Koselugo®
(selumetinib)
10 mg & 25 mg capsules

AE Management During the SPRINT Study

This content is based on recommendations from the SPRINT clinical study protocol.

INDICATION

Koselugo 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).

IMPORTANT SAFETY INFORMATION

Cardiomyopathy. A decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline occurred in 23% of 74 pediatric patients who received Koselugo in SPRINT. Four percent of patients experienced decreased LVEF below the institutional lower limit of normal (LLN). Grade 3 decreased LVEF occurred in one patient and resulted in dose reduction. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in 71% of these patients. Decreased LVEF resulting in permanent discontinuation of Koselugo occurred in a pediatric population with NF1 in an expanded access program. 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 LLN.

Assess ejection fraction by echocardiogram prior to initiating 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. In patients who interrupt Koselugo for decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks. Upon resolution of decreased LVEF, obtain an echocardiogram or a cardiac MRI every 2 to 3 months.

Please read additional Important Safety Information on pages 8 and 9 and full Prescribing Information at KoselugoHCP.com.

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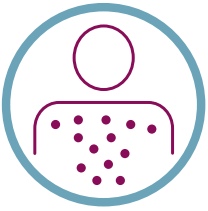
ADVERSE EVENT (AE) MANAGEMENT RECOMMENDATIONS

This resource was designed to help inform you of how specific toxicities were managed based on institutional policies and guidelines during the SPRINT study. **It does not contain information about all AEs associated with Koselugo—please refer to the full Prescribing Information for more information.**

SPRINT Phase II Stratum 1 was an open-label, multicenter, single-arm study coordinated with the National Cancer Institute to assess the efficacy and safety of Koselugo in pediatric patients (N=50) with NF1 and symptomatic, inoperable plexiform neurofibromas (PN).

TABLE OF CONTENTS

Dermatologic AEs



The use of medication for the supportive care of rash was permitted, provided that compliance with concomitant medication was observed.

- Early initiation of treatment for rashes was strongly recommended to minimize the duration and severity of the AE

NF1=neurofibromatosis type 1.

IMPORTANT SAFETY INFORMATION (Cont'd)

Ocular Toxicity. Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving Koselugo in SPRINT. Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients. Retinal pigment epithelial detachment (RPED) occurred in the pediatric population during treatment with single agent Koselugo and resulted in permanent discontinuation.

Conduct ophthalmic assessments prior to initiating Koselugo, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue Koselugo in patients with retinal vein occlusion (RVO). Withhold Koselugo in patients with RPED, conduct ophthalmic assessments every 3 weeks until resolution, and resume Koselugo at a reduced dose. For other ocular toxicities, withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

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For pediatric patients, the following suggested guidelines have been found to be useful:

Acneiform rash

The SPRINT study of Koselugo suggested that **topical clindamycin gel or lotion applied twice daily**, rather than steroids, is the most helpful for pustular rash (typically seen in the older child/adolescent).

- In severe cases, **semisynthetic oral tetracyclines** such as doxycycline or minocycline was recommended for older children and adolescents, but should be avoided in children younger than 8 years old because of risk to their tooth development

Eczematous rash/xerosis

Recommended treatment for eczematous/dry skin rash and other macular (non-acneiform) rash was to **moisturize with CeraVe® or Eucerin®**.

- A **low-potency topical steroid** was recommended if symptomatic
- **Ketoconazole shampoo** was recommended for any rash involving the scalp

Paronychia

For patients who did not undergo drainage, silver nitrate was recommended, as well as topical bactroban, steroids, and/or antifungals.

- **Silver nitrate** was only of value when there was open, inflamed skin or granulation tissue (eg, pyogenic, granuloma-like lesions)
  - If the periungual skin was swollen but intact (whether infectious or non-infectious), silver nitrate was not recommended
  - Patients were cautioned to avoid trauma to the area. Podiatry consult was considered for partial nail removal
- Patients who underwent incision and drainage and were found to have no infectious organisms on culture were recommended to be treated as above. If infection was identified, patients were recommended to be treated with **systemic antibiotics (oral tetracyclines)**
  - If paronychia recurred or developed in other fingers or toes, **flurandrenolide (eg, Cordran)** tape or topical steroid cream such as **triamcinolone** was recommended for use in the morning and **bactroban and ketoconazole (eg, Nizoral®) topical ointments** in the evening

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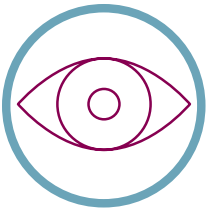

Visual AEs

All patients had a detailed ophthalmologic evaluation at baseline. In patients who developed visual symptoms, a repeat ophthalmologic evaluation was recommended to include:

- best corrected visual acuity
- intraocular pressure
- slit lamp fundoscopy (photograph if abnormal)

Physicians considered optical coherence tomography.

