PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKOSELUGO®

Selumetinib capsules

Capsules, 10 mg and 25 mg selumetinib (as selumetinib sulfate)

PrKOSELUGO® Granules

Selumetinib oral granules

Granules, 5 mg and 7.5 mg (as selumetinib sulfate)

Oral use

Antineoplastic Agent

Alexion Pharma GmbH
Neuhofstrasse 34
6340 Baar, Switzerland

Imported By:
Alexion Pharma Canada Corp.
1004 Middlegate Road, Suite #5000, Mississauga, ON L4Y 1M4
https://alexion.com/worldwide/canada

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1 INDICATIONS	06/2026
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	02/2026
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations, 4.2 Recommended Dose and Dosage Adjustment	06/2026
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KOSELUGO® (selumetinib capsules) / KOSELUGO® Granules (selumetinib oral granules) are indicated for:

Capsules
The treatment of adult and pediatric patients aged 2 years and older, with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

Granules
The treatment of pediatric patients aged 1 year and older, with NF1 who have symptomatic, inoperable PN.

1.1 Pediatrics

Safety and effectiveness have been established in pediatric patients 1 year to less than 7 years with NF1 who have inoperable PN and information supporting this use is discussed throughout the Product Monograph. Pediatric patients 1 year of age and older were studied using the granules formulation, and clinical efficacy was demonstrated in patients 3 years of age and older treated with the capsule formulation. For the capsule formulation, this indication was expanded to pediatric patients who are 2 years of age and older, because the safety, efficacy and pharmacokinetics of KOSELUGO / KOSELUGO Granules in patients who are 2 years of age is expected to be similar to patients at 3 years of age and older. Use in pediatric patients 1 year of age and older is additionally supported by extrapolation based on similar disease characteristics and comparable pharmacokinetic exposure across age groups and formulations.

1.2 Geriatrics

Geriatrics (≥*65* years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

KOSELUGO / KOSELUGO Granules are contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment with KOSELUGO / KOSELUGO Granules should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours.

Treatment with KOSELUGO / KOSELUGO Granules should continue as long as clinical benefit is observed, or until PN progression, or the development of unacceptable toxicity.

Do not administer KOSELUGO capsules to patients who are unable to swallow a whole

capsule.

Administer KOSELUGO Granules to pediatric patients aged 1 year and older who have difficulty swallowing a whole capsule.

If vomiting occurs after KOSELUGO / KOSELUGO Granules administration, do not take an additional dose, but continue with the next scheduled dose.

4.2 Recommended Dose and Dosage Adjustment

Capsules
The recommended dose of KOSELUGO is 25 mg/m^2 based on body surface area (BSA), taken orally twice daily (approximately every 12 hours).

Dosing in adult and pediatric patients is individualized based on BSA (mg/m^2) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of KOSELUGO capsules can be combined to attain the desired dose (See **Table 1**).

Table 1 – KOSELUGO capsules Recommended Dosage Based on Body Surface Area

Body Surface Area (BSA)[a]	Recommended Dosage	
0.55 – 0.69 m^2	20 mg in the morning	10 mg in the evening
0.70 – 0.89 m^2	20 mg twice daily	
0.90 – 1.09 m^2	25 mg twice daily	
1.10 – 1.29 m^2	30 mg twice daily	
1.30 – 1.49 m^2	35 mg twice daily	
1.50 – 1.69 m^2	40 mg twice daily	
1.70 – 1.89 m^2	45 mg twice daily	
≥1.90 m^2	50 mg twice daily	

[a] The recommended dosage for patients with a BSA less than 0.55 m^2 has not been established.

Granules
The recommended dose of KOSELUGO Granules is equivalent to 25 mg/m^2 of BSA, taken orally twice daily (approximately every 12 hours).

Dosing is individualized based on BSA (mg/m^2) and rounded to the nearest achievable 2.5 mg, 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of KOSELUGO Granules can be combined to attain the desired dose (**Table 2**).

Table 2 - KOSELUGO Granules Recommended Dosage Based on Body Surface Area

Body surface area (BSA)[a]	Recommended Dosage
0.40 – 0.49 m^2	10 mg twice daily

Body surface area (BSA)[a]	Recommended Dosage
0.50 – 0.59 m^2	12.5 mg twice daily
0.60 – 0.69 m^2	15 mg twice daily
0.70 – 0.89 [b] m^2	20 mg twice daily
0.90 – 1.09 m^2	25 mg twice daily
1.10 – 1.29 [c] m^2	30 mg twice daily
1.30 – 1.49 m^2	35 mg twice daily
1.50 – 1.69 m^2	40 mg twice daily
1.70 – 1.89 m^2	45 mg twice daily
≥1.90 m^2	50 mg twice daily

a. The recommended dosage for patients with a BSA less than 0.40 m^2 has not been established.
b. For patients with a BSA 0.70 m^2 and above, dosing recommendations for the Granules are in line with the dosing recommendations for capsules.
c. If a patient is unable to transition to capsules when they attain a BSA ≥1.29 m^2 patients can continue to receive the granules at the dose shown in Table 1.

Dose Adjustments
Interruption and/ordose reduction or permanent discontinuation of KOSELUGO / KOSELUGO Granules may be required based on individual safety and tolerability (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

Recommended dose reductions are given in **Table 3** and **Table 4**.

Table 3 - KOSELUGO capsules Recommended Dose Reductions for Adverse Reactions

Body Surface Area (BSA)	Initial dose (mg/dose)	First dose reduction (mg/dose)		Second dose reduction[a] (mg/dose)	
		Morning	Evening	Morning	Evening
0.55 – 0.69 m^2	20 in the morning; 10 in the evening	10	10	10 mg once daily	
0.70 – 0.89 m^2	20 twice daily	20	10	10	10
0.90 – 1.09 m^2	25 twice daily	25	10	10	10
1.10 – 1.29 m^2	30 twice daily	25	20	20	10
1.30 – 1.49 m^2	35 twice daily	25	25	25	10
1.50 – 1.69 m^2	40 twice daily	30	30	25	20
1.70 – 1.89 m^2	45 twice daily	35	30	25	20
≥1.90 m^2	50 twice daily	35	35	25	25

[a] Permanently discontinue KOSELUGO in patients unable to tolerate KOSELUGO after two dose reductions

Table 4 - KOSELUGO Granules Recommended Dose Reductions for Adverse Reactions

Body surface area (BSA)	Initial dose (mg/twice daily)	First dose reduction (mg/ dose)		Second dose reduction[a] (mg/dose)	
		Morning	Evening	Morning	Evening
0.40 – 0.49 m^2	10	7.5	7.5	5	5
0.50 – 0.59 m^2	12.5	10	10	7.5	7.5
0.60 – 0.69 m^2	15.0	12.5	12.5	10	10
0.70 – 0.89 m^2	20	15	15	12.5	12.5
0.90 – 1.09 m^2	25	20	20	15	15
1.10 – 1.29[b] m^2	30	22.5	22.5	15	15
1.30 – 1.49 m^2	35	25	25	25	10
1.50 – 1.69 m^2	40	30	30	25	20
1.70 – 1.89 m^2	45	35	30	25	20
≥1.90 m^2	50	35	35	25	25

[a.] Permanently discontinue KOSELUGO Granules in patients unable to tolerate KOSELUGO after two dose reductions.

[b.] If a patient is unable to transition to capsules when they attain a BSA ≥ 1.29 m^2, patients can continue to receive the granules at the dose shown in **Table 1**, and dose modifications in **Table 3**.

Table 5 - Recommended KOSELUGO / KOSELUGO Granules Dosage Modifications for Adverse Reactions

CTCAE Grade [a]	Recommended Dose Modification
Grade 1 or 2 (tolerable)	Continue treatment and monitor as clinically indicated
Grade 2 (intolerable) or **Grade 3**	Interrupt treatment until toxicity is grade 0 or 1 and reduce by one dose level when resuming therapy (see **Table 3** and **Table 4**)
Grade 4	Interrupt treatment until toxicity is grade 0 or 1 and reduce by one dose level when resuming therapy (see **Table 3** and **Table 4**). Consider discontinuation.

[a] Common Terminology Criteria for Adverse Events (CTCAE)

Dose modification advice for left ventricular ejection fraction (LVEF) reduction

In cases of asymptomatic LVEF reduction by ≥10% from baseline value and less than the institutional lower level of normal (LLN), KOSELUGO / KOSELUGO Granules treatment should be interrupted until resolution. Once resolved, reduce KOSELUGO by one dose level when resuming therapy (see **Table 3**).

In patients who develop symptomatic LVEF reduction or a grade 3 or 4 LVEF reduction, KOSELUGO / KOSELUGO Granules should be discontinued and a prompt cardiology referral should be carried out (see 7 WARNINGS AND PRECAUTIONS).

Dose modification advice for retinal toxicities
KOSELUGO / KOSELUGO Granules treatment should be interrupted in patients diagnosed with retinal pigment epithelial detachment (RPED) or central serous retinopathy (CSR) with reduced visual acuity until resolution; reduce KOSELUGO / KOSELUGO Granules by one dose level when resuming therapy (see **Table 2**). In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmic assessment should be conducted every 3 weeks until resolution. In patients who are diagnosed with retinal vein occlusion (RVO), treatment with KOSELUGO / KOSELUGO Granules should be permanently discontinued (see 7 WARNINGS AND PRECAUTIONS).

Dose adjustments for co-administration with CYP3A4 and CYP2C19 inhibitors

Concomitant use of strong or moderate CYP3A4 or CYP2C19 inhibitors is not recommended and alternative agents should be considered. If a strong or moderate CYP3A4 or CYP2C19 inhibitor must be co-administered, the recommended KOSELUGO / KOSELUGO Granules dose reduction is as follows: If a patient is currently taking 25 mg/m^2 twice daily, dose reduce to 20 mg/m^2 twice daily (see **Table 6** and **Table 7**). If a patient is currently taking 20 mg/m^2 twice daily, dose reduce to 15 mg/m^2 twice daily (see **Table 6** and **Table 7** and 9 DRUG INTERACTIONS).

Table 6 - Recommended Capsules dosage to achieve 20 mg/m^2 or 15 mg/m^2 twice daily dose level

Body Surface Area	20 mg/m^2 twice daily (mg/dose)		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

Table 7 - Recommended Granules dosage to achieve 20 mg/m^2 or 15 mg/m^2 twice daily dose level

Body Surface Area	20 mg/m^2 twice daily (mg/dose)		15 mg/m^2 twice daily (mg/dose)	
	Morning	Evening	Morning	Evening
0.40 – 0.49 m^2	7.5	7.5	7.5	5
0.50 – 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

Dose modifications for special patient populations

Renal impairment

Based on clinical studies no dose adjustment is recommended in patients with mild, moderate, or severe renal impairment or those with End Stage Renal Disease (ESRD) (see 10.3 Pharmacokinetics).

Hepatic impairment

Based on clinical studies, no dose adjustment is recommended in patients with mild hepatic impairment. The starting dose should be reduced in patients with moderate hepatic impairment to 20 mg/m^2 BSA, twice daily (see **Table 6** and **Table 7**). KOSELUGO / KOSELUGO Granules are not recommended for use in patients with severe hepatic impairment (see 10.3 Pharmacokinetics).

Ethnicity

Increased systemic exposure has been seen in Asian subjects, although there is considerable overlap with Western subjects when corrected for body weight. No specific adjustment to the starting dose is recommended for Asian patients, however, these patients should be closely monitored for adverse events (see 10.3 Pharmacokinetics).

4.4 Administration

KOSELUGO is available in two dosage forms: KOSELUGO capsules and KOSELUGO Granules. Prescribe KOSELUGO Granules for pediatric patients aged 1 year and older who have difficulty swallowing whole capsules.

Capsules

KOSELUGO capsules can be taken with or without food (see 10 CLINICAL PHARMACOLOGY).

Swallow KOSELUGO capsules whole with water.
Do not chew, dissolve or open capsules.

