Koselugo®
(selumetinib)
10 mg & 25 mg capsules
5 mg & 7.5 mg oral granules

5+ YEARS OF REAL-WORLD EXPERIENCE[1*]

KOSELUGO® (selumetinib)

DOSING INFORMATION AND AE MANAGEMENT GUIDE

KOSELUGO® (selumetinib)—the FIRST FDA-approved therapy for pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)[1,2]

*Since FDA approval: April 10, 2020.[1]
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.

INDICATION

KOSELUGO is indicated for the treatment of pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

SELECT IMPORTANT SAFETY INFORMATION

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

ADVERSE REACTIONS (≥40%) include vomiting, diarrhea, increased creatine phosphokinase, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

DRUG INTERACTIONS include strong/moderate CYP3A4 inhibitors or fluconazole and strong/moderate CYP3A4 inducers.

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code.

AE=adverse event; FDA=Food and Drug Administration.

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 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/m^2 (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.

Kassidy, age 11, living with NF1 PN. Kassidy is not a Koselugo patient.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cardiomyopathy. Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline can occur with Koselugo. Grade 2 LVEF decrease occurred in 17% of evaluable patients of the 134 patients in the NF1 PN pediatric pool. Decreased LVEF of ≥20% occurred in 0.7% of patients and resulted in dose interruption and dose reduction. The median time to first occurrence of LVEF decrease was approximately 12 months.

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code on front cover.

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

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5 mg & 7.5 mg oral granules

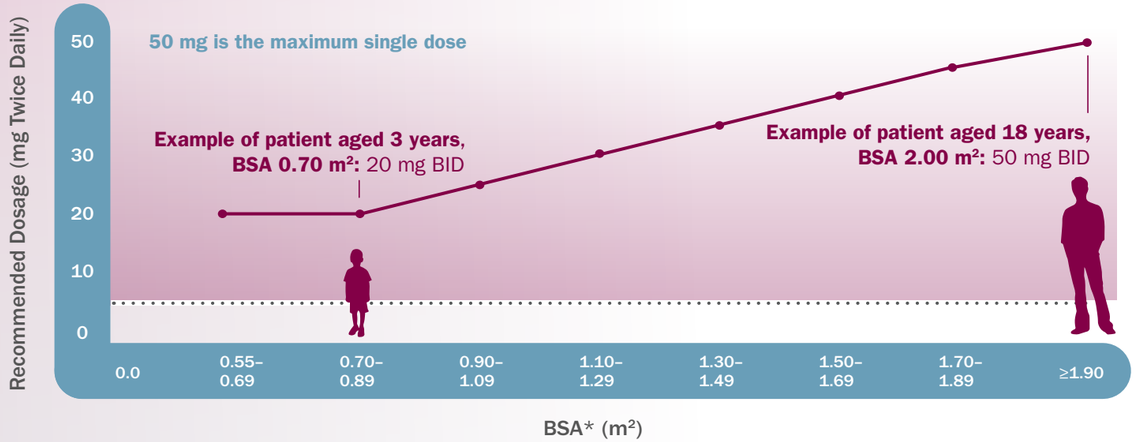
2 DISTINCT ORAL FORMULATIONS

Koselugo Capsules Are an Established Formulation for Pediatric Patients With NF1 PN[1]

- **Swallowed whole with water:** Do not chew, dissolve, or open the capsule
- **No fasting requirement**
- **Can be taken with or without food**

Before prescribing Koselugo, children should be assessed for their ability to swallow capsules.

Recommended Dosage: Koselugo Capsules



Koselugo capsules dosing is 25 mg/m² based on BSA and rounded to the nearest achievable 5-mg or 10-mg dose (up to a maximum single dose of 50 mg).*

Two formulations with identical dosing schedules and consistent safety profiles, providing options for your patients

*The recommended dosage of Koselugo capsules for patients with a BSA less than 0.55 m² has not been established.

