



Koselugo[®]

(selumetinib)

10 mg & 25 mg capsules

KOSELUGO[®] (selumetinib)

DOSING INFORMATION & AE MANAGEMENT GUIDE

KOSELUGO[®] (selumetinib)—The **FIRST** and **ONLY FDA-approved therapy** for pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)^{1,2}

All families featured in this brochure have been compensated by Alexion.
The AE information included in this piece is based on recommendations from the SPRINT clinical study protocol.
AE=adverse event; FDA=Food and Drug Administration.

INDICATION

KOSELUGO[®] (selumetinib) 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).

SELECT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS associated with Koselugo (selumetinib) include Cardiomyopathy, Ocular Toxicity, Gastrointestinal Toxicity, Skin Toxicity, Increased Creatine Phosphokinase, Increased Levels of Vitamin E and Risk of Bleeding, and Embryo-Fetal Toxicity.

ADVERSE REACTIONS (≥40%) include vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

DRUG INTERACTIONS include strong/moderate CYP3A4 Inhibitors or Fluconazole and CYP3A4 Inducers.

Please see full Important Safety Information throughout and on page 15 and scan the QR code, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.



You play a critical role in your patients' dosing and AE management

This resource provides Koselugo dosing information and presents how specific AEs were managed in the SPRINT study, based on institutional policies and guidelines.*

SPRINT: a landmark study in the treatment of NF1 PN^{1,3}

SPRINT Phase 2 Stratum 1 was an open-label, multicenter, single-arm study coordinated with the NCI. This study of 50 pediatric patients with NF1-related inoperable PN that caused significant morbidity was designed to assess the efficacy and safety of KOSELUGO® (selumetinib) in reducing the volume of NF1 PN. Patients with a median age of 10.2 years (range: 3.5-17.4 years) received Koselugo 25 mg/m² (BSA) twice daily.^{1,3}

*Does not contain information about all AEs associated with Koselugo—please refer to the full Prescribing Information for more information.

AE=adverse event; BSA=body surface area; NCI=National Cancer Institute; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cardiomyopathy. A decrease in left ventricular ejection fraction (LVEF) $\geq 10\%$ below baseline occurred in pediatric patients who received Koselugo in SPRINT with some experiencing decreased LVEF below the institutional lower limit of normal (LLN), including one patient with Grade 3. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography.

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Kassidy, age 11, living with NF1 PN.

Please see full Important Safety Information on page 15 and scan the QR code on front cover, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.

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(selumetinib)
10 mg & 25 mg capsules

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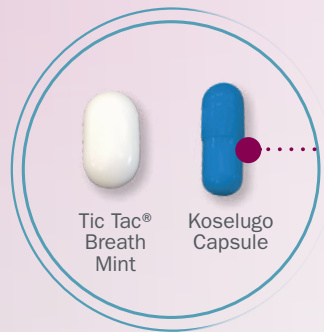
NO FASTING REQUIREMENT

Koselugo allows you to prescribe with the confidence of easy-to-maintain, continuous dosing¹

Recommended dosage 25 mg/m² | twice daily

Dosing is individualized based on BSA (mg/m²) and is rounded to the nearest achievable 5-mg or 10-mg dose (up to a maximum single dose of 50 mg).

Koselugo is available in 25- and 10-mg capsules and 28- and 60-count bottles



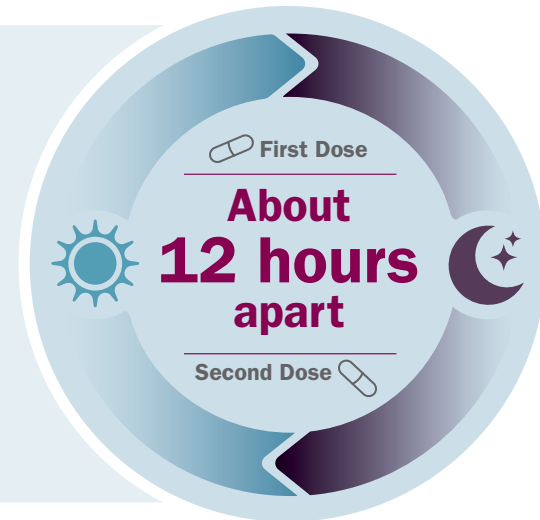
Each Koselugo capsule is about the size of a Tic Tac[®] breath mint.

