PDL DRUG REVIEW

Proprietary Name: Koselugo®
Common Name: selumetinib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Selumetinib, the active ingredient of Koselugo®, is a kinase inhibitor. It is an inhibitor of mitogen-activated protein kinases 1 and 2 (MEK1/2), which 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 pathways, which is often activated in different types of cancers.

Indication: For the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Koselugo® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to assess a drug-associated risk. Advise pregnant women of the potential risk to the fetus. In addition, verify the pregnancy status of females of reproductive potential prior to starting Koselugo®, and advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during Koselugo® treatment and for 1 week after the last dose. The safety and efficacy of use in the pediatric population younger than 2 years of age have not been established.

Dosage Form: Capsules: 10mg, 25mg. Swallow capsules whole with water; do not chew, dissolve or open capsules. Do not administer to patients who are unable to swallow a whole capsule.

Recommended Dosage: Take 25mg/m^2 PO BID until disease progression or unacceptable toxicity. Take on an empty stomach; do not consume food 2 hours before each dose or 1 hour after each dose. If vomiting occurs after administration, do not take an additional dose, but continue with the next scheduled dose.

Dose modifications may be required for adverse reactions, such as cardiomyopathy, ocular toxicity, gastrointestinal toxicity, skin toxicity, increased creatinine phosphokinase (CPK), or other adverse reactions. Refer to the prescribing information for additional information.

Dose adjustments are not required with renal impairment or with mild hepatic impairment. With moderate hepatic impairment, reduce the recommended dosage to 20mg/m^2 PO BID. The recommended dosage for use in patients with severe hepatic impairment has not been established.

Drug Interactions: Avoid the coadministration of strong or moderate CYP3A4 inhibitors or fluconazole with Koselugo®. If coadministration with strong or moderate CYP3A4 inhibitors or fluconazole cannot be avoided, reduce the Koselugo® dosage. Refer to the prescribing information for dosage information with this combination.

Avoid the concomitant use of strong or moderate CYP3A4 inducers with Koselugo®.

Koselugo® contains vitamin E and daily vitamin E intake that exceeds the recommended or safe limits may increase the risk of bleeding. An increased risk of bleeding may occur in patients taking a vitamin K antagonist or an anti-platelet agent with Koselugo®. Thus, supplemental vitamin E is not recommended if daily vitamin E intake (including the amount of vitamin E in Koselugo® and supplement) will exceed the recommended or safe limits. In addition, monitor for bleeding in patients co-administered a vitamin K antagonist or an anti-platelet agent with Koselugo®. Increase INR monitoring, as appropriate, in patients taking a vitamin K antagonist.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Koselugo®) for all grades. Please note that there is no placebo data in the prescribing information to compare with Koselugo®.* The most frequently reported adverse events included vomiting (82%), abdominal pain (76%), diarrhea (70%), nausea (66%), stomatitis (50%), constipation (34%), rash (all; 80%), dry skin (60%), rash acneiform (50%), paronychia (48%), pruritus (46%), dermatitis (36%), hair changes (32%), musculoskeletal pain (58%), fatigue (56%), pyrexia (56%), edema (20%), headache (48%), epistaxis (28%), hematuria (22%), proteinuria (22%), decreased appetite (22%), decreased ejection fraction (22%), sinus tachycardia (20%), and skin infection (20%).

Laboratory abnormalities included increased creatine phosphokinase (79%), decreased albumin (51%), increased aspartate aminotransferase (AST, 41%), increased alanine aminotransferase (ALT, 35%), increased lipase (32%), increased potassium (27%), decreased potassium (18%), increased alkaline phosphatase (18%), increased amylase (18%), increased sodium (18%), decreased sodium (16%), decreased hemoglobin (41%), decreased neutrophils (33%), and decreased lymphocytes (20%).

Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline, occurred in 23% of 74 pediatric patients treated with Koselugo® in a clinical study. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in 71% of these patients. Left ventricular dysfunction or decreased LVEF resulting in permanent discontinuation of Koselugo® occurred in an unapproved population of adult patients with multiple tumor types who received Koselugo®. The safety of Koselugo® has not been established in patients with a history of impaired LVEF or a baseline ejection fraction that is below the institutional lower limit of normal (LLN). Assess ejection fraction by echocardiogram prior to starting treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue Koselugo® based on severity of adverse reaction.

Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving Koselugo® in a clinical study. Ocular toxicity resolved in 82% of 11 patients. Serious ocular toxicities including retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED) occurred in an unapproved population of adult patients with multiple tumor types who received Koselugo® as a single agent or in combination with other anti-cancer agents. Conduct comprehensive ophthalmic assessments prior to starting Koselugo®, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue Koselugo® in patients with RVO. Withhold Koselugo® in patients with RPED, follow-up with optical coherence tomography assessments every 3 weeks until resolution, and resume Koselugo® at a reduced dose. For other ocular toxicities, withhold, reduce dosage, or permanently discontinue Koselugo® based on severity of the adverse reaction.

Diarrhea occurred in 77% of 74 pediatric patients who received Koselugo® in a clinical trial, including Grade 3 in 15% of patients. The median time to first onset of diarrhea was 17 days and the median duration was 2 days. Serious GI toxicities, including perforation, colitis, ileus, and intestinal obstruction, occurred in an unapproved population of adult patients with multiple tumor types who received Koselugo® as a single agent or in combination with other anti-cancer agents. Advise patients to start an anti-diarrheal agent (e.g. loperamide) immediately after the first episode of unformed, loose stool and to increase fluid intake during diarrhea episodes. Withhold, reduce dose, or permanently discontinue Koselugo® based on severity of adverse reaction.

Rash occurred in 91% of 74 pediatric patients who received Koselugo® in a clinical study. Rash resulted in dose interruption in 11% of patients and dose reduction in 4% of patients. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo® based on severity of adverse reaction.

Increased creatine phosphokinase (CPK) occurred in 76% of 74 pediatric patients who received Koselugo® in a clinical study. Increased CPK resulted in dose reduction in 7% of patients. Increased CPK concurrent with myalgia occurred in 8% of patients, including one patient who permanently discontinued Koselugo® for myalgia. Obtain serum CPK prior to starting Koselugo®, periodically during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue Koselugo® based on severity of adverse reaction.

Koselugo® capsules contain vitamin E (10mg capsules contain 32mg vitamin E as the excipient, D-alpha-tocopherol polyethylene glycol 1000 succinate [TPGS]; while Koselugo® 25mg capsules contain 36mg vitamin E as TPGS). Daily

vitamin E intake that exceeds the recommended or safe limits may increase the risk of bleeding. Supplemental vitamin E is not recommended if daily vitamin E intake will exceed the recommended or safe limits. An increased risk of bleeding may occur in patients who are co-administered vitamin K antagonists or anti-platelet antagonists with Koselugo®. Monitor for bleeding in these patients. Increase INR monitoring, as appropriate, in patients taking a vitamin K antagonist. Perform anticoagulant assessments, including INR or PT, more frequently and adjust the dose of vitamin K antagonists or anti-platelet agents as appropriate.

Contraindications: There are no contraindications listed with this product.

Manufacturer: AstraZeneca Pharmaceuticals

Analysis: The efficacy of Koselugo® was assessed in SPRINT phase II Stratum 1, an open label, multicenter, single arm study that included patients who 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 proximity to, vital structures, invasiveness, or high vascularity of the PN. Patients were also required to have significant morbidity related to the target PN. The median age of included pediatric patients (N=50) was 10.2 years (range 3.5 to 17.4 years), while 60% were male and 84% were white.

The major efficacy outcome measure was overall response rate (ORR), 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 conformed at a subsequent tumor assessment within 3-6 months). The target PN, defined as the PN that caused relevant clinical symptoms or complications was assessed for response rate using centrally read volumetric MRI analysis per Response Evaluation in Neurofibromatosis and Schwannomatosis criteria. Tumor response was assessed at baseline and while on treatment after every 4 cycles for 2 years, and then every 6 cycles. An additional efficacy outcome measure was duration of response. Results can be seen in the table below, which was adapted from the prescribing information. Note that the median time to onset of response was 7.2 months.

Efficacy Outcome	SPRINT (N=50)
Overall Response Rate	
Overall Response Rate, n (%)	33 (66%)
Complete Response	0
Confirmed Partial Response	33 (66%)
Duration of Response	
DOR ≥12 months, n (%)	27 (82%)

Place in Therapy: Koselugo®, an oral kinase inhibitor, is indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). It is the first agent FDA approved as treatment for this rare condition. Its efficacy was based on a single arm study that included pediatric patients (N=50) who had an overall response rate of 66%.

It is recommended that Koselugo® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Recommended**
- ☒ **Non-Recommended with Conditions**

References

[1] Koselugo [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2020.

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