IMPORTANT SAFETY INFORMATION (CONT'D)

Cardiomyopathy (Cont'd). 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 until resolution. Upon resolution of decreased LVEF, obtain an echocardiogram or a cardiac MRI every 2 to 3 months.

Koselugo Oral Granules Are an Option for Patients Who May Have Difficulty Swallowing Capsules[1]

- **Koselugo oral granules should be mixed with smooth yogurt, or fruit purée** containing the following fruits: apple, banana, pear, or strawberry, and given to children
- **Mixture must be consumed within 30 minutes** of preparation and not stored for future use
- **Granules should not be mixed** in grapefruit or any juice, fruit purée, or jam containing Seville orange

Patients as young as 1 year of age can be given Koselugo oral granules. Oral granules are also dosed as 25 mg/m², like the Koselugo capsules, and can be mixed into smooth yogurt or fruit purée as described above.

Koselugo oral granules dosing is 25 mg/m² based on BSA and rounded to the nearest achievable 5-mg or 7.5-mg dose (up to a maximum single dose of 50 mg).†

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

The observed safety profile of Koselugo oral granules in the SPRINKLE study was consistent with the known safety profile of Koselugo capsules.

†The recommended dosage of Koselugo oral granules for patients with a BSA less than 0.40 m² has not been established.

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code on front cover.

BID=twice daily; BSA=body surface area; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

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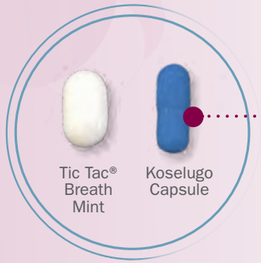
Koselugo Capsules Are the First FDA-Approved Treatment for NF1 PN[1,2]



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.

Koselugo capsules are available in 25- and 10-mg capsules and 28- and 60-count bottles.[1]

Koselugo Capsules:

Recommended Dosage and Dose Reductions for Adverse Reactions[1]

BSA	Initial Koselugo Dose* (mg/dose)		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 m^2 has not been established.[1]
†Permanently discontinue Koselugo in patients unable to tolerate Koselugo after 2 dose reductions.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

Ocular Toxicity. Blurred vision, photophobia, cataracts, ocular hypertension, and retinal tear occurred in 13% of the 134 patients in the NF1 PN pediatric pool. Blurred vision resulted in dose interruption. 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.

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code on front cover.

BSA=body surface area; CPK=creatine phosphokinase; FDA=Food and Drug Administration; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas; RPED=retinal pigment epithelial detachment; RVO=retinal vein occlusion.

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Koselugo Oral Granules Are for Patients Who Have Difficulty Swallowing Pills or Capsules[1]

- **Poured from a sprinkle capsule that contains oral granules**
- **Mixed with smooth yogurt or fruit purée**
- **Offers an alternative option for patients who have difficulty swallowing capsules**

Koselugo Oral Granules:

Recommended Dosage and Dose Reductions for Adverse Reactions

BSA	Koselugo Oral Granules Dosage*	First Dose Reduction (mg/dose)		Second Dose Reduction† (mg/dose)	
		Morning	Evening	Morning	Evening
0.40-0.59 m^2	12.5 mg BID	10	10	7.5	7.5
0.60-0.69 m^2	15 mg BID	12.5	12.5	10	10
0.70-0.89 m^2	20 mg BID	15	15	12.5	12.5
0.90-1.09 m^2	25 mg BID	20	20	15	15
1.10-1.29 m^2	30 mg BID	22.5	22.5	15	15
1.30-1.49 m^2	35 mg BID	25	25	25	10
1.50-1.69 m^2	40 mg BID	30	30	25	20
1.70-1.89 m^2	45 mg BID	35	30	25	20
≥1.90 m^2	50 mg BID	35	35	25	25

*The recommended dosage for patients with a BSA less than 0.40 m^2 has not been established.
†Permanently discontinue Koselugo in patients unable to tolerate Koselugo after 2 dose reductions.