Shown to scale.
Tic Tac[®] and the three-dimensional design are registered trademarks of Ferrero S.A.

Recommended administration of Koselugo:

- **Before prescribing**, children should be assessed for the ability to swallow capsules
- **Orally twice daily** (approximately every 12 hours) until disease progression or unacceptable toxicity
- **Swallowed whole with water:** Do not chew, dissolve, or open capsule

No fasting requirement



Advise patients:

Do not take a missed dose unless it is more than 6 hours until the next scheduled dose

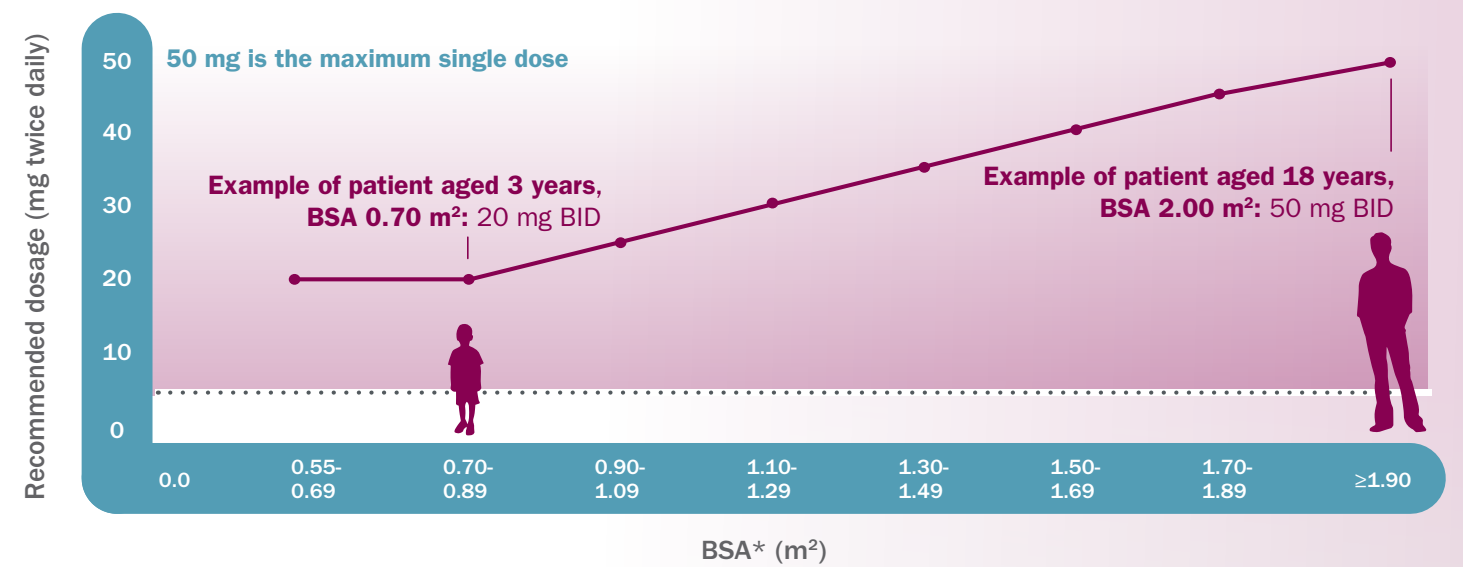
If vomiting occurs, do not take an additional dose but continue with the next scheduled dose

BSA=body surface area.

IMPORTANT SAFETY INFORMATION (CONT'D)

Cardiomyopathy (Cont'd). 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.

Koselugo dosing is based on BSA¹



Recommended dosage and dose reductions for adverse reactions

BSA	Initial Koselugo dose* (mg/twice daily)		First dose reduction (mg/dose)		Second dose reduction [†] (mg/dose)	
	Morning	Evening	Morning	Evening	Morning	Evening
0.55-0.69 m ²	20	10	10	10	10 mg once daily	
0.70-0.89 m ²	20	20	20	10	10	10
0.90-1.09 m ²	25	25	25	10	10	10
1.10-1.29 m ²	30	30	25	20	20	10
1.30-1.49 m ²	35	35	25	25	25	10
1.50-1.69 m ²	40	40	30	30	25	20
1.70-1.89 m ²	45	45	35	30	25	20
≥1.90 m ²	50	50	35	35	25	25

*The recommended dosage for patients with a BSA less than 0.55 m² has not been established.
[†]Permanently discontinue Koselugo in patients unable to tolerate Koselugo after 2 dose reductions.

