Koselugo® (selumetinib)
10 mg & 25 mg capsules

KOSELUGO® (selumetinib) is the FIRST and ONLY FDA-approved treatment for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)[1]

Your Healthcare Professional Therapy Management Guide

Guidance for the administration and management of Koselugo in the treatment of pediatric patients with NF1 PN based on results from SPRINT Phase II Stratum 1, a landmark study coordinated with the National Cancer Institute (NCI).[1,2]

Koselugo can be used in patients regardless of whether or not they have had previous surgery for PN.[2]

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 18 and 19.
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A BRIEF OVERVIEW


Not an actual patient.

Neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN)

Due to its variability and potential for debilitating morbidities, NF1 PN is a particularly challenging disease.[3,4] **This therapy management guide was created to support healthcare professionals in their essential role of caring for patients with NF1 PN.** Knowing more about the disease and Koselugo, a breakthrough medication, can help you **and your pediatric patients.**

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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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EXPLORING THE IMPACT OF NF1 PN

PN are prevalent and progressive[4]

- **30% to 50%** of patients with NF1 may develop PN[5]
- PN can occur in any nerve, anywhere in the body, with the potential to affect multiple organs, causing pain, disfigurement, and loss of function[3,4,6]
- PN are most likely congenital, and usually grow most rapidly during the first decade of life[5]

PN may cause major clinical complications

PN-related morbidities tend to worsen as tumor volume increases.[3]

- The presence of NF1 PN may result in tumor-related pain[3,7]
  - Some PN are undetectable by sight or touch and may only be noticed when they begin to cause pain[4]
- Other major PN-related morbidities include:
  - Disfigurement[4]
  - Airway compromise[3]
  - Bladder/bowel dysfunction[4]
  - Motor dysfunction (functional impairment)[4]
  - Vision impairment[4]

Addressing PN early may help to prevent or mitigate clinical complications.[3]

Maintaining an open dialogue, and engaging patients and caregivers throughout the treatment journey, can help them cope with this complex condition[4]

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.

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Koselugo® (selumetinib) 10 mg & 25 mg capsules

KOSELUGO IS THE FIRST FDA-APPROVED TREATMENT FOR PEDIATRIC PATIENTS WITH NF1 PN[1]

Koselugo is the FIRST and ONLY FDA-approved treatment for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)[1]

SPRINT, a landmark study coordinated with the National Cancer Institute (NCI), assessed PN volume reduction in 50 pediatric patients with NF1 and symptomatic, inoperable PN treated with Koselugo.[1,2]

Actual patient.

IMPORTANT SAFETY INFORMATION (Cont'd)

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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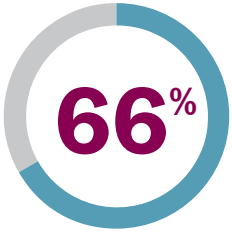
KOSELUGO IS THE FIRST FDA-APPROVED TREATMENT FOR PEDIATRIC PATIENTS WITH NF1 PN[1] *(CONT'D)*

The SPRINT study, a landmark trial in pediatric patients with NF1 PN[1,2]

- N=50
- Age eligibility range: 2 to 18 years
  - Median age: 10.2 years (range 3.5 to 17.4 years)
- All patients had at least 1 clinically significant PN-related morbidity
- Sponsored by the NCI
- Primary endpoint: Overall Response Rate (ORR) per REiNS criteria, defined as the percentage of patients with complete response (defined as disappearance of the HCP-identified target PN) or confirmed partial response (defined as ≥20% reduction of the HCP-identified target PN)
- Secondary endpoints: Duration of response, safety, and (exploratory) PN-related pain intensity improvement using the NRS-11*
- Dosing: Koselugo (capsules) 25 mg/m^2 (BSA) twice daily, approximately 12 hours apart

PRIMARY ENDPOINT: Overall Response Rate[1]



66% (33/50) of patients achieved ≥20% tumor reduction
95% CI: 51, 79

- 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)
- 33 partial responses were confirmed by 3D MRI volumetric analyses at a subsequent tumor assessment within 3 to 6 months†
- **82% (27/33) of patients had duration of response ≥12 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]

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

Onset of response in SPRINT[1]

3.3 months	7.2 months	19.2 months
Earliest response	Median response	Latest response

*Pain intensity of the target PN was self-reported by patients ≥8 years of age using the NRS-11.[2]

BSA=body surface area; CI=confidence interval; MRI=magnetic resonance imaging; NCI=National Cancer Institute; NRS-11=Numeric Rating Scale-11; PN=plexiform neurofibromas; REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis.