Granules

KOSELUGO Granules must be administered by carefully opening the capsules and sprinkling the entire contents on a small amount of smooth yogurt or fruit puree containing the following fruits: apple, banana, pear or strawberry. This medicinal product dispensed on or mixed with food must be swallowed within 30 minutes and must not be stored for future use. If a dose has been partially consumed within 30 minutes of preparation, the remainder of the dose should be discarded and a new dose should not be prepared. The KOSELUGO Granules should be free-flowing. Granules that are clumped or stuck inside the capsule shell should not be used. The empty capsule shells must be discarded after use.

The capsule shells of KOSELUGO Granules must not be swallowed, chewed, or dissolved. KOSELUGO Granules must not be mixed in water, milk, vegetable puree, grapefruit or any juice, fruit puree or jam containing Seville orange.

4.5 Missed Dose

If a dose of KOSELUGO / KOSELUGO Granules is missed, it should only be taken if it is more than 6 hours until the next scheduled dose.

5 OVERDOSAGE

There is no specific treatment for overdose. If overdose occurs, patients should be treated supportively with appropriate monitoring as necessary. Dialysis is ineffective in the treatment of overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 8 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Capsule, 10 mg selumetinib (as selumetinib sulfate)	Ammonium hydroxide 28%, Carnauba wax, Carrageenan, Hypromellose, Iron oxide black, Potassium chloride, Propylene glycol, Purified water, Shellac glaze, Titanium dioxide, Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol 1000 succinate)
oral	Capsule, 25 mg selumetinib (as selumetinib sulfate)	Carnauba wax and/or Corn starch, Carrageenan, FD&C Blue 2, FD&C blue 2 aluminum lake, Ferric oxide red, Ferric oxide yellow, Glyceryl monooleate, Hypromellose, Potassium chloride, Purified water, Titanium dioxide, Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol 1000 succinate), White shellac
oral	Granules, 5 mg selumetinib (as selumetinib sulfate)	Glyceryl dibehenate, Hypromellose acetate succinate, Stearic acid and Stearoyl polyoxylglycerides. The capsule shells (not to be consumed) contain Ferric oxide yellow, Hypromellose, Pharmaceutical ink and Titanium dioxide.
oral	Granules, 7.5 mg selumetinib (as	Glyceryl dibehenate, Hypromellose acetate succinate, Stearic acid and Stearoyl polyoxylglycerides. The capsule shells (not

	selumetinib sulfate)	to be consumed) contain Ferric oxide red, Hypromellose, Pharmaceutical ink and Titanium dioxide.

KOSELUGO / KOSELUGO Granules are sold in 60 capsules HDPE plastic bottles with child-resistant closure and silica gel desiccant.

Capsules, hard (capsules)
KOSELUGO 10 mg hard capsule
White to off-white, opaque, size 4 hard capsule, banded and marked with “SEL 10” in black ink.

KOSELUGO 25 mg hard capsule
Blue, opaque, size 4 hard capsule, banded and marked with “SEL 25” in black ink.

Granules
KOSELUGO Granules 5 mg (granules in capsule for opening)
Size 0 hard capsule with a yellow cap and a white body. The cap is printed with ‘sel 5’ and the body is printed with a sprinkle capsule image indicating opening.

KOSELUGO Granules 7.5 mg (granules in capsule for opening)
Size 0 capsule with a pink cap and a white body. The cap is printed with ‘sel 7.5’ and the body is printed with a sprinkle capsule image indicating opening.

7 WARNINGS AND PRECAUTIONS

General
Vitamin E Supplementation (only applicable to KOSELUGO capsules)
Advise patients not to take any supplemental vitamin E.

KOSELUGO 10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). KOSELUGO 25 mg capsules contain 36 mg vitamin E as TPGS. High doses of vitamin E may increase the risk of bleeding in patients taking concomitant anticoagulant or antiplatelet medications (e.g., warfarin or aspirin). Anticoagulant assessments, including international normalized ratio or prothrombin time, should be conducted more frequently to detect when dose adjustments of the anticoagulant or antiplatelet medication are warranted (see Monitoring and Laboratory Tests, 9 DRUG INTERACTIONS).

Cardiovascular
Cardiomyopathy
KOSELUGO / KOSELUGO Granules have not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 55% prior to treatment (lower limit of normal, LLN) (see 14.1 Clinical Trials by Indication). Prior to starting KOSELUGO treatment, patients should have an ejection fraction above the institutional LLN.

Pediatric subjects: Cardiomyopathy, defined as reduction in left ventricular ejection fraction (LVEF) ≥ 10% below baseline, occurred in 28% of 74 pediatric patients with NF1. 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. The median time to first onset of AEs in the sub-group term of ejection

fraction decreased events was 232.0 days, with a median duration of 252 days. Decreased LVEF resolved in 81% of these patients.

Adult subjects: In the NF1-PN adult patients (N = 137), left ventricular ejection fraction (LVEF) decrease occurred in 10 (7%) patients; among them, in 1 (0.7%) patient, the reported ADR was grade 3. In 2 (1.5%) patients, LVEF decrease led to dose interruption. LVEF decrease resolved in 7 of the 10 (patients. The median time to first onset of maximum CTCAE grade LVEF reduction was 169 days (approximately 6 months) [median duration 112.5 days (approximately 4 months)] [see 8 ADVERSE REACTIONS].

Left ventricular dysfunction or decreased LVEF resulting in permanent discontinuation of KOSELUGO occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO. Decreased LVEF resulting in permanent discontinuation of KOSELUGO occurred in a pediatric population with NF1 in an expanded access program.

LVEF should be evaluated before initiation of treatment to establish baseline values and at approximately 3-month intervals, or more frequently as clinically indicated, during treatment (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests). Reduction in LVEF can be managed using treatment interruption, dose reduction or treatment discontinuation (see 4.2 Recommended Dose and Dosage Adjustment).

Driving and Operating Machinery
No studies on the effects on the ability to drive and use machines have been performed. KOSELUGO may have a minor influence on the ability to drive and use machines. Fatigue, asthenia and visual disturbances have been reported during treatment with KOSELUGO and patients who experience these symptoms should observe caution when driving or using potentially dangerous machines.

Gastrointestinal

Pediatric subjects: Diarrhea occurred in 81% 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 20 days and the median duration was 2 days.

Adult subjects: In the NF1-PN adult patients (N = 137), gastrointestinal toxicities, primarily including diarrhea (41 patients, 30%), vomiting (27 patients, 20%), nausea (23 patients, 17%), stomatitis (19 patients, 14%), and constipation (13 patients, 10%) occurred in patients who received KOSELUGO. Most of these events were Grade 1 or 2. In 1 patient (0.7%), grade 3 event was reported for stomatitis. Dose interruption was required in 2 patients (1.5%) each with nausea and vomiting, and in 1 patient (0.7%) each with diarrhea and stomatitis. Dose reduction occurred in 1 patient (0.7%) each with an ADR of nausea and stomatitis. One patient reported an event of nausea that led to treatment discontinuation. The median time to first onset of maximum CTCAE grade diarrhea was 57 days and the median duration was 7 days [see 8 ADVERSE REACTIONS].

Colitis occurred in an unapproved population of pediatric patients with multiple tumour types who received KOSELUGO as a single agent. In addition, serious gastrointestinal toxicities, including perforation, colitis, ileus and intestinal obstruction occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO as a single

agent or in combination with other anti-cancer agents.

Advise patients to start an anti-diarrheal agent (e.g., loperamide) immediately after the first episode of unformed, loose stool and to increase fluid intake during diarrhea episodes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION).

Increased Creatine Phosphokinase

Pediatric subjects: Increased creatine phosphokinase (CPK) occurred in 77% 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.

Adult subjects: In the NF1-PN adult patients (N = 137), increased creatine phosphokinase (CPK) occurred in patients who received KOSELUGO and led to dose interruption in 6 patients and dose reduction in 3 patients. Forty-two patients (30.7%) had maximum grade of 1 or 2. A maximum grade 3 events occurred in 5 (3.6%) patients, and grade 4 events occurred in 4 (2.9%) patients. The median time to first onset of maximum CTCAE grade blood CPK increase was 103 days (approximately 3 months), and the median duration of maximum grade events was 122 days (approximately 4 months). Increased CPK concurrent with myalgia occurred in some patients (see 8 ADVERSE REACTIONS).

Rhabdomyolysis occurred in an unapproved adult population who received KOSELUGO as a single agent.

Withhold, reduce dose, or permanently discontinue KOSELUGO / KOSELUGO Granules based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION).

Serum CPK level should be evaluated before initiation of treatment, periodically during the treatment and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests).

Monitoring and Laboratory tests

- Cardiac function: Assess left ventricular ejection fraction (LVEF) by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. In patients who interrupt KOSELUGO / KOSELUGO Granules 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 (see 7 WARNINGS AND PRECAUTIONS).

- Ophthalmic assessments: Conduct comprehensive ophthalmic assessments prior to initiating KOSELUGO / KOSELUGO Granules, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue KOSELUGO / KOSELUGO Granules in patients with retinal vein occlusion (RVO). Withhold KOSELUGO / KOSELUGO Granules in patients with retinal pigment epithelial detachment (RPED), follow up with optical coherence tomography assessments every 3 weeks until resolution, and resume KOSELUGO KOSELUGO Granules at a reduced dose (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND

ADMINISTRATION)

- Anticoagulant assessment: In patients taking a vitamin-K antagonist, perform anticoagulant assessments, including INR or prothrombin time, more frequently and adjust the dose of vitamin K antagonists or anti-platelet agents as appropriate (see 7 WARNINGS AND PRECAUTIONS).

- Creatine phosphokinase (CPK): 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 / KOSELUGO Granules based on severity of adverse reaction (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

- Skin rashes: Monitor for severe skin rashes (see 7 WARNINGS AND PRECAUTIONS). Withhold, reduce dose, or permanently discontinue KOSELUGO / KOSELUGO Granules based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION).

Ophthalmologic

Visual Impairment

Pediatric subjects: Advise patients to report any new visual disturbances. Adverse events of blurred vision, photophobia, cataracts, and ocular hypertension occurred in 20% of 74 pediatric patients receiving KOSELUGO. Blurred vision resulted in dose interruption in 2.7% of patients.

Adult subjects: In the NF1-PN adult patients (N = 137), ocular toxicity, mainly blurred vision, was reported in 5 (4%) patients who received KOSELUGO and led to dose interruption in 1 (0.7%) patient. All events were managed without dose reduction. Ocular toxicity resolved in all these patients (see 8 ADVERSE REACTIONS).

Serious ocular toxicities including retinal pigment epithelial detachment (RPED), central serous retinopathy (CSR) and retinal vein occlusion (RVO) have been observed in an unapproved population of adult patients with multiple tumour types, receiving treatment with KOSELUGO monotherapy or in combination with other anti-cancer agents. RPED occurred in the pediatric population during treatment with single agent KOSELUGO and resulted in permanent discontinuation (see 8 ADVERSE REACTIONS).

An ophthalmological evaluation prior to treatment initiation and at any time a patient reports new visual disturbances should be conducted (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory tests). In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmic assessment should be conducted every 3 weeks until resolution. If RPED or CSR is diagnosed and visual acuity is affected KOSELUGO Capsules / KOSELUGO Granules therapy should be interrupted and the dose reduced when treatment is resumed (see **Table 3** and **Table 4**). If RVO is diagnosed, treatment with KOSELUGO / KOSELUGO Granules should be permanently discontinued (see 4 DOSAGE AND ADMINISTRATION).

Reproductive Health Female and Male Potential

Fertility

There are no data on the effect of KOSELUGO on human fertility.