BID=twice daily; BSA=body surface area.

Please see full Important Safety Information on page 15 and scan the QR code on front cover, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.



Dosage reductions and modifications¹

Recommended dosage of Koselugo for moderate hepatic impairment

Moderate Hepatic Impairment (Child-Pugh B) (mg/dose)

BSA	Moderate Hepatic Impairment (Child-Pugh B) (mg/dose)	
	Morning	Evening
0.55-0.69 m ²	10	10
0.70-0.89 m ²	20	10
0.90-1.09 m ²	20	20
1.10-1.29 m ²	25	25
1.30-1.49 m ²	30	25
1.50-1.69 m ²	35	30
1.70-1.89 m ²	35	35
≥1.90 m ²	40	40

Hepatic Impairment

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

Recommended dosage of Koselugo for coadministration with strong or moderate CYP3A4 inhibitors or fluconazole

If 25 mg/m² twice daily, reduce to 20 mg/m² twice daily (mg/dose)

If 20 mg/m² twice daily, reduce to 15 mg/m² twice daily (mg/dose)

BSA	If 25 mg/m ² twice daily, reduce to 20 mg/m ² twice daily (mg/dose)		If 20 mg/m ² twice daily, reduce to 15 mg/m ² twice daily (mg/dose)	
	Morning	Evening	Morning	Evening
0.55-0.69 m ²	10	10	10 mg once daily	
0.70-0.89 m ²	20	10	10	10
0.90-1.09 m ²	20	20	20	10
1.10-1.29 m ²	25	25	25	10
1.30-1.49 m ²	30	25	25	20
1.50-1.69 m ²	35	30	25	25
1.70-1.89 m ²	35	35	30	25
≥1.90 m ²	40	40	30	30

Drug Interactions

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 the Koselugo dosage as recommended in the table on the left. After discontinuation of the strong or moderate CYP3A4 inhibitor or fluconazole for 3 elimination half-lives, resume the Koselugo dose that was taken prior to initiating the inhibitor or fluconazole.

Dosage modifications for retinal toxicities

- Withhold Koselugo treatment in patients with retinal pigment epithelial detachment (RPED) and follow up with optical coherence tomography assessments every 3 weeks until resolution, and resume Koselugo at a reduced dose
- Permanently discontinue Koselugo treatment in patients diagnosed with retinal vein occlusion (RVO)
- For other ocular toxicities, withhold, reduce dose, or permanently discontinue Koselugo based on severity of the adverse event

BSA=body surface area.

IMPORTANT SAFETY INFORMATION (CONT'D)

Ocular Toxicity. Blurred vision, photophobia, cataracts, and ocular hypertension occurred. 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.

Recommended dosage modifications for adverse events on Koselugo^{1*}

Severity of adverse events

Recommended dosage modifications for Koselugo

Cardiomyopathy

- Asymptomatic decrease in LVEF of 10% or greater from baseline and less than LLN

Withhold until resolution. Resume at reduced dose.

- Symptomatic decreased LVEF
- Grade 3 or 4 decreased LVEF

Permanently discontinue.

Ocular toxicity

- RPED

Withhold until resolution. Resume at reduced dose.

- RVO

Permanently discontinue.

Gastrointestinal toxicity

- Grade 3 diarrhea

Withhold until improved to Grade 0 or 1. Resume at same dose. Permanently discontinue if no improvement within 3 days.

- Grade 4 diarrhea

Permanently discontinue.

- Grade 3 or 4 colitis

Permanently discontinue.

Skin toxicity

- Grade 3 or 4

Withhold until improvement. Resume at reduced dose.

Increased CPK

- Grade 4 increased CPK
- Any increased CPK and myalgia

Withhold until improved to Grade 0 or 1. Resume at reduced dose. Permanently discontinue if no improvement within 3 weeks.

- Rhabdomyolysis

Permanently discontinue.

Other adverse events

- Intolerable Grade 2
- Grade 3

Withhold until improved to Grade 0 or 1. Resume at reduced dose.

- Grade 4

Withhold until improved to Grade 0 or 1. Resume at reduced dose. Consider discontinuation.

*Per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

CPK=creatinine phosphokinase; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; RPED=retinal pigment epithelial detachment; RVO=retinal vein occlusion.

Please see full Important Safety Information on page 15 and scan the QR code on front cover, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.