IMPORTANT SAFETY INFORMATION (CONT'D)

Gastrointestinal Toxicity. Gastrointestinal toxicities, including diarrhea and Grade 3 diarrhea, vomiting, nausea and stomatitis occurred in 59% of the 134 patients in the NF1 PN pediatric pool. Diarrhea resulting in permanent discontinuation and dose interruption occurred. The median time to first onset of diarrhea was approximately 2 months and the median duration was 5 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.

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.

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BID=twice daily; BSA=body surface area; CPK=creatine phosphokinase; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; RPED=retinal pigment epithelial detachment; RVO=retinal vein occlusion.

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Dosage Reductions and Modifications for Koselugo Capsules[1]

Recommended Dosage of Koselugo Capsules for Moderate Hepatic Impairment

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/m^2 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 Capsules for Coadministration With Strong or Moderate CYP3A4 Inhibitors or Fluconazole

BSA	If 25 mg/m^2 BID, reduce to 20 mg/m^2 BID (mg/dose)		If 20 mg/m^2 BID, reduce to 15 mg/m^2 BID (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 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 RVO
- For other ocular toxicities, withhold, reduce dose, or permanently discontinue Koselugo based on severity of the adverse event

IMPORTANT SAFETY INFORMATION (CONT'D)

Skin Toxicity. Rash occurred in 68% of 134 pediatric patients in the NF1 pediatric pool. The most frequent rashes included dermatitis acneiform (47%) and maculopapular rash (31%). Pruritus (30%), alopecia (26%), and eczema (24%) occurred. Grade 3 rash occurred, in addition to rash resulting in dose interruption and dose reduction. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Reductions and Modifications for Koselugo Oral Granules[1]

Recommended Dosage of Koselugo Oral Granules for Moderate Hepatic Impairment

BSA	Moderate Hepatic Impairment (Child-Pugh B) (mg/dose)	
	Morning	Evening
0.40-0.59 m^2	10	10
0.60-0.69 m^2	12.5	12.5
0.70-0.89 m^2	15	15
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/m^2 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 Oral Granules for Coadministration With Strong or Moderate CYP3A4 Inhibitors or Fluconazole

BSA	If 25 mg/m^2 BID, reduce to 20 mg/m^2 BID (mg/dose)		If 20 mg/m^2 BID, reduce to 15 mg/m^2 BID (mg/dose)	
	Morning	Evening	Morning	Evening
0.40-0.59 m^2	10	10	7.5	7.5
0.60-0.69 m^2	12.5	12.5	10	7.5
0.70-0.89 m^2	15	15	10	10
0.90-1.09 m^2	20	20	15	15
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.

Please see prior page for dosage modifications for retinal toxicities.

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BID=twice daily; BSA=body surface area; RPED=retinal pigment epithelial detachment; RVO=retinal vein occlusion.

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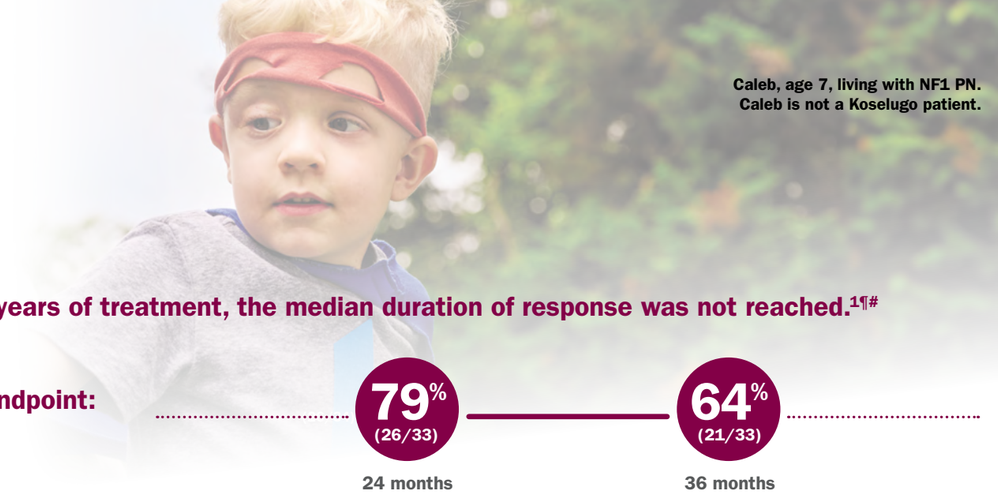
Koselugo Efficacy and Safety: What Your Patients May Experience During Their Treatment