KOSELUGO had no impact on fertility and mating performance in male (20 mg/kg twice daily) and female (2.5 mg/kg twice daily) mice, at exposures up to 32-times or 5-times, respectively, the human exposure (AUC) at the clinical dose of 25 mg/m^2 twice a day (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Teratogenic Risk: Embryo-Fetal Toxicity
A reduction in embryonic survival was observed in animal reproduction studies when selumetinib was administered at doses ≥ 12.5 mg/kg twice a day (approximately 5 times the human exposure by AUC) to female pregnant mice during organogenesis. Selumetinib also increased the incidence of malformations in pups even at sub-therapeutic exposures (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations and 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Skin
Pediatric subjects: Rash occurred in 93% of 74 pediatric patients who received KOSELUGO in SPRINT. The most frequent rashes included dermatitis acneiform (61%), maculopapular rash (50%), and eczema (26%). Grade 3 rash occurred in 9% of patients. Rash resulted in dose interruption in 14% of patients and dose reduction in 4% of patients.

Adult subjects: In the NF1-PN adult patients (N = 137), rashes (acneiform), mainly dermatitis acneiform, occurred in 73 (52%) patients who received KOSELUGO and led to dose interruption (2 patients, 1.5%), dose reduction (2 patients, 1.5%) and permanent discontinuation in 2 patients (1.5%). Seventy-one (52%) patients reported ADRs with maximum grade 1 or 2. Grade 3 events were reported in 2 (1.5 %) patients (see 8 ADVERSE REACTIONS).

Pediatric subjects: Paronychia was reported in 57% of patients with Grade ≥3 events reported in 13.5% of patients. Paronychia resulted in dose interruption in 16 (21.6%) patients, and dose reduction in 8 (10.8%) patients, with discontinuation of KOSELUGO reported in 1 (1.4%) patient.

Adult subjects: In the NF1-PN adult patients (N = 137), paronychia occurred in patients who received KOSELUGO and led to dose interruption (1 patient, 0.7%), dose reduction (3 patients, 2.2%). Paronychia did not lead to dose discontinuation in any of the patients. Nineteen (14%) patients had a maximum CTCAE grade of 1 or 2. Grade 3 events occurred in 4 (3%) patients. (see 8 ADVERSE REACTIONS).

Other skin toxicities, including severe palmar-plantar erythrodysesthesia syndrome, occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO as a single agent or in combination with other anti-cancer agents.

7.1 Special Populations

7.1.1 Pregnancy

Women of childbearing potential should be advised to avoid becoming pregnant while receiving KOSELUGO. Both male and female patients (of reproductive potential) should be advised to use effective contraception during and for at least 1 week after completion of treatment with KOSELUGO.

KOSELUGO is not recommended in women of child-bearing potential not using contraception.

There is a very limited experience on the use of KOSELUGO in pregnant women. Reproduction studies in mice have shown that administration of KOSELUGO during organogenesis at exposures > 5 times the human exposure (based on AUC) at the clinical dose (25 mg/m^2 twice daily), caused reduced fetal weight, adverse structural defects, and effects on embryo-fetal survival in the absence of apparent maternal toxicity. Administration of KOSELUGO to pregnant mice increased the incidence of malformations in pups even at low doses, equivalent to ~0.6 times the human C_{max} at the 25 mg/m^2 twice daily clinical dose (see Reproductive and Developmental Toxicology).

KOSELUGO / KOSELUGO Granules are not recommended during pregnancy. If a female patient or a female partner of a male patient receiving KOSELUGO becomes pregnant, she should be apprised of the potential hazard to the fetus.

It is recommended that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment.

In KOMET, a first trimester spontaneous abortion was reported in a patient receiving KOSELUGO.

7.1.2 Breast-feeding

It is not known whether KOSELUGO, or its metabolites, are excreted in human milk or their effects on the breastfed child or milk production. KOSELUGO and its active metabolite were found in the milk of lactating mice (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Pre- and postnatal development). 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.

7.1.3 Pediatrics

Pediatrics (0 – 2 years of age): Based on the data submitted and reviewed by Health Canada, the safety and effectiveness of KOSELUGO / KOSELUGO Granules have not been established in pediatric patients younger than 1 year of age; Therefore, Health Canada has not authorized an indication for use in pediatric population younger than 1 year of age.

In a general toxicology study conducted with rats some animals showed growth plate dysplasia at exposures > 60 times the human exposure (based on AUC) (see 16 NON-CLINICAL TOXICOLOGY, General Toxicology).

7.1.4 Geriatrics

Geriatrics (≥65): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in patients 65 years of age or older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of KOSELUGO monotherapy has been evaluated in a combined safety population of 74 pediatric patients (20-30 mg/m^2 twice daily) and 13 7 adult patients (25 mg/ m^2 twice daily) with NF1 who had inoperable PN that was causing significant morbidity and 347 adult patients (75-100 mg/m^2 twice daily) with multiple tumour types.

Pediatric

The median total duration of KOSELUGO treatment in pediatric patients with NF1 PN was 55 months (range: <1 – 97 months), 61% of patients were exposed to KOSELUGO treatment for >48 months and 16% for >72 months. The safety database is supported by serious adverse event reports from 291 pediatric patients enrolled in externally sponsored studies across a range of indications.

In the Phase II Stratum 1 pivotal study (SPRINT), 50 pediatric patients with NF1 PN were treated with KOSELUGO 25 mg/m^2 twice daily (see 14.1 Clinical Trials by Indication). The most common adverse reactions of any grade (incidence ≥20%) were vomiting, blood creatine phosphokinase increased, diarrhea, nausea, dry skin, pyrexia, asthenic events, dermatitis acneiform, paronychia, rashes (non-acneiform), hypoalbuminemia, stomatitis, aspartate aminotransferase increased, hemoglobin decreased, ALT increased, AST increased, hair changes, blood creatinine increased, abdominal pain, constipation, musculoskeletal pain, edema, headache, hematuria, proteinuria, decreased appetite, sinus tachycardia, epistaxis, pruritis, hypertension and ejection fraction decreased.

Dose interruptions and reductions due to adverse events were reported in 80% and 24% of patients, respectively. The adverse events leading to dose modification of KOSELUGO in ≥ 5% of patients were vomiting (12 [24.0%]), paronychia (7 [14.0%]), diarrhea (6 [12.0%]), nausea (5 [10.0%], abdominal pain (4 [8.0%]), skin infection (4 [8.0%]), influenza-like illness (7 [14.0%]), pyrexia (4 [8.0%]) and weight gain (3 [6.0%]).

Permanent discontinuation due to adverse events was reported in 12% of the patients and included events of increased creatinine, increased weight, diarrhea, paronychia, malignant peripheral nerve sheath tumour, acute kidney injury and skin ulcer. Serious adverse reactions that occurred in 2 or more patients were anemia, hypoxia and diarrhea.

In the Pediatric pool of 74 patients, the most commonly reported SAEs by preferred term (PT) were abdominal pain, anemia, blood creatine phosphokinase increased, dehydration, diarrhea, fracture, hypoxia, pyrexia and skin infection, (occurred in 2 [2.7%] patients each).

Adult

The median total duration of KOSELUGO treatment in adult patients with NF1 PN was 12 months with a range of 10 days to approximately 31 months.

In the Phase III pivotal study (KOMET), 137 adult patients with NF1 PN were treated with KOSELUGO 25 mg/m^2 twice daily (see 14.1 Clinical Trials by Indication).

The most common adverse reactions (≥ 40%) were rash (all) and rash (acneiform).

Serious adverse reactions occurred in 13% of patients who received KOSELUGO. Cellulitis as a serious adverse reaction, occurred in 2 or more patients.

Dosage interruptions and dose reductions due to adverse reactions occurred in 31% and 12% of patients who received KOSELUGO, respectively. Adverse reactions requiring a dosage reduction in 2 or more patients were paronychia, increased CPK, alopecia, dermatitis acneiform, increased ALT, and increased AST. Adverse reactions requiring a dosage interruption in 2 or

more patients were increased CPK, cellulitis, decreased appetite, headache, abdominal pain, nausea, vomiting, dermatitis acneiform, pyrexia, and ejection fraction decreased.

Permanent discontinuation due to an adverse reaction occurred in 7% of patients who received KOSELUGO. Adverse reactions resulting in permanent discontinuation of KOSELUGO included cellulitis, nausea, dermatitis acneiform, and nail disorder.

In addition, selumetinib safety for the granule formulation was also evaluated in 36 pediatric patients (dose equivalent to 25 mg/m^2 twice daily, granules) with NF1 and symptomatic inoperable PN from the Phase I/II SPRINKLE study (D1346C00004).

In the SPRINKLE study, the median total duration of selumetinib treatment was approximately 11 months (range: 3 – 25 months). Thirty-six pediatric patients were treated with selumetinib equivalent to 25 mg/m^2 twice daily. The most common adverse reactions of any grade (incidence ≥ 40%) were pyrexia and dry skin (47% patients each); and paronychia (44%). Adverse events leading to dose interruptions were reported in 30.6% of patients, while no patients had AEs leading to dose reductions. A total of 22.2% patients had adverse reactions leading to dose modification of selumetinib (dose interruptions). The adverse reactions leading to dose modification (incidence ≥ 5%) were vomiting and pyrexia (11.1% patients each) and diarrhea (5.6%). No patient had adverse reactions that led to treatment discontinuation.

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

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of KOSELUGO was evaluated in selumetinib pediatric and adult studies in NF1-PN patients (14.1 Clinical Trials by Indication).

Pediatrics 2-18 years of Age (SPRINT Phase II Stratum 1)

Eligible pediatric patients were 2-18 years of age with NF1 who had inoperable PN that was causing significant morbidity. Patients were excluded for abnormal LVEF, uncontrolled hypertension (blood pressure ≥ the 95th percentile for age, height, and sex), any current or past history of RVO or RPED, intraocular pressure > 21 mmHg (or upper limit of normal adjusted by age), uncontrolled glaucoma, and inability to swallow whole capsules. All patients (N=50) received KOSELUGO 25 mg/m^2 orally twice daily. Among these patients, 88% were exposed for 12 months or longer and 56% were exposed for more than 4 years.

Table 9 Table 9 - Adverse Reactions Reported in Patients Treated with KOSELUGO in SPRINT (Phase II; Stratum 1) presents the adverse reactions identified in the SPRINT Phase II Stratum.

Table 9 - Adverse Reactions Reported in Patients Treated with KOSELUGO in SPRINT (Phase II; Stratum 1)

MedDRA System Organ Class MedDRA Term	**All CTCAE Grades** **N=50** **n (%)**	**CTCAE Grade ≥ 3** [a] **N=50** **n (%)**
Cardiac Disorders		
Decreased Ejection Fraction	13 (26.0%)	0 (0%)
Sinus Tachycardia	11 (22.0%)	0 (0%)
Eye Disorders		
Vision Blurred	7 (14.0%)	0 (0%)
Gastrointestinal Disorders		
Vomiting	43 (86.0%)	4 (8.0%)
Abdominal Pain	38 (76.0%)	0 (0%)
Diarrhea	37 (74.0%)	8 (16.0%)
Nausea	36 (72.0%)	2 (4.0%)
Stomatitis	26 (52.0%)	0 (0%)
Dry Mouth	2 (4.0%)	0 (0%)
Skin and Subcutaneous Tissue Disorders		
Dry Skin	34 (68.0%)	1 (2.0%)
Dermatitis Acneiform [b]	28 (56.0%)	3 (6.0%)
Paronychia	28 (56.0%)	4 (8.0%)
Pruritis	26 (52.0%)	0 (0%)
Dermatitis	18 (36.0%)	2 (4.0%)
Rashes (non-acneiform) [b]	27 (54.0%)	1 (2.0%)
Hair Changes	16 (32.0%)	0 (0%)
General Disorders		
Pyrexia	31 (62.0%)	4 (8.0%)
Asthenic Events [b]	28 (56.0%)	0 (0%)
Peripheral edema [b]	17 (34.0%)	0 (0%)
Facial edema [b]	3 (6.0%)	0 (0%)
Infections		
Skin Infection	11 (22.0%)	2 (4.0%)
Investigations		

MedDRA System Organ Class MedDRA Term	**All CTCAE Grades** **N=50** **n (%)**	**CTCAE Grade ≥ 3** [a] **N=50** **n (%)**
Blood CPK increased	39 (78.0%)	3 (6.0%)
Hemoglobin decreased [b]	27 (54.0%)	2 (4.0%)
Hypoalbuminemia	26 (52.0%)	0 (0%)
AST increased	23 (46.0%)	1 (2.0%)
ALT increased	19 (38.0%)	2 (4.0%)
Blood creatinine increased	17 (34.0%)	1 (2.0%)
Increased blood pressure [b]	10 (20.0%)	0 (0%)
Nervous System Disorders		
Headache	28 (56.0%)	1 (2.0%)
Renal and Urinary System Disorders		
Hematuria	15 (30.0%)	1 (2.0%)
Respiratory, Thoracic & Mediastinal Disorders		
Epistaxis	16 (32.0%)	0 (0%)
Dyspnea [b]	4 (8.0%)	0 (0%)

[a] Per the National Cancer Institute CTCAE version 4.03, all events were CTCAE grade 3, except for one CTCAE grade 4 event of blood CPK increased and one CTCAE grade 4 event of blood creatinine increased. There were no deaths.

