypertension, any current
or history of retinal vein occlusion (RVO) or central serous retinopathy (CSR), intraocular pressure > 21
mmHg, uncontrolled glaucoma, and inability to swallow whole capsules. Patients received selumetinib 25
mg/m² orally twice daily (n=50). Eighty-eight percent of patients received the drug for 12 months or
longer and 36% of patients received the drug for greater than 2 years. There was no death report in this
trial.2

The risks discussed below reflects exposure to selumetinib in 74 pediatric patients who received doses of
20 mg/m² to 30 mg/m³ orally twice daily. Among the 74 patients, 90% received the drug ≥ 12 months
and 59% for more than 2 years.

All risks listed below are currently included in the draft labeling in Warnings and Precautions5.

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d  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.

e  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.
5.1 Twenty-three percent of 74 pediatric patients received selumitinib was reported to have a decrease in LVEF \( \geq 10\% \) below baseline. LVEF below the institutional lower limit of normal (LLN) was observed in 4% of patients. One patient developed grade 3 decreased LVEF and resulted in dose reduction. All patients with a decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in \( \frac{1}{4} \)% of patients.

If selumitinib is approved, labeling will include that ejection fraction (EF) by echocardiogram should be assessed prior to initiating therapy, every 3 months in the first year, then every 6 months, and as clinically indicated.

The Dosage and Administration in the labeling will also include recommendations on when to withhold, reduce dose, or discontinue the therapy. Labeling will also include to obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks in patients who interrupt therapy for decreased LVEF and an echocardiogram or a cardiac MRI every 2-3 months or as directed by the cardiologist when decreased LVEF resolved.

5.2 OCULAR TOXICITY

\( \frac{1}{4} \)% of 74 pediatric patients was observed to have ocular toxicities, including blurred vision, photophobia, cataract, ocular hypertension, and retinal vein occlusion (RVO). Serious ocular toxicities, including retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), and ocular hypertension, resulted in dose interruption in 2.7% of patients. Blurred vision resolved in 2.7% of patients. The ophthalmic examinations of these patients did not observe retinal involvement. Ocular toxicity resolved in \( \frac{1}{4} \)% of patients. Serious ocular toxicities, including retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), and ocular hypertension, were reported in pediatric and adult patients with multiple tumor types who received selumitinib as a single agent or in combination with other anticancer agents.

If approved, labeling will state to conduct ophthalmic assessments prior to initiating selumitinib, at regular intervals, and upon any new or worsening visual disturbance. Patients who develop RVO should permanently discontinue selumitinib. Selumitinib should be withheld in patients with RPED and ophthalmic assessments should be conducted every 3 weeks until resolution. If there is resolution of the toxicities, Table 2 in Section 2 Dosage and Administration, includes recommendations for resuming treatment at a reduced dose.

5.3 GASTROINTESTINAL (GI) TOXICITY

In the clinical trial, 77% of 74 pediatric patients developed diarrhea, including grade 3 diarrhea in 15% of patients. Selumitinib was permanently discontinued in 1.4% of patients. Dose interruption or dose reduction due to diarrhea occurred in 15% and 1.4% of patients respectively. The median duration of diarrhea was 2 days and the median time to first onset was 4 days.

Serious GI toxicities, including perforation, colitis, ileus, and intestinal obstruction occurred in and adult patients with multiple tumor types who received selumitinib as a single agent or in combination with other anti-cancer agents.
Labeling states to advise patients to start an anti-diarrhea agent (e.g., loperamide) immediately after the first episode of unformed, loose stool and to increase fluid intake. Based on severity of adverse reaction, Section 2 Dosage and Administration provides recommendations on when to withhold, reduce dose, or discontinue selumitinib.

5.4 SKIN TOXICITY
In SPRINT trial, the rash incidence was 91% in 74 pediatric patients, included dermatitis acneiform (54%), eczema (28%), and maculopapular rash (18%). Eight percent of patient developed grade 3 rash and dose interruption occurred in 8% of patients due to rash. There were adult patients with multiple tumor types who received selumitinib as a single agent developed severe palmer-plantar erythrodysesthesia syndrome (PPES).

Labeling will communicate when to withhold, reduce dose, or permanently discontinue selumitinib per instructions in section 2 Dosage and Administration of the labeling.

5.5 INCREASED CREATININE PHOSPHOKINASE (CPK)
Seventy-seven percent of 74 pediatric patient developed increased CPK in SPRINT trial. Among them, 9% of patients was reported to have grade 3 or 4 increase. Seven percent of patients had their doses reduced due to increased CPK. Increased CPK concurrent with myalgia occurred in 8% of patients including one patient who discontinued selumitinib permanently for myalgia. There were adult patients with multiple tumor types who received selumitinib as a single agent developed rhabdomyolysis.