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Duration of treatment with Koselugo[1]

- Of patients in the SPRINT study (N=50), 88% (44/50) were exposed to Koselugo for ≥12 months and 66% (33/50) were exposed for ≥2 years

Actual patient.

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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SPRINT STUDY SAFETY PROFILE *(CONT'D)*

Adverse reactions (≥20%) in patients who received Koselugo in SPRINT Phase II Stratum 1[1]

Adverse Reaction	Koselugo N=50	
	All Grades (%)	Grade ≥3 (%)*
Gastrointestinal		
Vomiting	82	6
Abdominal pain†	76	0
Diarrhea	70	16
Nausea	66	2
Stomatitis†	50	0
Constipation	34	0
Skin and subcutaneous tissue		
Rash (all)§	80	6
Dry skin	60	0
Rash acneiform‖	50	4
Paronychia¶	48	6
Pruritus	46	0
Dermatitis#	36	4
Hair changes**	32	0
Musculoskeletal and connective tissue		
Musculoskeletal pain††	58	0
General		
Fatigue††	56	0
Pyrexia	56	8
Edema§§	20	0
Nervous system		
Headache	48	2
Respiratory, thoracic and mediastinal		
Epistaxis	28	0
Renal and urinary system		
Hematuria	22	2
Proteinuria	22	0
Metabolism and nutrition		
Decreased appetite	22	0
Cardiac system		
Decreased ejection fraction	22	0
Sinus tachycardia	20	0
Infections		
Skin infection‖‖	20	2

*All events were Grade 3.
†Abdominal pain includes abdominal pain, abdominal pain upper.
†Stomatitis includes stomatitis, mouth ulceration.
§Rash (all) includes dermatitis acneiform, rash maculo-papular, erythema, rash pustular, rash, urticaria, exfoliative rash, rash pruritic, rash erythematous.
‖Rash (acneiform) includes dermatitis acneiform.
¶Paronychia includes paronychia, nail infection.
#Dermatitis includes dermatitis, dermatitis atopic, dermatitis diaper, eczema, seborrheic dermatitis, skin irritation.
**Hair changes include alopecia, hair color change.
††Musculoskeletal pain includes pain in extremity, back pain, neck pain, musculoskeletal pain.
††Fatigue includes fatigue, malaise.
§§Edema includes peripheral swelling, edema, localized edema.
‖‖Skin infection includes skin infection, abscess, cellulitis, impetigo, staphylococcal skin infection.

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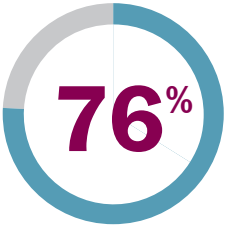
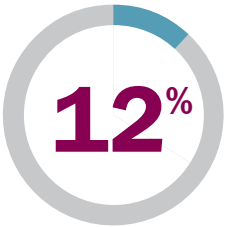


76% (38/50) of patients were able to stay on a full dose of Koselugo, without the need for a dose reduction[1]

80% (40/50) of patients required a dose interruption[1]

- Adverse reactions 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



12% (6/50) of patients permanently discontinued due to any adverse reaction[1]

- 10% (5/50) of patients discontinued due to treatment-related AEs[2]
- The median time to discontinuation for those 5 patients was **277 days** (range: 64 days to 636 days)[2]
  - Adverse reactions resulting in permanent discontinuation of Koselugo included increased creatine, increased weight, diarrhea, paronychia, malignant peripheral nerve sheath tumor (MPNST), acute kidney injury, and skin ulcer[1]

AE=adverse event.

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.

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.

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SPRINT STUDY SAFETY PROFILE *(CONT'D)*

Select laboratory abnormalities (≥15%) worsening from baseline in patients who received Koselugo in SPRINT Phase II Stratum 1[1]

Laboratory Abnormality	Koselugo	
	All Grades (%)*	Grade ≥3 (%)†
Chemistry		
Increased CPK	79	7
Decreased albumin	51	0
Increased AST	41	2
Increased ALT	35	4
Increased lipase	32	5
Increased potassium	27	4
Decreased potassium	18	2
Increased alkaline phosphatase	18	0
Increased amylase	18	0
Increased sodium	18	0
Decreased sodium	16	0
Hematology		
Decreased hemoglobin	41	4
Decreased neutrophils	33	4
Decreased lymphocytes	20	2

*The denominator used to calculate the rate varied from 39 to 49 based on the number of patients with a baseline value and at least one post-treatment value.
†Includes one Grade 4 increased CPK and one Grade 4 increased potassium.