[b] ADRs based on grouping of individual Preferred Terms (PT):
Rashes (non-acneiform): Rash maculo-papular, Rash papular, Rash, Rash erythematous, Rash macular, Rash pruritis
Hair changes: Alopecia, Hair colour change
Asthenic events: Fatigue, Asthenia
Peripheral edema: Edema peripheral, Edema, Localized edema, Peripheral swelling
Facial edema: Periorbital edema, Face edema
Hemoglobin decreased: Anemia, Hemoglobin decreased
Dyspnea: Dyspnea exertional, Dyspnea, Dyspnea at rest
Increased blood pressure: Hypertension, Blood pressure increased
CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Hair changes

In SPRINT, sixteen (32%) of patients experienced hair changes (reported as hair lightening [preferred term (PT): hair colour changes] and hair thinning [PT: alopecia]). In the pediatric pool 13 of 74 (18%) patients experienced both events during treatment, 22 (30%) experienced at least one adverse event of alopecia and 20 (27%) experienced at least one event of hair colour change. All cases were grade 1 and did not require dose interruption or dose reduction.

Adults ≥ 18 years of Age (KOMET Phase III)

Eligible patients were 18 years of age or older with NF1 who had symptomatic, inoperable PN that could not be completely surgically removed without a risk of substantial morbidity. Patients were excluded for abnormal LVEF, uncontrolled hypertension, any current or past history of RVO or RPED/CSR, intraocular pressure > 21 mmHg (or upper limit of normal adjusted by age), uncontrolled glaucoma, and inability to swallow whole capsules.

Table 10 presents the adverse reactions in the KOMET study. The 12 cycle (48 weeks) randomization period for KOSELUGO versus placebo was followed by a single arm treatment period where all patients received KOSELUGO (66 patients on placebo crossed over to KOSELUGO at end of the randomized period). No new adverse reactions were identified during the open-label period.

Table 10 - Adverse Reactions ≥ 5% in Patients Who Received KOSELUGO (N=137) and at a greater frequency than in Placebo -Treated Patients in KOMET

Adverse Reactions	Randomized to KOSELUGO* (n=71)		Randomized to Placebo* (n=74)		All Receiving KOSELUGO† (Overall N=137)	
	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)
Skin and Subcutaneous Tissue						
Rash (all)[1]	82	3	20	0	75	2
Rash acneiform[2]	66	3	11	0	53	2
Hair changes[3]	18	0	11	0	18	0
Paronychia[4]	13	3	4	0	17	3
Dry skin	18	0	5	0	13	0
Gastrointestinal						
Diarrhea	42	0	12	0	30	0
Vomiting	25	0	8	0	20	0
Nausea	25	0	16	0	17	0
Stomatitis[5]	18	0	5	0	14	1
Abdominal pain[6]	11	3	8	0	10	2
Constipation	10	0	1	0	10	0
General						
Edema[7]	21	0	1	0	16	0
Fatigue[8]	24	0	18	0	15	0
Pyrexia	7	0	4	0	5	1
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[9]	14	0	11	0	12	0
Cardiac System						
Ejection fraction decreased	7	1	3	0	7	1

Adverse Reactions	Randomized to KOSELUGO* (n=71)		Randomized to Placebo* (n=74)		All Receiving KOSELUGO† (Overall N=137)	
	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)
Infections						
Skin infection[10]	6	3	1	0	6	2

* ADRs of patients during the 12 Cycle (48 weeks) randomization period.

† Includes ADRs from all patients after they have commenced KOSELUGO, including patients randomized to placebo who crossed over to KOSELUGO treatment.

[1] Rash (all): acne, dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, urticaria, rash macular, and rash papular.

[2] Rash acneiform: acne and dermatitis acneiform.

[3] Hair changes: alopecia and hair color change.

[4] Paronychia: paronychia and nail infection.

[5] Stomatitis: stomatitis, mouth ulceration, gingival swelling, and aphthous ulcer.

[6] Abdominal pain: abdominal pain and upper abdominal pain.

[7] Edema: localized edema, edema, edema peripheral, and peripheral swelling.

[8] Fatigue: asthenia, fatigue, and malaise.

[9] Musculoskeletal pain: back pain, musculoskeletal pain, neck pain, and pain in extremity.

[10] Skin infection: abscess, cellulitis, impetigo, skin infection, staphylococcal skin infection.

Adverse Drug Reactions in Other Clinical trials

Adverse drug reactions reported in adult patients with multiple tumour types (N=347) included Retinal Pigment Epithelial Detachment (RPED)/Central Serous Retinopathy (CSR) (2 [0.6%]; Detachment of macular retinal pigment epithelium, Chorioretinopathy) and Retinal Vein Occlusion (RVO) (1 [0.3%]; Retinal vein occlusion, Retinal vein thrombosis, Retinal vascular disorder).

In addition, a single event of RPED was reported in a pediatric patient receiving KOSELUGO monotherapy (25 mg/m^2 twice daily) for a not approved indication in an externally sponsored pediatric study.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 11 presents the laboratory abnormalities in SPRINT Phase II Stratum 1.

Table 11 - Select Laboratory Abnormalities (≥ 15%) Worsening from Baseline in Patients Who Received KOSELUGO in SPRINT (Phase II; Stratum 1)

Laboratory Abnormality	KOSELUGO	
	All Grades (%) [a]	Grade ≥ 3 (%)
Chemistry		
Increased creatine phosphokinase (CPK)	79	7[b]
Decreased albumin	53	0

Laboratory Abnormality	KOSELUGO	
	All Grades (%) [a]	Grade ≥ 3 (%)
Increased aspartate aminotransferase (AST)	43	2
Increased alanine aminotransferase (ALT)	44	4
Increased lipase	39	12
Increased potassium	29	4[b]
Decreased potassium	22	4[b]
Increased alkaline phosphatase	22	0
Increased creatinine	22	2[b]
Increased amylase	26	0
Decreased sodium	20	0
Increased sodium	16	0
Hematology		
Decreased hemoglobin	51	4
Decreased neutrophils	40	4
Decreased lymphocytes	27	2

[a] 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. Change from baseline was derived from laboratory data collected at protocol-scheduled assessments.

[b] Includes one Grade 4 increased CPK one Grade 4 increased creatinine, one Grade 4 decreased potassium and one Grade 4 increased potassium.

CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 12 presents the laboratory abnormalities in the KOMET study.

Table 12 - Selected Laboratory Abnormalities (≥ 15%) Worsening from Baseline in Patients Who Received KOSELUGO or Placebo in KOMET

Laboratory Abnormalities	Randomized to KOSELUGO* (n=71)		Randomized to Placebo* (n=74)		All Receiving KOSELUGO† (Overall N=137)	
	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)
Chemistry						
Increased creatinine	89	0	89	3	82	0
Increase creatine phosphokinase	70	7	15	1.4	61	7
Increased aspartate aminotransferase (AST)	48	3	12	0	41	2
Increased alanine aminotransferase (ALT)	39	4.3	14	0	37	2
Decreased albumin	24	1.4	6	0	21	1

Increased alkaline phosphatase (ALP)	17	1.4	7	0	‡	‡
Increased amylase	17	1.4	5	0	15	2
Increased gamma glutamyl transferase (GGT)	17	1.4	10	0	‡	‡
Decreased magnesium	16	0	5	0	‡	‡
Hematology						
Decreased hemoglobin	24	0	14	0	22	1
Decreased lymphocytes	16	2	15	0	‡	‡

* Lab abnormalities of patients during the 12 Cycle (48 weeks) randomization period.
† Includes lab abnormalities from all patients after they have commenced KOSELUGO, including patients randomized to placebo who crossed over to KOSELUGO treatment.
‡ Data did not meet the ≥ 15% threshold.

9 DRUG INTERACTIONS

9.2 Overview

Interaction studies have only been performed in healthy adults (aged ≥18 years). Strong CYP3A4 or CYP2C19 inhibitors increase the exposure and strong and moderate CYP3A4 inducers reduce the exposure of KOSELUGO / KOSELUGO Granules.

Active substances that may increase selumetinib plasma concentrations
Co-administration with a strong CYP3A4 inhibitor (200 mg itraconazole twice daily for 11 days and 25 mg selumetinib, single oral dose at Day 8) increased selumetinib C_{max} by 19% (90% CI 4, 35) and AUC by 49% (90% CI 40, 59) in healthy adult volunteers.

Co-administration with a strong CYP2C19/moderate CYP3A4 inhibitor (400 mg fluconazole single dose at Day 1 followed by 200 mg fluconazole once daily for 10 days and 25 mg selumetinib single oral dose at Day 8) increased selumetinib C_{max} by 26% (90% CI 10, 43) and AUC by 53% (90% CI 44, 63) in healthy adult volunteers.

Concomitant use of erythromycin (moderate CYP3A4 inhibitor) or fluoxetine (moderate CYP2C19/strong CYP2D6 inhibitor) is predicted to increase selumetinib AUC by ~30-40% and C_{max} by ~20%.

Co-administration with strong inhibitors of CYP3A4 (e.g., clarithromycin, grapefruit and grapefruit products, oral ketoconazole) or CYP2C19 (e.g., ticlopidine) should be avoided. Co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin and fluconazole) or CYP2C19 (e.g., omeprazole) should be avoided. If co-administration is unavoidable, patients should be carefully monitored for adverse events and the selumetinib dose should be reduced (see 9 DRUG INTERACTIONS and **Table 6** and **Table 7**).

Active substances that may decrease selumetinib plasma concentrations
Co-administration with a strong CYP3A4 inducer (600 mg rifampicin daily for 8 days) decreased selumetinib C_{max} by -26% (90% CI -17, -34) and AUC by -51% (90% CI -47, -54).

Avoid concomitant use of strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) or moderate CYP3A4 inducers with KOSELUGO / KOSELUGO Granules.

Active substances whose plasma concentrations may be altered by KOSELUGO / KOSELUGO Granules
In vitro, selumetinib may be an inhibitor of OAT3 and the potential for a clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 (e.g. methotrexate and furosemide) cannot be excluded (see 10.3 Pharmacokinetics-*In vitro studies*).

Effect of gastric acid reducing agents on KOSELUGO / KOSELUGO Granules
KOSELUGO does not exhibit pH dependent dissolution. KOSELUGO can be used concomitantly with gastric pH modifying agents (i.e., H2-receptor antagonists and proton pump inhibitors) without any restrictions except omeprazole which is a CYP2C19 inhibitor.