Labeling will communicate to obtain serum CPK and creatinine levels prior to initiating selumitinib, periodically during therapy, and as clinically indicated. To evaluate for signs and symptoms of rhabdomyolysis if CPK increases. Section 2 Dosage and Administration of the labeling will include recommendations on when to withhold, reduce dose, or permanently discontinue selumitinib for increased CPK.

5.6 VITAMIN E
Selumitinib 10 mg capsules contain 32 mg vitamin E as the excipient, whereas 25 mg capsules contain 36 mg vitamin E. High dose of vitamin E may increase the risk of bleeding in patients taking concomitant anticoagulant or antiplatelet medications. If patients are taking anticoagulant or antiplatelet medications, HCPs educate patients and caregivers not to take supplemental vitamin E during selumetinib therapy, as well as to perform anticoagulant assessment, including international normalized ratio (INR) or prothrombin time (PT), more frequently in order to adjust these medications accordingly.

5.7 EMBRYO-FETAL TOXICITY
Selumitinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. The draft label states to advise pregnant women of the potential risk to a fetus and to use effective contraception during therapy and for 1 week after the last dose. Males with female partners of reproductive potential should be advised to use effective contraception during therapy and for 1 week after the last dose.
6 Expected Post-market Use

If approved, it is expected that pediatricians and pediatric medical subspecialists, will be the likely health care providers to prescribe selumetinib in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of selumetinib based on the efficacy and safety information currently available. DRM and DO2 agree that a REMS is not necessary to ensure the benefits outweigh its risk.

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for selumetinib, this reviewer considered were the patient population size, seriousness of the disease, the expected benefit of the drug, the expected duration of treatment, and the seriousness of known or potential adverse reactions.

NF1 is the most common type of NF. NF1 affects about 1 in 2600 - 3000 individuals. It is estimated that there are more than 80,000 cases in United States. NF1 is a multisystem disorder that involves non-malignant features and cancer predisposition features. In 20-50% of these patients, tumors develop on the nerve sheaths called plexiform neurofibromas (PNs). PNs can cause debilitating complications, including pain, disfigurement, and functional limitations. PNs may compress the vital structures (e.g., airway), or spinal cord and may transform into malignant peripheral nerve sheath tumors (MPNSTs). Symptoms begin during early childhood, with varying degrees of severity, and can reduce life expectancy by up to 15 years.

There is no systemic treatment available for NF1 associated PN. The primary treatment option for NF1 associated PN is surgical debulking, which is often challenging. Complete surgical resection is often not feasible, and even when it is, the tumors often recur. There remains a clear medical need to develop a new therapies to treat NF1 with PN.

In the clinical trial, selumetinib demonstrated 44% of partial response with duration of response of ≥12 month in 59% of these responders. The trial also provided evidence of improvement in clinical outcomes, such as pain relief, motor/airway function improvement, and disfigurement decrease. The administration of selumetinib is a chronic and continuous therapy, the labeling will be used to communicate the risks associated with selumetinib.

Selumetinib is a MEK inhibitor, which has MEK inhibitor class effects, such as ventricular dysfunction, ocular toxicity, GI toxicity, and skin toxicity. Trametinib is a MEK inhibitor, which was approved by FDA 2013 to treat melanoma. Trametinib has the similar ventricular and ocular toxicities that was
communicated through labeling in Warnings and Precautions\textsuperscript{8}. If approved, the labeling will communicate risks, ventricular dysfunction, ocular toxicity, GI toxicity, skin toxicity, increased CPK, Vitamin E toxicity, and embryo-fetal toxicity in Section 5 Warnings and Precautions and instructions how to withhold, reduce dose, and discontinue in Section 2 Dosage and Administration. Patients with NF1 and PN are typically treated by a clinical team that include geneticists, neurologists, oncologists and surgeons. The likely prescribers for selumitinib will likely be from these medical specialties.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for selumetinib 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


2 Casey, D. Safety review for NDA 213756 selumetinib for the treatment of pediatric patients with NF1 and symptomatic, inoperable plexiform neurofibromas (PN). Midcycle presentation 01/06/2020.


4 Miller, DT Freedenberg, DL et al. Health Supervision for Children with neurofibromatosis type 1, www.pediatrics.aappublicaitons.org/content/pediatrics/143/5/e20190660.full.pdf Accessed 01/03/2020

5 Selumitinib draft prescribing information, 02/05/2020


7 Lugowska, I Kosela-Paterczyk, H et al. Trametinib: a MEK inhibitor for management of metastatic melanoma Onco Targets Ther. 2015; 8:2242-2259

8 Trametinib (Mekinist) prescribing information, Drugs@FDA, accessed 02/02/2020
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/

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