REQUIRED TESTING[1]	Before Treatment	3 Months Into Treatment	6 Months Into Treatment	9 Months Into Treatment	12 Months Into Treatment	>12 Months Into Treatment
Ejection Fraction by Echocardiogram	✓	✓	✓	✓	✓	Every 6 months thereafter, and as clinically indicated
Ophthalmic Assessment	✓	Conduct comprehensive ophthalmic assessments at regular intervals during treatment and for new or worsening visual changes.				
Serum CPK	✓	Obtain serum CPK periodically during treatment and as clinically indicated.				
Pregnancy Test	✓	Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Koselugo and for 1 week after the last dose.				

Additional Evaluation Guidelines[1]:

Ejection Fraction by Echocardiogram: 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 to greater than or equal to the institutional LLN, obtain an echocardiogram or a cardiac MRI every 2 to 3 months or as directed by the cardiologist.

Ophthalmic Assessment: Permanently discontinue Koselugo in patients with RVO. Withhold Koselugo in patients with RPED, follow up with optical coherence tomography assessments every 3 weeks until resolution, and resume Koselugo at a reduced dose. For other ocular toxicities, withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Serum CPK: If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Pregnancy Test: Assess the pregnancy status of females of reproductive age. Advise pregnant women of the potential risk to a fetus.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; RPED=retinal pigment epithelial detachment; RVO=retinal vein occlusion.

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Koselugo® (selumetinib) 10 mg & 25 mg capsules

DOSING AND ADMINISTRATION

Dosage form and strengths

- Capsules are available in 2 strengths: 10 mg and 25 mg[1]
- Koselugo comes in a child-resistant bottle

Koselugo twice-daily dosing is customized based on body surface area (BSA) (mg/m²)[1]

Recommended dosage based on body surface area[1]

Body Surface Area*	Recommended Dosage
0.55 – 0.69 m²	20 mg in the morning and 10 mg in the evening
0.70 – 0.89 m²	20 mg twice daily
0.90 – 1.09 m²	25 mg twice daily
1.10 – 1.29 m²	30 mg twice daily
1.30 – 1.49 m²	35 mg twice daily
1.50 – 1.69 m²	40 mg twice daily
1.70 – 1.89 m²	45 mg twice daily
≥1.90 m²	50 mg twice daily

- Minimum BSA is 0.55 m²
- Dosing is rounded to the nearest achievable 5-mg or 10-mg dose (up to a maximum single dose of 50 mg)

Dosage examples

- **Patient aged 3 years, BSA 0.70 m²:** 20 mg BID (2 doses daily, 20 mg each)
- **Patient aged 18 years, BSA 2.00 m²:** 50 mg BID (2 doses daily, 50 mg each)

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

Recommended administration of Koselugo[1]:

- **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
- **On an empty stomach,** do not consume food 2 hours before each dose or 1 hour after each dose

- **Swallowed whole with water:** Do not chew, dissolve, or open capsule

Advise patients[1]:

- **Not to take a missed dose** unless it is more than 6 hours until the next scheduled dose
- **If vomiting occurs,** not to take an additional dose, but continue with the next scheduled dose

Continue treatment with Koselugo until disease progression or unacceptable toxicity[1]

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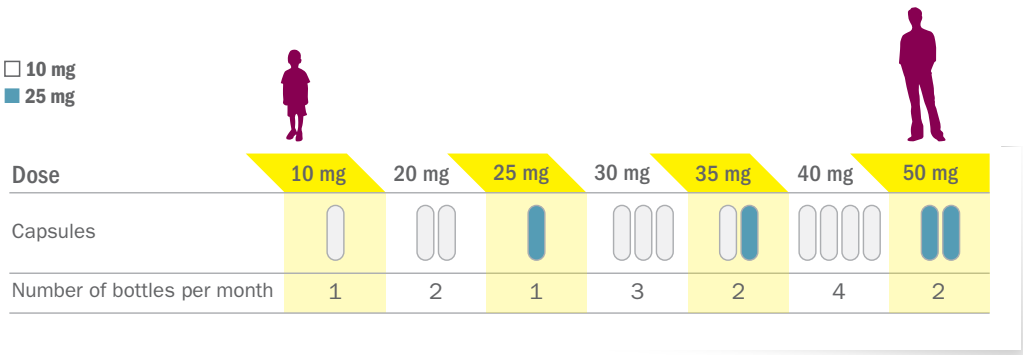
KOSELUGO TWICE-DAILY DOSING IS CUSTOMIZED ACCORDING TO EACH PATIENT'S BODY SURFACE AREA (BSA)

Unique packaging for each strength (10 mg and 25 mg)[1]

Dosing is individualized based on BSA (mg/m^2) and is rounded to the nearest achievable 5-mg or 10-mg dose (up to a maximum single dose of 50 mg).[1]

Available in both 28- and 60-count bottles.