Vitamin E (only applicable to KOSELUGO capsules)
KOSELUGO capsules contain vitamin E as the excipient TPGS. Therefore, patients should avoid taking supplemental vitamin E, and anticoagulant assessments should be performed more frequently in patients taking concomitant anticoagulant or antiplatelet medications (see 7 WARNINGS AND PRECAUTIONS, General).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 13 - Established or Potential Drug-Drug

Drug/Drug Class	Source of Evidence	Effect	Clinical Comment
Strong or moderate CYP3A4 or CYP2C19 inhibitors	CT/T	Increased selumetinib plasma concentrations which may increase the risk of adverse reactions.	Avoid coadministration of strong or moderate CYP3A4 or CYP2C19 inhibitors with KOSELUGO / KOSELUGO Granules. If coadministration with strong or moderate CYP3A4 or CYP2C19 inhibitors cannot be avoided, reduce KOSELUGO / KOSELUGO Granules dosage
Strong or Moderate CYP3A4 Inducers	CT/T	Decreased selumetinib plasma concentrations which may reduce KOSELUGO efficacy.	Avoid concomitant use of strong or moderate CYP3A4 inducers with KOSELUGO / KOSELUGO Granules.

Vitamin E	T	KOSELUGO contains vitamin E and daily vitamin E intake that exceeds the recommended or safe limits may increase the risk of bleeding. An increased risk of bleeding may occur in patients taking a vitamin-K antagonist or an anti-platelet agent with KOSELUGO.	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. Monitor for bleeding in patients co-administered a vitamin-K antagonist or an anti-platelet agent with KOSELUGO. Increase International Normalized Ratio (INR) monitoring, as appropriate, in patients taking a vitamin-K antagonist

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

In healthy adult subjects, co-administration of a single 75 mg dose (3 x 25 mg capsules) of KOSELUGO capsules with a high-fat meal resulted in a mean decrease in C_{max} of 50% compared to dose administration under fasting condition. Selumetinib mean AUC was also reduced by 16% when dosing was conducted under high-fat fed condition, and the time to reach maximum concentration (t_{max}) was delayed by approximately 1.5 hours. Similar results were obtained in a food effect study conducted in adult patients with advanced solid malignancies.

In healthy adult subjects at a dose of 50 mg, co-administration of KOSELUGO capsules with a low-fat meal resulted in 60% lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 38%, and t_{max} was delayed by approximately 0.9 hours. Similarly, in healthy male subjects, co-administration of KOSELUGO granules with a low-fat meal (400 to 500 calories, 25% of calories from fat) resulted in a mean decrease in C_{max} of 39% and t_{max} was delayed by approximately 1.3 hours compared to fasting conditions. There was no significant effect of a low-fat meal on AUC for the granules.

In adolescent patients with NF-1 and inoperable PN treated with multiple doses of 25 mg/m^2 twice daily, co-administration of selumetinib capsules with a low-fat meal resulted in 24% lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 8%, and t_{max} was delayed by approximately 0.57 hours (see 4.4 Administration).

A population PK analysis including children and adolescent patients with NF-1 and inoperable PN, adult patients with advanced solid malignancies and healthy adult subjects taken from 15 studies showed that concomitant administration of a low or high fat meal did not have a clinically relevant effect on the exposure (AUC) of selumetinib.

Based on the above results, the effect of food (high-fat, low-fat and without regard to food) for both formulations are not expected to result in a clinically relevant impact on the AUC of selumetinib since the magnitude of effect on the oral administration bioavailability (F1) is less than 30%.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Selumetinib is an orally available, selective inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are critical components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in neurofibromatosis type 1 syndrome and different types of cancers. Selumetinib blocks MEK activity and inhibits growth of RAF-MEK-ERK pathway activated cell lines.

10.2 Pharmacodynamics

In genetically modified mouse models of Type 1 neurofibroma that recapitulate the genotype and phenotype of human NF1, oral dosing of selumetinib inhibited ERK phosphorylation, and reduced neurofibroma numbers, volume, and proliferation.

Cardiac electrophysiology
The effect of selumetinib on the QTc interval following a single 75 mg oral dose, in a placebo- and positive-controlled (moxifloxacin) study, in 48 healthy adults showed no clinically relevant effect on the QTc interval (<10 msec change). A pharmacokinetic-pharmacodynamic analysis predicted a <10 msec change at 150 mg dose (3 times higher than the recommended maximum dose of 50 mg in pediatric patients with NF1).

10.3 Pharmacokinetics

The pharmacokinetic (PK) parameters in pediatric patients (3 to ≤ 18 years old) with NF1-PN and in adult patients (≥ 18 years old) with NF1-PN are comparable.

Table 14 - Summary of selumetinib Pharmacokinetic Parameters in Pediatric Patient Population

Dose (mg/m^2)	N	C_{max} (ng/mL) (GCV%)[a]	t_{max} (h) (range)[b]	AUC (ng*h/mL) (GCV%)[a]	CL/F (L/h) (SD)[c]	Vz/F (L) (SD)[c]	$t_{1/2}$ (h) (SD)[c]
Single Dose							
20	9	755 (48)	1 (0.98-3.0)	2231 (18)	11.5 (5.1)	146 (62.4)	9.4 (4.6)
25	4	928 (18)	1 (1-2)	2550 (14)	8.8 (2.5)	78 (20.6)	6.2 (0.9)
30	5	963 (51)	1 (1-2)	3055 (39)	15.0 (7.5)	171 (121.0)	7.3 (6.9)
25 Phase II	50	731 (62)	1.5 (0.5-6)	2009 (35)[d]	NC	NC	NC
Multiple Dose							
25 Phase II	45	798 (52)	1.5 (0.2-3.2)	1958 (41)[e]	NC	NC	NC

a. Geometric mean, GCV% geometric coefficient of variation
b. Median (range)

c. Arithmetic mean (SD)
d. AUC_{0-12}
e. AUC_{0-6}
AUC Area under the plasma concentration time curve; C_{max} Maximum plasma concentration; CL/F Apparent clearance; N Number of subjects enrolled to the study; NC Not calculated; $t_{1/2}$ Half-life; t_{max} Time to reach maximum concentration; Vss/F Apparent volume of distribution.

Selumetinib AUC and C_{max} increases proportionally over a dose range from 20 mg/m^2 to 30 mg/m^2 (0.8 to 1.2 times the recommended dose). Minimal accumulation of ~1.1 fold was observed at steady state upon twice daily dosing.

In the KOMET study, at the recommended dosage of 25 mg/m^2 twice daily in adult patients (≥ 18 years old), the geometric mean (geometric coefficient of variation [gCV%]) maximum plasma concentration (C_{max}) was 789 (47%) ng/mL and the area under the plasma drug concentration curve (AUC0-12) following the first dose was 2986 (43%) ng·h/mL.

Across all ages, the minimal accumulation range was 1.2 to 1.5 following administration of selumetinib.

In adult patients (≥ 18 years old), at a dose level of 25 mg/m^2, selumetinib has an apparent oral clearance of 14.1 L/h, mean apparent volume of distribution at steady state of 126.1 L and mean elimination half-life of ~9.0 hours.

The SPRINKLE study is a Phase I/II, single-arm, multicentre, open-label study in 36 pediatric patients aged from 1 year to less than 7 years at study entry (15 patients in global cohort 1 [≥ 4 to < 7 years], 17 patients in global cohort 2 [≥ 1 to < 4 years], and 4 patients in the Japan cohort [1 patient ≥ 1 to < 4 years and 3 patients ≥ 4 to < 7 years]) with a clinical diagnosis of NF1 with symptomatic, inoperable PN. The study was designed to evaluate the pharmacokinetics (PK), safety, efficacy, and tolerability of selumetinib granules and to define a dosing regimen accordingly. Study patients were to receive selumetinib for at least 25 cycles at a dose equivalent to 25 mg/m^2 BSA twice daily.

In the SPRINKLE study (DCO: 08-April-2024), the granules dose schema of equivalent to 25 mg/m^2 twice daily, 12 hours apart was confirmed in the dose-finding phase and achieved single-dose exposure within the target single-dose exposure from the Phase II Stratum 1 SPRINT study. At the primary analysis, the 95% CI of the geometric mean AUC_{0-12} of the granules in global cohort 1 (1902 ng·h/mL), and global cohort 2 (1699 ng·h/mL) fell within the prespecified target of 60% to 140% of the geometric mean AUC_{0-12} (2009 ng·h/mL) achieved by the capsules in the pivotal SPRINT Phase II Stratum 1 study. The observed selumetinib and N-desmethyl selumetinib exposure are similar between SPRINKLE and SPRINT studies.

Absorption:
In healthy adult subjects, the mean absolute oral bioavailability of selumetinib was 62%.

Following oral dosing, selumetinib is rapidly absorbed, producing peak steady state plasma concentrations (t_{max}) at 2 hours post-dose.

Distribution:
The mean apparent volume of distribution at steady state of selumetinib across 20 to 30 mg/m^2 ranged from 78 to 171 L in pediatric patients. Comparable values were observed in adult

patients across 25 mg/m^2 and ranged from 40 to 3710 L. These values, indicate moderate distribution into tissue.

In vitro plasma protein binding is 98.4% in humans. Selumetinib mostly binds to serum albumin (96.1%) and α-1 acid glycoprotein (<35%).

Metabolism:
In vitro, selumetinib undergoes Phase 1 metabolic reactions including oxidation of the side chain, N-demethylation, and loss of the side chain to form amide and acid metabolites. CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. *In vitro* studies indicate that selumetinib also undergoes direct Phase 2 metabolic reactions to form glucuronide conjugates principally involving the enzymes UGT1A1 and UGT1A3. It is estimated that 56% of the observed intrinsic clearance of selumetinib could be attributed to CYP metabolism and about 29% to direct glucuronidation by UGT enzymes in vitro.

Following a single oral dose of ^{14}C-selumetinib to healthy male subjects, unchanged selumetinib was identified as the major circulating drug-related component (~40% of the radioactivity). The main circulating metabolites identified in human plasma were glucuronide of imidazoindazole metabolite (M2; 22%), selumetinib glucuronide (M4; 7%), N-desmethyl selumetinib (M8; 3%), and N-desmethyl carboxylic acid (M11; 4%). N-desmethyl selumetinib represents less than 10% of selumetinib levels in human plasma but is approximately 3 to 5 times more potent than the parent compound, contributing to about 21% to 35% of the overall pharmacologic activity.

In vitro studies
Selumetinib is not a reversible inhibitor of CYP1A2, CYP2A6, CYP2C8, CYP2C19, CYP3A4 or CYP2E1. Selumetinib does not induce CYP1A2 or CYP2B6 and did not cause time-dependent inhibition of CYP2C9, CYP2D6 or CYP3A4/5.

Selumetinib is a reversible inhibitor of CYP2C9, CYP2B6, CYP2D6, UGT1A3, UGT1A4, UGT1A6 and UGT1A9, an inducer of CYP3A4 and a time-dependent inhibitor of CYP1A2 and CYP2C19; however, these effects are not expected to be clinically relevant.

Based on in vitro studies, selumetinib is a substrate for breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) transporters but is unlikely to be subjected to clinically relevant drug interactions at the recommended pediatric dose. Based on *in vitro* studies, selumetinib is not a substrate forOATP1B1, OATP1B3, or OCT1 transporters. *In vitro*, selumetinib is an inhibitor of BRCP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2K but does not inhibit P-gp or OCT1. These in vitro inhibitory effects are not expected to be clinically relevant with the exception of OAT3 where a clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 cannot be excluded.

Elimination:
In healthy adult volunteers, following a single oral 75 mg dose of radiolabelled selumetinib, 59% of the dose was recovered in feces (19% unchanged) while 33% of the administered dose (<1% as parent) was found in urine by 9 days of sample collection.

Special Populations and Conditions

Other adult patients (>18 years old):
The PK parameters in adult subjects are similar to those in pediatric patients (3 to ≤18 years

old) with NF1.