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

Primary endpoint: ORR[1]*

Percentage of patients who achieved ≥20% tumor reduction (95% CI: 51, 79)

66% (n=33/50)

ORR was defined as the percentage of patients with **complete response** (defined as the 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 ICR of tumor response per REiNS criteria resulted in an ORR of 44% (95% CI: 30, 59).[1]

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]

After over 3 years of treatment, the median duration of response was not reached.[1¶#]

Secondary endpoint: DOR[1]

79% (26/33) — 24 months

64% (21/33) — 36 months

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]

TIME TO RESPONSE[1‡]
(For 33 patients who responded at the DCO of June 2018)

Median time to onset of response[1] (7.2 months)

Earliest tumor response[1] (3.3 months)

42% (14/33) responded within **4 cycles[4§]** (3.7 months)

73% (24/33) responded within **8 cycles[4]** (7.4 months)

97% (32/33) responded within **12 cycles[4]** (11 months)

Month 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 · 10 · 11 · 12

EXPECTED ADVERSE EVENTS[5,6]
(DCO 2019)

+1 to 12 weeks
Acneiform rash,[5] nausea,[6] dry mouth,[6] diarrhea,[6] vomiting,[6] fatigue[6]

+3 months
Stomatitis[5]
Dry skin[6]
Increased CPK[5]

+4 to 8 months
Hair color changes[6]
LVEF reduction[5‖]
Pyrexia[6]

+8 to 12 months
Paronychia[5]

+12 months
Blurry vision[5††]

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

*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).[1] Time to response was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of the first documentation of a complete response or a subsequently confirmed partial response.[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]

¶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]

IMPORTANT SAFETY INFORMATION (CONT'D)

Increased Creatine Phosphokinase (CPK). Increased CPK, including Grade 3 or 4, occurred in 55% of the 134 patients in the NF1 PN pediatric pool and resulted in dose interruption and dose reduction in 4% of patients. 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.

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code on front cover.

3D=three-dimensional; CI=confidence interval; CPK=creatine phosphokinase; DCO=data cutoff; DOR=duration of response; ICR=independent centralized review; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; NCI=National Cancer Institute; NE=not evaluable; NF1=neurofibromatosis type 1; ORR=overall response rate; PN=plexiform neurofibromas; REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis.

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Dermatologic AEs[9]

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

Visual AEs[9]

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 AE[9]

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 PN

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

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code on front cover.

AE=adverse event; PN=plexiform neurofibromas.

Koselugo® (selumetinib)
10 mg & 25 mg capsules
5 mg & 7.5 mg oral granules

Gastrointestinal AEs[9]

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

AEs Are Well Characterized, Can Be Manageable, and May Not Require Discontinuation[1]

76% (38/50) **of patients**

stayed on a full dose of Koselugo, **without the need for a dose reduction[1]***

80% (40/50) **of patients**

required dose interruption but **avoided discontinuation[1]***

AEs 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 ulcer[1]
- 10% (5/50) of patients discontinued due to treatment-related AEs[4]
- 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 AEs. DCO June 2018.[1]
†This statement reflects 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 Phase 1 and Phase 2 Stratum 1. At the DCO of February 2021, the median duration of exposure was 4.4 years (range: 28 days to 7.7 years).[8]

Please see additional Important Safety Information throughout and on page 19 and the accompanying full Prescribing Information for Koselugo, also available by scanning the QR code on front cover.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; DCO=data cutoff; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

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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 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**.