Retinal pigment epithelial detachment (RPED) or central serous retinopathy (CSR)

The study recommended that treatment with Koselugo be held and repeat ophthalmologic evaluations were performed until resolution. The study recommended that treatment restart after a dose reduction.

Retinal vein occlusion (RVO)

If RVO was diagnosed, the study recommended that Koselugo be discontinued permanently. If a patient experiences cornea or lens opacification, the study recommended that the patient recover to Grade ≤1 to restart treatment. If that doesn't happen within 21 days, the patient permanently discontinues treatment, unless there is a clear clinical benefit (partial response or stable disease), in which case the patient waits for up to 3 months to achieve Grade ≤1.

IMPORTANT SAFETY INFORMATION (Cont'd)

Gastrointestinal Toxicity. Diarrhea occurred in 77% of 74 pediatric patients who received Koselugo in SPRINT, including Grade 3 in 15% of patients. Diarrhea resulting in permanent discontinuation occurred in 1.4% of patients. Diarrhea resulting in dose interruption or dose reduction occurred in 15% and 1.4% of patients, respectively. The median time to first onset of diarrhea was 17 days, and the median duration was 2 days.

Advise patients to start an anti-diarrheal agent (eg, loperamide) and to increase fluid intake immediately after the first episode of diarrhea. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Skin Toxicity. Rash occurred in 91% of 74 pediatric patients who received Koselugo in SPRINT. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred in 8% of patients. 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.

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Gastrointestinal AE: Diarrhea

Patients were made aware that they may experience diarrhea and were encouraged to record the number of stools and possible associated symptoms in a patient diary. The study recommended that patients be given **loperamide** to take home and start taking it immediately after the first episode of unformed, loose stool (in accordance with local regulations and practice). The study recommended that **additional agents** be used concurrently if loperamide was not adequate to control diarrhea as a single agent.

- The following additional **dietary advice** was recommended:
  - **BRAT diet** (bananas, rice, apple sauce, toast)
  - **Readily digestible food**
  - **Avoidance of lactose-containing products** and fried, fatty, or spicy foods
  - **Increased fluid intake** (8 to 10 glasses of clear fluids/day, including water, clear broth, and fluids containing salt and sugar)

Patients were encouraged to seek advice early from their physician or study nurse if they had persistent diarrhea, diarrhea complicated by vomiting, or inability to take oral liquids.

IMPORTANT SAFETY INFORMATION (Cont'd)

Increased Creatine Phosphokinase (CPK). Increased CPK occurred in 76% of 74 pediatric patients who received Koselugo in SPRINT, including Grade 3 or 4 in 9% of patients. 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 initiating Koselugo, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

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Gastrointestinal AE: Oral mucositis

The study recommended that patients follow a daily oral healthcare regimen, both before and during treatment with Koselugo.

- Patients with a **healthy mouth were recommended to use non-alcoholic mouthwash** 4 to 6 times daily (eg, after each meal), or according to the instructions
- **The use of mouthwash immediately following Koselugo administration was recommended. During the study, saline mouthwashes (sodium chloride 0.9%) were recommended in cases of stomatitis** and were to be used at a different time than toothbrushing (eg, after tea)
- The study recommended that the **tongue be gently brushed** (if not sore) with a soft toothbrush

Patients with, or at risk of, stomatitis were not recommended to use commercial/over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes were not recommended for the treatment of established stomatitis.

The study recommended the mouth be regularly inspected by the patient and healthcare professionals.

- The study recommended that teeth be **brushed twice daily with a fluoride toothpaste and soft toothbrush**, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating
- The toothbrush was recommended to be replaced regularly (at least every 3 months). Patients with stomatitis were recommended to change their toothbrush every 4 to 6 weeks. The study recommended a culture to rule out herpes simplex

IMPORTANT SAFETY INFORMATION (Cont'd)

Increased Levels of Vitamin E and Risk of Bleeding. Koselugo capsules contain vitamin E (10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate [TPGS], while Koselugo 25 mg capsules contain 36 mg vitamin E as TPGS). Vitamin E can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. 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 (including the amount of vitamin E in Koselugo and supplement) will exceed the recommended or safe limits.