▸ **Koselugo dosing is customized based on BSA (mg/m^2)[1]**

IMPORTANT SAFETY INFORMATION (Cont'd)

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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HELPING CHILDREN START AND STAY ON KOSELUGO

Helpful tips to consider for pill swallowing[8,9]

Get into the right position

- Sitting or standing up straight is the best position for pill swallowing
- Have your patient hold their head straight or even tip it forward to avoid choking
- Allow them to hold something comforting, such as a blanket or stuffed animal

Practice with candy

- Use candy that dissolves easily to prevent risk of choking
- Start by having your patient place a small-sized candy on their tongue, then take a small sip of water and swallow
- Continue with bigger-sized candy to help ensure that your patient can swallow Koselugo capsules

Use a straw

- For some children, drinking water through a straw could help because the suction used to pull the liquid upward makes it easier to swallow a pill
- Also, many children concentrate on the straw and don't think about the pill, so it goes down easily

For additional suggestions on teaching your patients how to swallow pills, you may want to download the brochure *Medicine & Your Child: A Guide for Parents on Adherence and Administration* at https://ccr.cancer.gov/sites/default/files/medbooklet.pdf or visit www.kidshealth.org to review *Teaching Your Child How to Swallow Pills*.

IMPORTANT SAFETY INFORMATION (Cont'd)

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.

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Help them establish a dosing routine that works for them

- **First dose:** It may work well to suggest having the first dose of Koselugo in the morning, upon awakening, as the child's stomach is empty. Then, while waiting for the hour after the dose to eat or drink, the child can get dressed and keep busy with a favorite activity
- **Second dose:** For the second dose of the day, it may be best between late afternoon and dinner when the child hasn't had anything to eat or drink for 2 hours. Then, while waiting for the hour after the dose before eating dinner, use that time for activities such as playing, having a bath, homework, and chatting about the day

Examples of schedules you may want to share with your patient and their caregiver

1	First Dose Second Dose	6:00 AM 6:00 PM	Breakfast between 7AM-9AM Dinner between 7PM-9PM
2	First Dose Second Dose	7:00 AM 7:00 PM	Breakfast between 8AM-10AM Dinner between 8PM-10PM
3	First Dose Second Dose	8:00 AM 8:00 PM	Breakfast between 9AM-11AM Dinner between 9PM-11PM

These sample schedules are designed as suggestions only.

You may want to advise caregivers to use a dose-alert timer or the alarm on their smartphone as a dosing reminder that fits into their child's daily routine.

Reinforce that taking each dose of Koselugo as directed, every day, is the best way to get benefit from treatment

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DOSE MODIFICATIONS FOR SPECIFIC GROUPS

Recommended dose reductions for Koselugo for adverse reactions[1]

Body Surface Area	First Dose Reduction (mg/dose)		Second Dose Reduction* (mg/dose)	
	Morning	Evening	Morning	Evening
0.55 – 0.69 m^2	10	10	10 once daily	
0.70 – 0.89 m^2	20	10	10	10
0.90 – 1.09 m^2	25	10	10	10
1.10 – 1.29 m^2	25	20	20	10
1.30 – 1.49 m^2	25	25	25	10
1.50 – 1.69 m^2	30	30	25	20
1.70 – 1.89 m^2	35	30	25	20
≥1.90 m^2	35	35	25	25

*Permanently discontinue Koselugo in patients unable to tolerate Koselugo after 2 dose reductions.

Hepatic impairment[1]

- 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

Drug interactions[1]

- 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 above
- 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 the Prescribing Information for additional information on dose modifications.

IMPORTANT SAFETY INFORMATION (Cont'd)

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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DOSE MODIFICATIONS FOR SPECIFIC GROUPS *(CONT'D)*

Recommended dosage modifications for Koselugo for adverse reactions[1]

Severity of Adverse Reaction	Recommended Dosage Modifications for Koselugo
Cardiomyopathy	
• Asymptomatic decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline and less than lower level of normal	Withhold until resolution. Resume at reduced dose.
• Symptomatic decreased LVEF • Grade 3 or 4 decreased LVEF	Permanently discontinue.
Ocular Toxicity	
• Retinal Pigment Epithelial Detachment (RPED)	Withhold until resolution. Resume at reduced dose.
• Retinal vein occlusion (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 Creatine Phosphokinase (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 Reactions	
• Intolerable Grade 2 • Grade 3	Withhold Koselugo until improved to Grade 0 or 1. Resume at reduced dose.
• Grade 4	Withhold Koselugo until improved to Grade 0 or 1. Resume at reduced dose. Consider discontinuation.

