RXADVANCE
2 Park Central Drive
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NEW DRUG APPROVAL

Brand Name	Koselugo™
Generic Name	selumetinib
Drug Manufacturer	AstraZeneca Pharmaceuticals LP

New Drug Approval

FDA Approval Date: April 10, 2020
Review Designation: New Chemical Entity; Orphan Drug
Type of Review: New Drug Application 213756

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

There are three clinically and genetically distinct forms of neurofibromatosis: neurofibromatosis types 1 and 2 (NF1 and NF2) and schwannomatosis. NF1, previously known as von Recklinghausen disease, is the most common type. The hallmarks of NF1 are multiple café-au-lait macules and neurofibromas. The condition is called segmental NF1 when clinical features are limited to one area of the body due to somatic mosaicism of a pathogenic variant in the NF1 gene.

NF1 is an autosomal-dominant genetic disorder with an incidence of approximately 1:2600 to 3000 individuals. Approximately one-half of the cases are familial (inherited). The de novo mutations occur primarily in paternally derived chromosomes. The incidence of segmental NF1 is unknown, but the prevalence is estimated at 1:36,000 to 1:40,000. A study of death certificates in the United States revealed a mean age at death for persons with NF1 at 54.4 years and median at 59 years, well below population norms (70.1 and 74 years, respectively). Malignant tumors and vascular disease were significantly overrepresented among those with NF1 who had died at an age <40 years. A population-based study in Finland revealed an overall prevalence of NF1 of approximately 1:4000, but the prevalence decreased with age, with a hazard ratio of death among NF1 individuals of 3.10.

Efficacy

The FDA approved Koselugo based on a clinical trial conducted by the National Cancer Institute of pediatric patients who had NF1 and inoperable PN (defined as a PN that could not be completely removed without risk for substantial morbidity to the patient). The efficacy results were from 50 of the patients who received the recommended dose and had routine evaluations of changes in tumor size and tumor-related morbidities during the trial. Patients received Koselugo 25 mg/m2 orally twice a day until disease progression or until they experienced unacceptable adverse reactions. The clinical trial measured the overall response rate (ORR), defined as the percentage of patients with a complete response and those who experienced more than a 20% reduction in PN volume on MRI that was confirmed on a subsequent MRI within 3-6 months. The ORR was 66% and all patients had a partial response, meaning that no patients had complete disappearance of the tumor. Of these patients, 82% had a response lasting 12 months or longer.

Other clinical outcomes for patients during Koselugo treatment including changes in PN-related disfigurement, symptoms and functional impairments. Although the sample sizes of patients assessed for each PN-related morbidity (such as disfigurement, pain, strength and mobility problems, airway compression, visual impairment and bladder or

bowel dysfunction) were small, there appeared to be a trend of improvement in PN-related symptoms or functional deficits during treatment.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 40%) are: vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

WARNINGS & PRECAUTIONS

- Cardiomyopathy: Assess ejection fraction prior to initiating treatment, every 3 months during the first year, then every 6 months thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction.
- Ocular Toxicity: Conduct ophthalmic assessments prior to initiating KOSELUGO, at regular intervals during treatment and for new or worsening visual changes. Permanently discontinue KOSELUGO for retinal vein occlusion (RVO). Withhold KOSELUGO for retinal pigment epithelial detachment (RPED), monitor with optical coherence tomography assessments until resolution, and resume at reduced dose.
- Gastrointestinal Toxicity: Advise patients to start an anti-diarrheal agent immediately after the first episode of loose stool and to increase fluid intake. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction.
- Skin Toxicity: Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction.
- Increased Creatinine Phosphokinase (CPK): Increased CPK and rhabdomyolysis can occur. Obtain serum CPK prior to initiating KOSELUGO, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction.
- Increased Vitamin E Levels and Risk of Bleeding: KOSELUGO capsules contain vitamin E and daily intake of vitamin E that exceeds the recommended or safe limits may increase the risk of bleeding. An increased risk of bleeding may occur in patients coadministered vitaminK antagonists or anti-platelet agents.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Selumetinib is an inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Both MEK and ERK are critical components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. In genetically modified mouse models of NF1 that generate neurofibromas that recapitulate the genotype and phenotype of human NF1, oral dosing of selumetinib inhibited ERK phosphorylation, and reduced neurofibroma numbers, volume, and proliferation.

Dose & Administration

ADULTS

Not Applicable

NEW DRUG APPROVAL

PEDIATRICS

The recommended dosage is 25 mg/m2 taken orally twice daily on an empty stomach. Do not consume food 2 hours before each dose or 1 hour after each dose.

The safety and effectiveness have been established in pediatric patients 2 years of age and older with NF1 who have inoperable PN and the information on this use is discussed throughout the labeling. The safety and effectiveness of KOSELUGO have not been established in pediatric patients younger than 2 years of age

GERIATRICS

Clinical studies did not include patients 65 years of age and older

RENAL IMPAIRMENT

No dose adjustment is recommended in patients with renal impairment or those with End Stage Renal

Disease

HEPATIC IMPAIRMENT

Reduce the recommended dosage to 20 mg/m2 orally twice daily for patients with moderate hepatic impairment (Child-Pugh B). The recommended dosage for use in patients with severe hepatic impairment (Child-Pugh C) has not been established

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 10 mg and 25 mg