Ethnic origin:
Selumetinib exposure appears to be higher in Japanese, non-Japanese-Asian and Indian healthy adult volunteers compared to Western adult volunteers. However, there is considerable overlap with Western subjects when corrected for body weight or BSA (see 4 DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency:
Adult subjects with normal hepatic function (N=8) and mild hepatic impairment (Child-Pugh A, n=8) were dosed with 50 mg selumetinib, subjects with moderate hepatic impairment (Child-Pugh B, N=8) were administered a 50 or 25 mg dose, and subjects with severe hepatic impairment (Child-Pugh C, N=8) were administered a 20 mg dose. Selumetinib total dose normalized AUC and unbound AUC were 86% and 69% respectively, in mild hepatic impairment patients, compared to the AUC values for subjects with normal hepatic function. Selumetinib exposure (AUC) was higher in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment; the total AUC and unbound AUC values were 159% and 141% (Child-Pugh B) and 157% and 317% (Child-Pugh C), respectively, of subjects with normal hepatic function (see 4 DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The exposure of 50 mg oral selumetinib was investigated in adult subjects with normal renal function (N=11) and subjects with ESRD (N=12). The ESRD group showed 16% and 28% lower C_{max} and AUC, respectively, with the fraction of unbound selumetinib being 35% higher in ESRD subjects. As a result, the unbound C_{max} and AUC ratios were 0.97 and 1.13 in the ESRD group when compared to the group with normal renal function. A small increase, approximately 20% AUC, in the N-desmethyl metabolite to parent ratio was detected in the ESRD group when compared to the normal group. As exposure in ESRD subjects was similar to those with normal renal function, investigations in mild, moderate and severe renally impaired subjects were not performed. Renal impairment is expected to have no meaningful influence on the exposure of selumetinib (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Capsules: Store KOSELUGO at room temperature, between 15°C - 30°C.

Granules: Before dispensing, store and transport KOSELUGO Granules refrigerated at 2°C to 8°C. After dispensing, store KOSELUGO Granules refrigerated or at room temperature (between 2°C to 25°C). Do NOT exceed 30°C. KOSELUGO Granules may clump together or stick to the capsule shell if exposed to high temperatures, which may lead to underdose.

Dispense and store in the original bottle to protect from moisture and light. Do not remove desiccant. Keep the bottle tightly closed after first opening.
Any unused product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

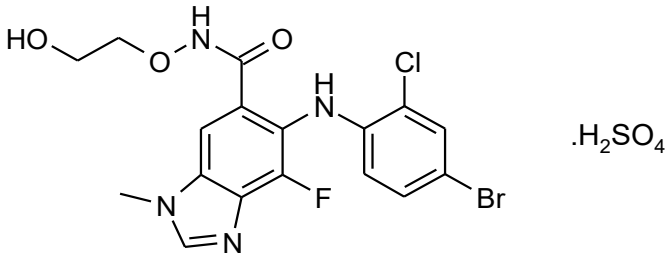
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name: Selumetinib sulfate

Chemical name: 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1H-benzimidazol-3-ium hydrogen sulfate

Structural formula:



Molecular formula: Selumetinib sulfate: $C_{17}H_{17}BrClFN_4O_7S$

Selumetinib free base: $C_{17}H_{15}BrClFN_4O_3$

Molecular mass: Selumetinib sulfate: 555.76

Selumetinib free base: 457.68

Physicochemical properties: Selumetinib sulfate is a monomorphic crystalline powder. The chosen form is non-solvated and non-hygroscopic. The drug substance has 2 dissociation constants, a pKa_1 of 2.8 and a pKa_2 of 8.4

Solubility:

Media	Solubility (µg/mL)	Temperature
Water	2.4	37 °C
Aqueous buffer at approx. pH 1.2	146.3	37 °C
Aqueous buffer at approx. pH 6.5	2.0	37 °C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The efficacy of selumetinib in pediatric and adult NF1-PN patients was evaluated in studies as described below.

Neurofibromatosis Type 1 with Inoperable Plexiform Neurofibromas

Table 15 - Summary of Patient Demographics for Clinical Trials in NF1 with PN

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
SPRINT (Phase II Stratum I)	Open-label, multi-centre, single-arm, Phase II study	25 mg/m^2 (BSA) twice daily oral administration for 28 days (1 treatment cycle), on a continuous dosing schedule.	50	10.3 years (3.5 – 17.4)	60% Male 40% Female
KOMET (Phase III)	A multi-centre, international study with a parallel, randomised, double-blind, placebo-controlled, 2 arm design.	25 mg/m^2 (BSA) or placebo twice daily oral administration for 12 cycles (28-day cycles). Treatment was open-label selumetinib after the end of cycle 12 (or earlier if disease progression was confirmed by Independent Central Review (ICR) in placebo patients).	145	31.2 years (18 – 60)	52% Male 48% Female

SPRINT

The efficacy of KOSELUGO was evaluated in an open-label, multi-centre, single-arm study (SPRINT Phase II Stratum I) of 50 pediatric patients with NF1 inoperable PN that caused significant morbidity. Inoperable PN was defined as a PN that could not be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN. Patients received KOSELUGO 25 mg/m^2 (BSA) twice daily, for 28 days (1 treatment cycle), on a continuous dosing schedule. Treatment

was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity or PN progression, or at the discretion of the investigator.

The target PN, the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was measured for determination of response rate using centrally read volumetric magnetic resonance imaging (MRI) analysis per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. Tumour size was evaluated at baseline and while on treatment after every 4 cycles for 2 years, and then every 6 cycles.

Patients had target PN MRI volumetric evaluations and clinical outcome assessments, which included functional assessments and patient reported outcomes.

Table 16 - Summary of Baseline Patient Disease Demographics for SPRINT (Phase II; Stratum I)

Disease Characteristics	SPRINT (N = 50)
Target PN volume (mL):	
Median (range)	487.5 (5.6 - 3820)
Number of PN related morbidities:	
Median (range)	3 (1 - 4)
Target PN related morbidities (%):	
Disfigurement	88%
Motor dysfunction	66%
Pain	52%
Airway dysfunction	32%
Visual impairment	20%
Bladder/bowel dysfunction	20%

The primary efficacy endpoint was Objective Response Rate (ORR), defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as ≥20% reduction in PN volume, confirmed at a subsequent tumour assessment within 3-6 months), based on NCI centralized review. Duration of Response (DoR) was also evaluated.

Efficacy results are provided based on a data cut-off of March 2021.

The primary endpoint, ORR was 68% (95% CI, 53.3 – 80.5). The median time to onset of response was 7.2 months (range 3.3 months to 3.2 years). The median (min-max) time to the maximal PN shrinkage from baseline was 15.1 months (3.3 months to 5.2 years).

The probability to remain in response after 12, 24 and 36 months, estimated using the Kaplan-Meier method, was 100% (95% CI not estimated), 90.0% (95% CI 72.1 – 96.7) and 86.3% (95% CI 67.3 – 94.6), respectively.

Table 17 - NF1 PN Efficacy Results from the SPRINT study (Phase II; Stratum I)

Efficacy Parameter	SPRINT (N=50)
Objective Response Rate [a]	
Objective Response Rate, % (95% CI)	68.0 (53.3 – 80.5)
Best objective response, n (%) [b, c]	
Complete Response	0
Confirmed Partial Response	34 (68%)
Unconfirmed Partial Response	3 (6%)
Stable Disease	11 (22%)
Progressive Disease	0
Duration of Response [d]	
Median (95% CI) months	NR (41.2 – NE)
Estimated percentage remaining in response [e]	
≥12 months, % (95% CI)	100 (NE – NE)
≥24 months, % (95% CI)	90.0 (72.1 – 96.7)
≥36 months, % (95% CI)	86.3 (67.3 – 94.6)
Number and percentage remaining in response	
≥ 12 months, n (%)	31 (91.2%)
≥ 24 months, n (%)	26 (76.5%)
≥ 36 months, n (%)	21 (61.8%)

CI - confidence interval, NE - not estimated, NR - not reached

[a] Responses required confirmation at least 3 months after the criteria for first partial response were met.

[b] Complete response: disappearance of the target lesion; Partial Response: decrease in target PN volume by ≥20% compared to baseline; Stable Disease: insufficient volume change from baseline to qualify for either partial response or progressive disease; Progressive Disease: increase in target PN volume by ≥20% compared to baseline or best response (maximal PN shrinkage) after a documented partial response.

[c] Two patients were not evaluable.

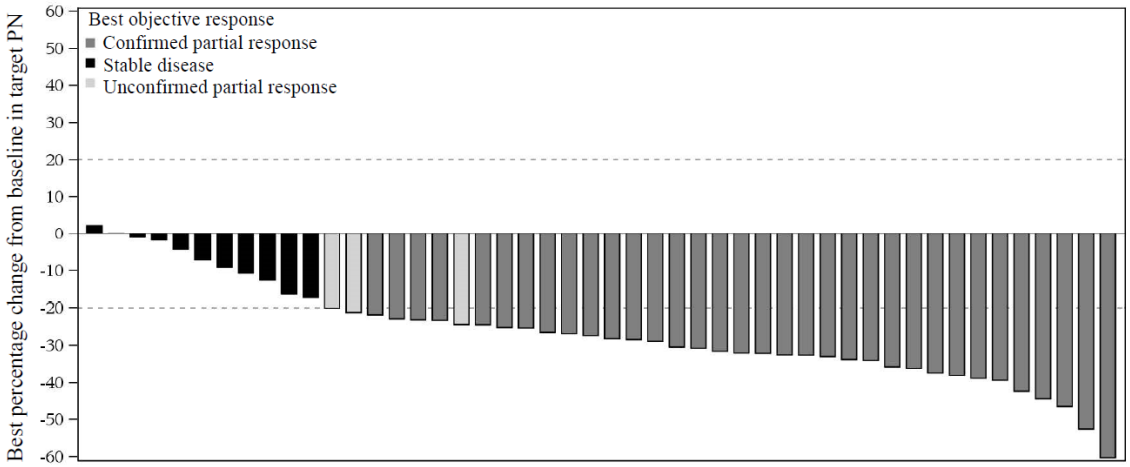
[d] Duration of Response from onset of response in patients with confirmed partial response.

[e] Calculated using Kaplan-Meier method.

The median DoR from onset of response was not reached; at the time of data cut-off the median follow-up time was 41.3 months from first dose. Of the 34 patients who had confirmed partial responses, 31 (91.2%) remained in response after 12 months, 26 (76.5%) remained in response after 24 months and 21 (61.8%) remained in response after 36 months. The median time from treatment initiation to disease progression while on treatment was not reached. At the time of data cut-off or last scan on treatment for patients who had discontinued treatment, 25 (50%) patients remained in confirmed partial response, 1 (2%) had unconfirmed partial responses, 12 (24%) had stable disease and 10 (20%) had progressive disease.

The median best percentage change in PN volume from baseline was -27.85% (range: -60.3 % to 2.2%). **Figure 1** shows the best percentage change in target PN volume for each patient.

Figure 1 – Waterfall Plot of Best Percentage Change from Baseline in Target PN Volume[a] for Patients in SPRINT (Phase II; Stratum I)



a Best percentage change in target PN volume is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. Two patients were not evaluable.

Pain intensity of the target PN was self-reported by patients ≥8 years of age using an 11-point Numeric Rating Scale (NRS-11). There were 24 patients who completed the NRS-11 both at baseline and pre-Cycle 13. At pre-Cycle 13, the mean change in pain intensity score from baseline was -2.07 (95% CI: -2.84, -1.31).

Based on mixed model repeated measures (MMRM) analysis, a clinically meaningful reduction in pain (defined as, ≥2-point decrease from baseline) was seen at pre-Cycle 25 (adjusted mean change from baseline: -2.17, 95% CI: -3.17, -1.17) and at pre-Cycle 49 (adjusted mean change from baseline: -2.43, 95% CI: -3.47, -1.40).

Parent reported (all patients) and patient reported (≥8 years of age) health-related quality of life (HRQoL) was assessed using the Peds-QL questionnaire. Based on Mixed Model Repeated Measures (MMRM) analysis, a clinically meaningful improvement in HRQoL (clinically meaningful threshold 11.90) was reported by parents at pre-Cycle 13 with a mean change from baseline in Peds-QL total score of 12.82 (95% CI 9.00 - 16.63) and was sustained at all remaining measurement cycles. Improvement in HRQoL was also reported by patients as pre-Cycle 13 with a mean change from baseline of 6.17 (95% CI 0.93 - 11.40). The improvement in patient reported Peds-QL total score was clinically meaningful (clinically meaningful threshold 10.33) at pre-Cycle 37, with a mean change from baseline in Peds-QL total score of 11.23 (95% CI 6.81 - 15.65) and was sustained at pre-Cycle 49.