Per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

Please read additional Important Safety Information on pages 18 and 19.
Please see full Prescribing Information, including Patient Information, by clicking here or at KoselugoHCP.com.

Koselugo® (selumetinib) 10 mg & 25 mg capsules

TRACK THEIR TREATMENT JOURNEY

When patients and caregivers start their treatment journey, it can be difficult to know what to expect.

The following is an overview of the first year of responses and adverse reactions based on the SPRINT study (N=50). Individual patient results may vary, but the following timeline based on the SPRINT study can help them understand the median time to response and onset of adverse events that were reported. Knowing these results can also help you ask the right questions, be aware of potential adverse reactions, and encourage compliance.

Koselugo treatment journey based on the pediatric population of the SPRINT study[1,10,11]

The timeline above represents results from patients in the SPRINT study, but **any of the efficacy results or adverse reactions may occur at any time during the course of treatment.** Therefore, routine monitoring for adverse reactions is critical. 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.[1] An increased risk of bleeding in patients may occur in patients who are coadministered vitamin-K antagonists or anti-platelet antagonists with Koselugo.[1] Monitor for bleeding in these patients.[1] Please see the Important Safety Information on pages 18 and 19 and review the full Prescribing Information for a full list of *Warnings and Precautions*.

Advise your patient, and his or her caregiver, to contact you about any adverse reactions experienced during treatment.

*The median time to response was 7.2 months. 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.[1,2]

†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 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. Please see the *Warnings and Precautions* section of the full Prescribing Information.[1]

‡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. Please see the *Warnings and Precautions* section of the full Prescribing Information.[1]

CPK=creatine phosphokinase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging.

Please read additional Important Safety Information on pages 18 and 19.
Please see full Prescribing Information, including Patient Information, by clicking here or at KoselugoHCP.com.

Having the right support can make all the difference in your patient's treatment journey. **Please see the last page to learn about the dedicated Patient Access Navigators who are ready to connect caregivers and patients to the personal assistance they need.**

Actual patient.

IMPORTANT SAFETY INFORMATION (Cont'd)

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.

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Koselugo® (selumetinib) 10 mg & 25 mg capsules

IMPORTANT SAFETY INFORMATION

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.

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.

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.

Please see full Prescribing Information, including Patient Information, by clicking here or at KoselugoHCP.com.

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.

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.

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.

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® 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.

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 provide:

- Education
- Health Insurance Navigation
- Community Connections
- Ongoing Support

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

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. Koselugo. Package insert. AstraZeneca Pharmaceuticals; 2021. **2.** Data on File, REF-75729, AstraZeneca Pharmaceuticals LP. **3.** Gross AM, Singh G, Akshintala S, et al. Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1. *Neuro Oncol.* 2018;20(12):1643-1651. **4.** Korf BR, Rubenstein AE. *Neurofibromatosis: A Handbook for Patients, Families, and Health Care Professionals*. Thieme Medical Publishers; 2005. **5.** Anderson JL, Gutmann DH. Neurofibromatosis type 1. In: Islam MP, Roach SE, eds. *Handbook of Clinical Neurology*. 3rd series; vol 132. Elsevier B.V.; 2015:75-86. **6.** Hersh JH; American Academy of Pediatrics Committee on Genetics. Health supervision for children with neurofibromatosis. *Pediatrics.* 2008;121(3):633-642. **7.** Wolters PL, Burns KM, Martin S, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. *Am J Med Genet A.* 2015;167A(9):2103-2113. **8.** National Cancer Institute. Medicine & your child: a guide for parents on adherence and administration. The National Cancer Institute website. Accessed April 19, 2021. https://ccr.cancer.gov/sites/default/files/medbooklet.pdf **9.** Ben-Joseph EP. Teaching your child how to swallow pills. Kids Health website. Accessed April 19, 2021. https://kidshealth.org/en/parents/swallowing-pills.html **10.** Data on File, REF-75730, AstraZeneca Pharmaceuticals LP. **11.** Data on File, REF-70330, AstraZeneca Pharmaceuticals LP.

For more information, visit **www.KoselugoHCP.com**.

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, call 1-800-FDA-1088.

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ALEXION® AstraZeneca Rare Disease