Koselugo efficacy & safety: what your patients may experience during their treatment

Primary endpoint: Overall response rate (ORR)^{1*}

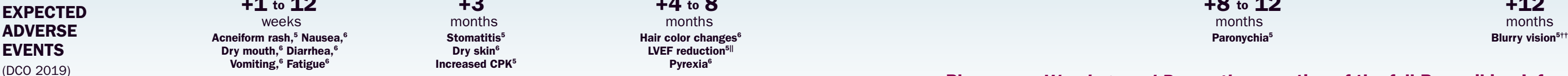
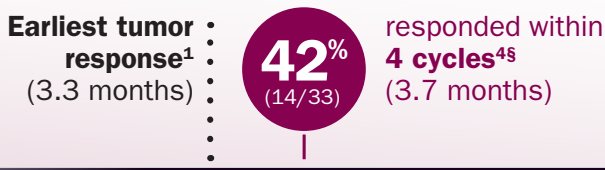


ORR was defined as the percentage of patients with **complete response** (defined as disappearance of the target PN) or **confirmed partial response** (defined as ≥20% reduction in PN volume confirmed at a subsequent tumor assessment within 3 to 6 months).^{1†}

An independent centralized review (ICR) of tumor response per REiNS criteria resulted in an ORR of 44% (95% CI: 30, 59).¹

The below is an overview of the first year of tumor response and adverse events, based on the SPRINT Phase 2 Stratum 1 study (N=50). Individual patient results may vary, but this visual can help patients and caregivers understand the median time to response and onset of adverse events that were reported in the SPRINT study.¹

TIME TO RESPONSE^{1†}
(For 33 patients who responded at the DCO of June 2018)



Please see **Warnings and Precautions** section of the full Prescribing Information.

After over 3 years of treatment, the median duration of response was not reached.^{1¶#}

Secondary endpoint: Duration of response (DOR)¹



Some Koselugo patients have been in response for over 4.5 years.^{8**}

DOR was defined as the time from the pre-cycle volumetric MRI assessment of the **first documented response** (which was subsequently confirmed) until the pre-cycle volumetric MRI assessment of documented progression.⁷

*Data cutoff June 2018.¹
[†]33 partial responses were confirmed by 3D MRI volumetric analyses per REiNS criteria at a subsequent tumor assessment within 3 to 6 months. The ORR assessment was conducted by a single NCI reviewer who was a SPRINT investigator and who evaluated all PN imaging from patients enrolled at all trial sites.¹
[‡]The median time to onset of response was 7.2 months (range: 3.3 months to 1.6 years; data cutoff June 2018). Time to response was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of the first documentation of complete response or a subsequently confirmed partial response.^{1,4}
[§]A cycle was defined as 28 days.⁷
^{||}Cardiomyopathy, defined as a decrease in LVEF ≥10% below baseline, occurred in 23% of 74 pediatric patients receiving Koselugo in SPRINT. Four percent of patients experienced decreased LVEF below the institutional 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.¹
 CI=confidence interval; CPK=creatinine phosphokinase; DCO=data cutoff; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; NCI=National Cancer Institute; PN=plexiform neurofibromas; REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis; 3D=three dimensional.

[¶]DCO March 2021.¹
[#]Median DOR was not reached (95% CI: 41.2 months, NE).¹
^{**}DCO February 2021. This information is from the SPRINT long-term follow-up study.⁸
^{††}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.¹
 DCO=data cutoff; MRI=magnetic resonance imaging; NE=not evaluable; NF1=neurofibromatosis type 1; PN=plexiform neurofibroma.

IMPORTANT SAFETY INFORMATION (CONT'D)

Gastrointestinal Toxicity. Diarrhea occurred, including Grade 3. Diarrhea resulting in permanent discontinuation, dose interruption or dose reduction occurred. 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.

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Dermatologic AEs⁹

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.

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 older children/adolescents).

- In severe cases, **semisynthetic oral tetracyclines**, such as doxycycline or minocycline, were recommended for older children and adolescents. These 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 mupirocin, 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 **mupirocin and ketoconazole (eg, Nizoral®)** topical ointments in the evening

AE=adverse event.

IMPORTANT SAFETY INFORMATION (CONT'D)

Skin Toxicity. Rash occurred in 91% of 74 pediatric patients. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred, in addition to rash resulting in dose interruption or dose reduction. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.



Visual AEs⁹

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, and 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 be performed until resolution. The study recommended restarting treatment after a dose reduction.