KOMET

The efficacy of KOSELUGO in adult patients was evaluated in a Phase III, multicentre, international study that had a parallel, randomized 1:1, double blind, placebo controlled, 2 arm

design. A total of 145 patients were randomized to receive either selumetinib 25 mg/m^2 (BSA) or placebo twice daily for 12 cycles (28-day cycles). After the end of Cycle 12, placebo patients crossed over to receive open label selumetinib or earlier if disease progression was confirmed by the Independent Central Review (ICR). Treatment was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity, patient decision, PN progression, or at the discretion of the investigator.

The target PN, the clinically most relevant PN, which is measurable by volumetric MRI analysis and, if relevant, one additional non-target PN, was evaluated for response rate using centrally read volumetric MRI analysis per REiNS criteria. Tumour response was evaluated at baseline and while on treatment after every 4 cycles for 2 years, and then every 6 cycles. Patients had target and non target PN MRI volumetric evaluations and clinical outcome assessments.

Demographics and baseline disease characteristics were generally well balanced between the selumetinib and placebo treatment arms. Baseline demographics in the selumetinib and placebo groups were as follows: median age at enrolment was 29 years (range: 18 to 60 years), male (51.7%), White (55.9%), and Asian (31%). The median volume of the target PN was 110.18 mL for the selumetinib group and 221.85 mL for the placebo group. The median number of PN related morbidities was 2 in both the selumetinib and placebo groups The most common reported target PN morbidity at baseline was pain (selumetinib: 87.3%; placebo: 82.4%), followed by motor (selumetinib: 42.3%; placebo: 36.5%), and disfigurement (selumetinib: 32.4%; placebo: 23.0%). Airway, vision, and bowel/bladder morbidities were less frequent, affecting 4.2% or less of the patients in both the selumetinib and placebo groups. The NF1-PN disease characteristics at baseline are provided in Table 18 below.

Table 18 - Baseline disease characteristics in the KOMET study

Characteristics	**Selumetinib (N = 71)**	**Placebo (N = 74)**
Target PN volume (mL):		
Median (range)	110.18 (3.3 – 13574.9)[1]	221.85 (9.1 – 5621.9)
Number of PN related morbidities:		
Target PN median (range)	2 (1 - 5)	2 (1 - 5)
Target PN related overall morbidities (%)		
Pain	87.3%	82.4%
Motor	42.3%	36.5%
Disfigurement	32.4%	23%
Airway	4.2%	4.1%
Vision	4.2%	4.1%
Bowel/bladder	2.8%	2.7%
Other	15.5%	27%

The primary efficacy endpoint was the overall response rate (ORR) for selumetinib by the end of Cycle 16. ORR was defined as the percentage of patients with confirmed complete response (disappearance of the target PN, confirmed by consecutive scan within 3–6 months after the first response) or confirmed partial response (target PN volume decrease ≥ 20%, compared to baseline, confirmed by a consecutive scan within 3–6 months after the first response) by the end of Cycle 16 as determined by ICR per REiNS criteria. Secondary endpoints including

single-arm (i.e. within the subset of patients randomized to selumetinib only) ORR, time to response (TTR), and duration of response (DoR) were also evaluated during selumetinib treatment up to the DCO date (05 August 2024).

At the planned primary analysis, the study met its primary endpoint demonstrating a statistically significant and clinically meaningful ORR in selumetinib group versus placebo. By the end of Cycle 16, the ORR for selumetinib was 19.7% (95% CI: 11.2, 30.9) versus an ORR for placebo of 5.4% (95% CI: 1.5, 13.3). At the time of DCO, the median total duration of exposure was 554 days (approximately 18.2 months) in patients randomized to selumetinib. The median TTR was 3.7 months (95% CI: 3.61, 11.07) and the median DoR from onset of response was not reached. Of the 14 patients who had confirmed partial response in the selumetinib group, 12 (85.7%) patients remained in response after 6 months. Efficacy results are presented in **Table 19** below.

Table 19 - NF1-PN efficacy results from the KOMET study

Efficacy Parameters [a]	**Selumetinib (N = 71)**	**Placebo (N = 74)**
Objective Response Rate (ORR) by the end of Cycle 16 [b, c]		
ORR % (95% CI)	19.7 (11.2, 30.9)	5.4 (1.5, 13.3)
p-value [d]	0.0112	
Best objective response (BOR) by the end of Cycle 16, n (%) [b, c, e]		
Confirmed Complete Response	0	0
Confirmed Partial Response	14 (19.7%)	4 (5.4%)
Overall Stable Disease	50 (70.4%)	63 (85.1%)
Unconfirmed Complete Response	0	0
Unconfirmed Partial Response	5 (7%)	8 (10.8%)
Stable Disease	45 (63.4%)	55 (74.3%)
Progressive Disease	1 (1.4%)	5 (6.8%)
Not Evaluable	6 (8.5%)	2 (2.7%)
Single arm ORR [h]		
ORR % (95% CI)	19.7 (11.2, 30.9)	ND
Time to Response (TTR) [h]		
Median (95% CI) months [g]	3.7 (3.61, 11.07)	ND
Duration of Response (DOR) [f, g, h]		
Median (95% CI) months	NR (11.5, NE)	ND
Number and percentage remaining in response		
≥ 6 months, n (%)	12 (85.7%)	ND

CI – confidence interval, NE – not estimated, NR - not reached, ND – Not determined for placebo treatment arm.

[a] Results are based on planned primary analysis (DCO: 05 August 2024) which occurred 32 months after study initiation. Total number of patients included in the primary analysis was 145.

[b] Each treatment cycle in the study is of 28 calendar days (Cycle 16 corresponds to approximately 15 months).

[c] Patients with confirmed complete response or partial response by independent central review (ICR) per REiNS criteria. Response confirmation was by a consecutive scan within 3 to 6 months after the first response as determined by ICR per REiNS criteria.

[d] 2-sided p-value calculated using Fisher's exact method (alpha of 0.047) by comparison of Selumetinib vs Placebo.

[e] Complete Response: disappearance of the target lesion; Partial Response: decrease in target PN volume by ≥ 20% compared to baseline; Stable Disease: insufficient volume change from

baseline to qualify for either partial response or progressive disease; Progressive Disease: increase in target PN volume by ≥ 20% compared to baseline or the documented time of best response.

[f] Duration of Response from date of first documented response (subsequently confirmed) until date of documented progression by ICR per REiNS criteria.

[g] Calculated using Kaplan-Meier method.

[h] Calculated for patients randomized to selumetinib arm including data until DCO (05 August 2024).

Pain intensity was assessed as a key secondary endpoint using the PAINS-pNF chronic target PN pain intensity score to characterize patient-reported pain associated with plexiform neurofibromas. At Cycle 12, the mean change from baseline in pain intensity was −2.0-points decrease in the selumetinib group and −1.3-point decrease in the placebo group. However, the results were not statistically significant.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In 26-week repeat toxicity studies conducted in mice and monkeys, gastrointestinal disturbances were identified as the most common adverse effect. In mice, selumetinib at a dose of 2 mg/kg/day (around 2 times the human exposure, based in AUC at the human clinical dose) produced minimal colon inflammation. At a higher dose (more than 35 times the human exposure) the inflammatory GI tract findings were associated with secondary changes in the liver and lymphoreticular system in both sexes. In addition, some male mice showed evidence of significant urinary tract obstruction.

Selumetinib administration in monkeys led to loose/liquid feces even at a low dose (1.5/mg/kg twice a day), equivalent to ~1.3 times the human exposure (AUC) at the 25 mg/m^2 twice daily clinical dose.

The main clinical sign seen after selumetinib administration in rats for 3 months, at levels > 5 times the human exposure (at the MRHD), were skin lesions or scabs associated with microscopic erosions and ulceration. GI findings showed evidence of reversibility following a recovery period. Reversibility for skin toxicities was not evaluated. Male rats receiving selumetinib at doses ≥ 10 mg/kg daily (equivalent to more than 60 times the human exposure at the clinical dose based on AUC) showed growth plate dysplasia.

Carcinogenicity

Selumetinib was not carcinogenic in a 6-month study in rasH2 transgenic mice at exposures 23 times (males) and 35 times (females) and in 2-year carcinogenicity study in rats at exposures 20 times (male) and 15 times (females) the human exposure (AUC) at maximum recommended human dose (MRHD) of 25 mg/m^2.

Genotoxicity

Selumetinib showed no mutagenic or clastogenic potential in vitro but produced an increase in micronucleated immature erythrocytes (chromosome aberrations) in mouse micronucleus studies, predominantly via an aneugenic mode of action. The aneugenic findings were observed

at doses that resulted in exposure levels (C_{max}) of at least 10 times the levels obtained at the maximum recommended human dose of 25 mg/m^2.

Reproductive and Developmental Toxicology

Fertility
In a 6-month mouse study, selumetinib did not affect male mating performance at any dose up to 20 mg/kg twice daily corresponding to approximately 32-times the human clinical exposure based on AUC at the maximum recommended human dose (MRHD). Repeated treatment of male mice with selumetinib at doses up to 5 mg/kg twice a day (~11 times the clinical exposure at 25 mg/m^2 BID) for 26 weeks had no adverse effects on progressive motility or sperm numbers. In female mice exposed to selumetinib at 12.5 mg/kg twice daily, mating performance and fertility were not affected, but the number of live fetuses was slightly reduced. Following a three-week treatment withdrawal period, no effects were apparent on any parameter. The No Observed Adverse Effect Level (NOAEL) for both maternal toxicity and effects on reproductive performance was 2.5 mg/kg twice daily (approximately, 5-fold human exposure at the MRHD, 25 mg/m^2 twice daily).

Embryofetal toxicity
In embryo-fetal development studies in mice at doses > 2.5 mg/kg twice daily (~5 times the human exposure based on AUC at the clinical dose of 25 mg/m^2 twice daily), selumetinib caused increases in post-implantation loss, a reduction in mean fetal and litter weights, and an increased occurrence of open eye and cleft palate but did not induce significant maternal toxicity.

These results indicate that selumetinib has potential to cause embryo-fetal defects.

Pre- and postnatal development
Administration of selumetinib to pregnant mice from gestation Day 6 through to lactation Day 20 resulted in reduced pup body weights, and fewer pups met the pupil constriction criterion on Day 21 post-partum. The incidence of malformations (e.g. prematurely open eye(s) and cleft palate) was increased even at the lowest dose of 0.5 mg/kg twice daily (maternal maximal concentration [C_{max}] of ~0.6 times the human C_{max} at the clinical dose of 25 mg/m^2 twice daily).

Selumetinib and its active metabolite were present in milk from mice dosed with selumetinib throughout gestation and lactation, with a mean plasma/milk ratio of 1.5 in lactating dams dosed at 5 mg/kg twice daily (>4.5 times the human exposure based on C_{max} at the clinical dose of 25 mg/m^2 twice daily).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrKOSELUGO®
Selumetinib capsules

PrKOSELUGO® Granules
Selumetinib oral granules

This Patient Medication Information is written for the person who will be taking **KOSELUGO / KOSELUGO Granules**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **KOSELUGO / KOSELUGO Granules**, talk to a healthcare professional.

What KOSELUGO / KOSELUGO Granules are used for:
KOSELUGO capsules are used to treat adults and children aged 2 to 18 years and older with:

- a genetic condition called Neurofibromatosis Type 1 (NF1) who have tumours that grow along nerves called Plexiform Neurofibromas (PNs). KOSELUGO capsules are used when those PNs cannot be removed by surgery.

KOSELUGO Granules are used to treat children aged 1 year and older with:

- NF1 who have PN that cannot be removed by surgery.