ALEXION ACCESS NAVIGATOR

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 June 16, 2025. 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 is indicated for the treatment of pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cardiomyopathy. Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline can occur with Koselugo. Grade 2 LVEF decrease occurred in 17% of evaluable patients of the 134 patients in the NF1 PN pediatric pool. Decreased LVEF of ≥20% occurred in 0.7% of patients and resulted in dose interruption and dose reduction. The median time to first occurrence of LVEF decrease was approximately 12 months. 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 until resolution. Upon resolution of decreased LVEF, obtain an echocardiogram or a cardiac MRI every 2 to 3 months.

Ocular Toxicity. Blurred vision, photophobia, cataracts, ocular hypertension, and retinal tear occurred in 13% of the 134 patients in the NF1 PN pediatric pool. Blurred vision resulted in dose interruption. 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. Gastrointestinal toxicities, including diarrhea and Grade 3 diarrhea, vomiting, nausea and stomatitis occurred in 59% of the 134 patients in the NF1 PN pediatric pool. Diarrhea resulting in permanent discontinuation and dose interruption occurred. The median time to first onset of diarrhea was approximately 2 months and the median duration was 5 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 68% of 134 pediatric patients in the NF1 pediatric pool. The most frequent rashes included dermatitis acneiform (47%) and maculopapular rash (31%). Pruritus (30%), alopecia (26%), and eczema (24%) occurred. Grade 3 rash occurred, in addition to rash resulting in dose interruption and 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, including Grade 3 or 4, occurred in 55% of the 134 patients in the NF1 PN pediatric pool and resulted in dose interruption and dose reduction in 4% of patients. 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). 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 co-administered vitamin-K antagonists or anti-platelet antagonists with Koselugo capsules. 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. Koselugo oral granules do not contain vitamin E.

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/m^2 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 ≥40% include vomiting, diarrhea, increased CPK, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

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 see full Prescribing Information for Koselugo (selumetinib) at https://alexion.com/Documents/koselugo_uspi.pdf.

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

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A Guide to AE Management and Dosing With Koselugo

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

Koselugo: The FIRST FDA-approved therapy proven to shrink NF1 PN in pediatric patients[1,2]*

Continuous dosing
that's easy to maintain with no mandatory monthly dosing interruptions[1]

7.7 years
of established safety in patients with NF1 PN[8†]

Most common adverse events in SPRINT
(≥40%) were vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus[1]

*In a clinical trial, 66% (33/50) patients achieved ≥20% tumor reduction (95% CI: 51, 79) (DCO June 2018).[1]
†This statement reflects exposure to Koselugo in 74 pediatric patients who received a dosage ranging from 20 mg/m^2 to 30 mg/m^2 orally twice daily in the SPRINT Phase 1 and Phase 2 Stratum 1 studies. At the DCO of February 2021, the median duration of exposure to Koselugo was 4.4 years (range: 28 days to 7.7 years).[8]

Discover and download tools to support you and your patients at KoselugoHCP.com

INDICATION

KOSELUGO is indicated for the treatment of pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

SELECT IMPORTANT SAFETY INFORMATION

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

ADVERSE REACTIONS (≥40%) include vomiting, diarrhea, increased creatine phosphokinase, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

DRUG INTERACTIONS include strong/moderate CYP3A4 inhibitors or fluconazole and strong/moderate CYP3A4 inducers.

Please see the full Important Safety Information on page 19 and scan the QR code on front cover, or visit bit.ly/KoselugoPI to see the accompanying full Prescribing Information for Koselugo.

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

ALEXION®
AstraZeneca Rare Disease

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