Retinal vein occlusion (RVO)

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



Pulmonary AE⁹

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

Dyspnea

If a patient developed Grade ≥ 2 pneumonitis, the study recommended withholding Koselugo, possibly restarting at a reduced dose.

Treatment procedures unrelated to plexiform neurofibromas (PN)

The study recommended that patients undergoing major surgery, unrelated to PN, hold Koselugo 1 week prior to surgery and until the wound healed completely.

AE=adverse event.

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Gastrointestinal AEs⁹

Patients were made aware that they may experience diarrhea and were encouraged to record the number of stools and possible associated symptoms.

Diarrhea

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.

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, caregiver, 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

The study recommended that physicians consider:

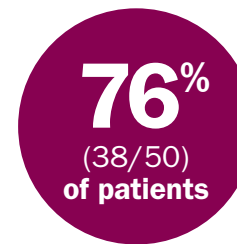
- Treating stomatitis at an early stage, such as CTCAE Grade 1, or as soon as the patient complained of a sore mouth
- Using an oral topical analgesic, with or without topical steroids, depending on the patient's clinical condition and the local standard medical practice

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.

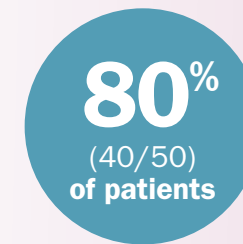
IMPORTANT SAFETY INFORMATION (CONT'D)

Increased Creatine Phosphokinase (CPK). Increased CPK occurred, including Grade 3 or 4 resulting in dose reduction. Increased CPK concurrent with myalgia occurred, 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 for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Adverse events are well characterized, can be manageable, and may not require discontinuation¹



stayed on a full dose of Koselugo, **without the need for a dose reduction***



required dose interruption but **avoided discontinuation***

Adverse events requiring a dosage interruption or reduction in ≥5% of patients were vomiting, paronychia, diarrhea, nausea, abdominal pain, rash, skin infection, influenza-like illness, pyrexia, and weight gain.¹

12% (6/50) of patients permanently discontinued due to an AE^{1*}

- These AEs included increased blood creatinine, increased weight, diarrhea, paronychia, malignant peripheral nerve sheath tumor, acute kidney injury, and skin ulcer¹
- 10% (5/50) of patients discontinued due to treatment-related AEs⁴
- The median time to discontinuation for those 5 patients was 277 days (range: 64 days to 636 days)⁴



Koselugo has been studied in patients with NF1 PN for up to 7.7 years.^{8†}

*Due to adverse events. DCO June 2018.¹

†These data reflect exposure to Koselugo in 74 pediatric patients who received a dosage ranging from 20 mg/m² to 30 mg/m² orally twice daily in SPRINT. At the DCO of February 2021, the median duration of exposure was 4.4 years (range: 28 days to 7.7 years).⁸

AE=adverse event; DCO=data cutoff; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

Please see full Important Safety Information on page 15 and scan the QR code on front cover, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.



Helping your patients and caregivers access the care they need



OneSource™ is a free, personalized patient support program offered by Alexion. Whether your patient is newly diagnosed or has had NF1 for some time, our specialists are available for patients and their caregivers.

Koselugo comes with a team

At OneSource, our team of specialists are trained in NF1 and are ready to give your patients the support they deserve—whatever their care plan may be.



Patient Education Manager (PEM)

- Hosts local patient educational initiatives
- Conducts treatment education sessions for patients
- Is available to help your patients understand more about NF1
- Provides educational materials, including a Koselugo Parent Readiness Kit



Case Manager

- Answers questions about Koselugo and NF1
- Provides support during treatment
- Helps answer any questions your patients may have about Koselugo, their insurance coverage, and more
- Helps get patients and caregivers involved with the NF1 community through events and meetings



To learn more or to contact a dedicated PEM or Case Manager, patients and caregivers can call **1-888-765-4747**, Monday through Friday, 8:30 AM – 8 PM ET, or visit [AlexionOneSource.com](https://www.alexiononesource.com).



Alexion Access Navigator is a dedicated resource website for US healthcare professionals and their offices that contains downloadable access and reimbursement materials for Koselugo. Visit www.alexionaccessnavigator.com/koselugo to learn more.

NF1=neurofibromatosis type 1; US=United States.