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The study recommended that physicians consider:

1. Treating stomatitis at an early stage, such as Common Terminology Criteria for Adverse Events (CTCAE) Grade 1, or as soon as the patient complained of a sore mouth.
2. Using an oral topical analgesic, with or without topical steroids, depending on the patient's clinical condition and the local standard medical practice.

Pulmonary AE: Dyspnea

For patients in the study who developed dyspnea while receiving Koselugo, clinical evaluations were recommended to rule out infectious etiology and pneumonitis.

- If patient develops Grade ≥2 pneumonitis, the study recommended the patient undergo evaluation per protocol

Treatment procedures unrelated to plexiform neurofibromas (PN)

- The study recommended that patients having major surgery unrelated to PN hold Koselugo 1 week prior to surgery and until wound healed completely

IMPORTANT SAFETY INFORMATION (Cont'd)

Increased Levels of Vitamin E and Risk of Bleeding (Cont'd). An increased risk of bleeding may occur in patients who are coadministered vitamin-K antagonists or anti-platelet antagonists with Koselugo. Monitor for bleeding in these patients and increase international normalized ratio (INR) monitoring in patients taking a vitamin-K antagonist. Perform anticoagulant assessments more frequently and adjust the dose of vitamin K antagonists or anti-platelet agents as appropriate.

Embryo-Fetal Toxicity. Based on findings from animal studies, Koselugo can cause fetal harm when administered to a pregnant woman. In animal studies, administration of selumetinib to mice during organogenesis caused reduced fetal weight, adverse structural defects, and effects on embryo-fetal survival at approximate exposures >5 times the human exposure at the clinical dose of 25 mg/m^2 twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Koselugo and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Koselugo and for 1 week after the last dose.

Breastfeeding. Due to the potential for adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Koselugo and for 1 week after the last dose.

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Breastfeeding. Due to the potential for adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Koselugo and for 1 week after the last dose.

Concomitant use of Koselugo with a strong or moderate CYP3A4 inhibitor or fluconazole increased selumetinib plasma concentrations, which may increase the risk of adverse reactions. Avoid 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 Koselugo dosage.

Concomitant use of Koselugo with a strong or moderate CYP3A4 inducer decreased selumetinib plasma concentrations, which may reduce Koselugo efficacy. Avoid concomitant use of strong or moderate CYP3A4 inducers with Koselugo.

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

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HELPING YOUR PATIENTS AND CAREGIVERS ACCESS THE CARE THEY NEED

ONESOURCE® Personalized Patient Support from Alexion

OneSource™ is a free, personalized patient support program offered by Alexion. Whether your patient is newly diagnosed or has had their condition for some time, our specialists are available for patients and their caregivers. We can help them make sense of their health insurance coverage, answer questions about treatment with Koselugo, and connect them to community resources.

We're committed to helping your patients start and stay on track with their prescribed treatment.

Advise your patients or their caregivers to call 1-888-765-4747 or visit www.AlexionOneSource.com to learn more or to contact their dedicated Patient Access Navigator

OneSource™ Support Services

A dedicated Patient Access Navigator is here to guide and give your patients the support they deserve—whatever their care plan may be. They can:

- Answer questions about neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN), Koselugo, your patient's insurance coverage, and more
- Provide support during treatment
- Help avoid interruptions in your patient's treatment during insurance changes, travel plans, or other life events
- Help patients and caregivers to get involved with the rare disease community through events and meetings

Health insurance can be complicated. We're here to help make sense of it all.

OneSource can help by:

- Providing information that explains your patient's insurance coverage for Koselugo
- Addressing financial concerns or gaps in coverage

To learn more or to contact a dedicated Patient Access Navigator, patients and caregivers can call 1-888-765-4747, Monday through Friday, 8:30 AM–8 PM ET, or visit www.AlexionOneSource.com.

References: 1. Data on File, REF-75728, AstraZeneca Pharmaceuticals LP. **2.** Koselugo. Package insert. AstraZeneca Pharmaceuticals LP; 2021. **3.** Data on File, REF-75729, AstraZeneca Pharmaceuticals LP.

For more information, visit KoselugoHCP.com.

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ALEXION® AstraZeneca Rare Disease