References: **1.** Koselugo. Package insert. AstraZeneca Pharmaceuticals LP **2.** Koselugo (selumetinib) approved in US for paediatric patients with neurofibromatosis type 1 plexiform neurofibromas. AstraZeneca. Published April 13, 2020. Accessed December 5, 2023. <https://www.astrazeneca.com/media-centre/press-releases/2020/koselugo-selumetinib-approved-in-us-for-paediatric-patients-with-neurofibromatosis-type-1-plexiform-neurofibromas.html#> **3.** Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med*. 2020;382(15):1430-1442. doi:10.1056/NEJMoa1912735 **4.** Data on File, REF-75729, AstraZeneca Pharmaceuticals LP **5.** Data on File, REF-37157, AstraZeneca Pharmaceuticals LP **6.** Data on File, REF-37158, AstraZeneca Pharmaceuticals LP **7.** Data on File, REF-36656, AstraZeneca Pharmaceuticals LP **8.** Gross AM, Dombi E, Wolters PL, et al. Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas. *Neuro Oncol*. 2023;25(10):1883-1894. doi:10.1093/neuonc/noad086 **9.** Data on File, REF-75728, AstraZeneca Pharmaceuticals LP

Indication & Important Safety Information

INDICATION

KOSELUGO® (selumetinib) 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

WARNINGS AND PRECAUTIONS

Cardiomyopathy. A decrease in left ventricular ejection fraction (LVEF) $\geq 10\%$ below baseline occurred in pediatric patients who received Koselugo in SPRINT with some experiencing decreased LVEF below the institutional lower limit of normal (LLN), including one patient with Grade 3. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. 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.

Ocular Toxicity. Blurred vision, photophobia, cataracts, and ocular hypertension occurred. 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.

Gastrointestinal Toxicity. Diarrhea occurred, including Grade 3. Diarrhea resulting in permanent discontinuation, dose interruption or dose reduction occurred. 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. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred, in addition to rash resulting in dose interruption or dose reduction. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Increased Creatine Phosphokinase (CPK). Increased CPK occurred, including Grade 3 or 4 resulting in dose reduction. Increased CPK concurrent with myalgia occurred, 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 for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Increased Levels of Vitamin E and Risk of Bleeding.

Koselugo capsules contain vitamin E which can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. 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 due to increased risk of bleeding. 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) 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 during pregnancy. 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/m² twice daily. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with Koselugo and for 1 week after the last dose.

ADVERSE REACTIONS

Common adverse reactions $\geq 40\%$ include vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

DRUG INTERACTIONS

Effect of Other Drugs on Koselugo
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 with Koselugo. If coadministration 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 with Koselugo.

SPECIAL POPULATIONS

Pregnancy & Lactation. Verify the pregnancy status of patients of reproductive potential prior to initiating Koselugo. Due to the potential for adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Koselugo and for 1 week after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca 1-800-236-9933 or at <https://us-aereporting.astrazeneca.com> or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.



Please scan the QR code, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.



A guide to AE management and dosing with Koselugo

Koselugo: The FIRST and ONLY FDA-approved therapy proven to shrink NF1 PN in pediatric patients^{1,2*}



No fasting required
Convenient, continuous dosing with the option to take with or without food¹



Adverse events are well characterized, can be manageable, and may not require discontinuation¹



Most common adverse events (≥40%) were vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus¹

*In a clinical trial, n=33/50 patients achieved ≥20% tumor reduction (95% CI: 51, 79) (DCO June 2018).¹

AE=adverse event; CI=confidence interval; DCO=data cutoff; FDA=Food and Drug Administration; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.



Caleb, age 7, living with NF1 PN.
Caleb is not a Koselugo patient.

Discover and download tools to support you and your patients at [KoselugoHCP.com](https://www.koselugohcp.com)



INDICATION

KOSELUGO® (selumetinib) 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).

SELECT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS associated with Koselugo (selumetinib) include Cardiomyopathy, Ocular Toxicity, Gastrointestinal Toxicity, Skin Toxicity, Increased Creatine Phosphokinase, Increased Levels of Vitamin E and Risk of Bleeding, and Embryo-Fetal Toxicity.

ADVERSE REACTIONS (≥40%) include vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

DRUG INTERACTIONS include strong/moderate CYP3A4 Inhibitors or Fluconazole and CYP3A4 Inducers.

Please see full Important Safety Information on page 15 and scan the QR code on front cover, or visit bit.ly/KoselugoPI, to see accompanying full Prescribing Information for Koselugo.



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