How KOSELUGO / KOSELUGO Granules works:
KOSELUGO **/** KOSELUGO Granules is a type of medicine called a 'MEK inhibitor'. It works by blocking certain proteins which are known to be involved in the growth of tumour cells. KOSELUGO / KOSELUGO Granules may reduce the size of PNs caused by NF1.

The ingredients in KOSELUGO / KOSELUGO Granules are:
Medicinal ingredient: selumetinib sulfate

Non-medicinal ingredients:
10 mg capsules: Ammonium hydroxide 28%, Carnauba wax, Carrageenan, Hypromellose, Iron oxide black, Potassium chloride, Propylene glycol, Purified water, Shellac glaze, Titanium dioxide, Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol 1000 succinate).

25 mg capsules: Carnauba wax and/or Corn starch, Carrageenan, FD&C Blue 2, FD&C blue 2 aluminum lake, Ferric oxide red, Ferric oxide yellow, Glyceryl monooleate, Hypromellose, Potassium chloride, Purified water, Titanium dioxide, Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol 1000 succinate), White shellac.

5 mg granules: Glyceryl dibehenate, Hypromellose acetate succinate, Stearic acid and Stearoyl polyoxylglycerides. The capsule shells (not to be consumed) contain Ferric oxide yellow, Hypromellose, Pharmaceutical ink and Titanium dioxide.

7.5 mg granules: Glyceryl dibehenate, Hypromellose acetate succinate, Stearic acid and Stearoyl polyoxylglycerides. The capsule shells (not to be consumed) contain Ferric oxide yellow, Hypromellose, Pharmaceutical ink and Titanium dioxide.

KOSELUGO / KOSELUGO Granules comes in the following dosage form:
Capsules: 10 mg and 25 mg selumetinib (as selumetinib sulfate)
Granules: 5 mg and 7.5 mg selumetinib (as selumetinib sulfate)

Do not use KOSELUGO / KOSELUGO Granules if:

- You are allergic to selumetinib or to any other ingredient in KOSELUGO / KOSELUGO Granules or the packaging.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KOSELUGO / KOSELUGO Granules. Talk about any health conditions or problems you may have, including if you:

- have eye problems
- have heart problems
- are taking Vitamin E supplements. KOSELUGO capsules contains vitamin E that may make you bleed more easily. You should tell your healthcare professional if you take other medicines that increase your risk of bleeding such as:
    - aspirin
    - blood thinners such as warfarin or other medications for blood clots
    - supplements that may increase your risk of bleeding such as vitamin E

Other warnings you should know about:

KOSELUGO / KOSELUGO Granules can cause the following side effects, including

Eye problems
KOSELUGO / KOSELUGO Granules can cause **eye problems** such as retinal pigment epithelial detachment (RPED), central serous retinopathy (CSR) and retinal vein occlusion (RVO). Tell your doctor as soon as possible if you have blurred vision, eye pain or pressure, dark spots in your vision, high sensitivity to light, or any other changes to your vision. Your healthcare professional should check your eyes if you experience new or worsening problems during treatment. They should also check your eyes before starting KOSELUGO / KOSELUGO Granules.

Heart problems
KOSELUGO / KOSELUGO Granules can lower the amount of blood pumped by your heart (cardiomyopathy).

Gastrointestinal Problems: KOSELUGO / KOSELUGO Granules can cause diarrhea. Your doctor might tell you to take medicine to treat diarrhea and to drink more fluids. KOSELUGO / KOSELUGO Granules can also cause stomach pain, nausea and vomiting.

Skin Problems: KOSELUGO / KOSELUGO Granules can cause **skin problems** like rashes and eczema (acne like bumps, flat or raised red skin, or skin that is itchy, dry, rough or flakey). KOSELUGO / KOSELUGO Granules can also cause skin infections around fingernails or toenails (**paronychia**) and a severe skin problem called **palmar-plantar erythrodysesthesia**

syndrome.

Muscle problems: KOSELUGO / KOSELUGO Granules can cause muscle aches and pains or a serious breakdown of muscle (**rhabdomyolysis**). This can be caused by higher levels of an enzyme called creatine phosphokinase.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Pregnancy, birth control and breastfeeding – Information for women and men:

Pregnancy and Breastfeeding

- You should not become pregnant or be pregnant while taking KOSELUGO / KOSELUGO Granules. KOSELUGO / KOSELUGO Granules may harm an unborn child or make you lose your pregnancy.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with KOSELUGO / KOSELUGO Granules.
- Your healthcare professional should do a pregnancy test on you before you start taking KOSELUGO / KOSELUGO Granules.
- Before you start taking KOSELUGO / KOSELUGO Granules, tell your healthcare professional if you are breastfeeding. It is not known if KOSELUGO / KOSELUGO Granules passes into the breast milk. For the safety of your baby, you should not breastfeed while taking KOSELUGO / KOSELUGO Granules and for 1 week after the last dose.

Birth Control

- Female patients:
  - Use effective birth control while you are taking KOSELUGO / KOSELUGO Granules and for 1 week after the last dose.
  - Ask your healthcare professional about methods of birth control available to you.

- Male patients:
  - You should use effective birth control while you are taking KOSELUGO / KOSELUGO Granules and for 1 week after the last dose.
  - If, during your treatment with KOSELUGO / KOSELUGO Granules, your sexual partner becomes pregnant or thinks she may be pregnant, tell your doctor right away.

Children under 2 years old:
KOSELUGO capsules should not be given to children under 2 years of age.
KOSELUGO Granules should not be given to children below 1 year of age.

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will check you for skin rashes and do the following tests:

- Eye tests to check your eyes for new or worsening eye problems.
- Heart tests to check that your heart is working properly.
- Blood clotting (anticoagulant) tests.
- Blood tests to check your blood and to help diagnose liver or muscle injury or other problems.

Driving and using machines:
KOSELUGO / KOSELUGO Granules can cause side effects that may affect your ability to drive or use machines. Avoid driving or using potentially dangerous machines if you feel tired or if you have problems with your vision (such as blurred vision).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KOSELUGO / KOSELUGO Granules:
- Aspirin, a medication used for pain relief or as a blood thinner/anti-platelet
- Supplements that may increase your risk of bleeding such as vitamin E
- Rifampicin, a medicine used to treat tuberculosis (TB)
- St. John's wort, a herbal treatment used to treat depression and other conditions
- Fluoxetine, an anti-depressant medicine used to treat depression and other mental disorders
- Grapefruit products. You should not eat grapefruit, drink grapefruit juice or use grapefruit products while you are taking KOSELUGO / KOSELUGO Granules
- Omeprazole, a medicine used to treat stomach and esophagus problems
- Medicines used as blood thinners or for blood clots, such as warfarin or ticlopidine
- Medicines used to treat bacterial infections such as clarithromycin and erythromycin
- Medicines used to treat seizures and epilepsy such as carbamazepine or phenytoin
- Medicines used to treat fungal infections such as fluconazole, itraconazole or ketoconazole
- Medicines used to treat rheumatoid arthritis such as methotrexate
- Medicines used to treat edema (swelling) such as furosemide
- Foods: water, milk, vegetable puree, grapefruit, or any juice, fruit puree or jam containing Seville orange (bitter orange). These can affect the way KOSELUGO Granules work.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

How to take KOSELUGO / KOSELUGO Granules:
Capsules:
- Always take KOSELUGO capsules exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take KOSELUGO capsules twice a day, about 12 hours apart with or without food.
- Swallow KOSELUGO capsules whole with water. Do not chew, dissolve, or open the capsules
    - Do not take KOSELUGO capsules if you are unable to swallow a whole capsule.
- Take KOSELUGO capsules for as long as your healthcare professional prescribes it.

Granules:
- Always prepare and take KOSELUGO Granules exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Carefully open the capsule and sprinkle or mix all the contents (granules) onto a small amount of smooth yogurt or fruit puree containing apple, banana, pear or strawberry).
    - Swallow the granules with the food within 30 minutes. Do not be store for later use.
    - If some of the dose is taken and the rest is not finished within 30 minutes of

preparation, throw away the unfinished dose. A new dose should not be prepared.
    - Do not mix granules in water, milk, vegetable puree, grapefruit or any juice, fruit puree or jam containing Seville orange (bitter orange).
    - The KOSELUGO oral granules should be free-flowing. Granules that are clumped or stuck inside the capsule shell should not be used.
- Take KOSELUGO Granules twice a day, about 12 hours apart.
- Do not swallow, chew, or dissolve the capsule shells of KOSELUGO Granules.
- Throw away empty capsule shells after use.

Usual dose:

- The healthcare professional will tell you your exact dose of KOSELUGO / KOSELUGO Granules. They will calculate your dose based on your height and weight.

Your doctor may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if:

- you experience serious side effects, or
- your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much KOSELUGO / KOSELUGO Granules, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose of KOSELUGO / KOSELUGO Granules and:

- there is more than 6 hours until your next dose: Take the missed dose as soon as you remember. Take the next dose at the normal time
- there is less than 6 hours until your next dose: Skip the missed dose. Take the next dose at the normal time

Do not take a double dose (two doses at the same time) to make up for a forgotten dose**.**

If you vomit at any time after taking KOSELUGO / KOSELUGO Granules, do not take another dose. Take the next dose at your usual time.

What are possible side effects from using KOSELUGO / KOSELUGO Granules?

These are not all the possible side effects that you may feel when taking KOSELUGO / KOSELUGO Granules. If you experience any side effects not listed here, contact your healthcare professional.

- Vomiting, feeling sick
- Diarrhea, constipation
- Mouth sores, redness
- Skin and nail problems: dry skin, rash, redness around the fingernails, itching, skin infection
- Hair thinning, hair colour change
- Headache
- Nosebleeds
- Tiredness, weakness or lacking energy
- Fever
- Swelling (including swelling of the face, hands or feet, or inside the mouth)
- Blurred vision
- Dry mouth
- Shortness of breath
- Stomach pain
- Weight gain
- Muscle and bone pain

KOSELUGO / KOSELUGO Granules can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how KOSELUGO / KOSELUGO Granules is affecting your blood, kidneys and liver.

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Flu like symptoms: fever, nausea, fatigue, asthenia (weakness), headache	✓		
Gastrointestinal problems: stomach pain, severe diarrhea, nausea, vomiting		✓	
Heart problems: a slight decrease in the pumping performance of the heart, persistent coughing or wheezing, shortness of breath, swelling of the ankles, legs and feet, tiredness, nausea, fatigue and weakness, abnormally fast heart rate, dizziness, fainting,		✓	

chest pain			
Hematuria (blood in the urine): pink, red or very dark urine		✓	
Hypertension (high blood pressure): new or worsening high blood pressure, severe headache, lightheadedness, dizziness		✓	
Paronychia (fingernail infection)**:** red, hot, painful pus-filled blisters around the nail, with swelling. Detached, dis-coloured or abnormally shaped fingernails		✓	
Skin problems including Palmar-plantar erythrodysesthesia syndrome: rash, dry skin, acne, itching, dermatitis, skin infection, redness, swelling and blistering on the palms of the hands and soles of the feet.		✓	
Skin rash: small, raised acne-like bumps on the skin; skin redness with flat spots or raised bumps		✓	
COMMON			
Acute kidney injury (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain		✓	
Eye Problems: blurred or hazy vision, loss of vision, dark spots in your vision, sensitivity to light, eye pain, difficulty seeing at night and other vision changes		✓	
Hypoxia (low blood oxygen): headache, shortness of breath, fast heartbeat, coughing, wheezing, confusion, bluish skin, fingernails, and lips		✓	
Muscle Aches and pain including Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine		✓	
RARE			

Cellulitis (skin infection): red skin that is swollen, painful and warm to the touch, fever, chills, blisters, skin dimpling			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in the original bottle to protect from moisture and light. Do not remove the desiccant pack. Keep the bottle tightly closed after first opening.
- Do not throw away any drugs via wastewater or household waste. Ask your healthcare professional about how to throw away drugs you no longer use.
  Keep out of reach and sight of children.
- **Capsules:** Store at room temperature between 15 to 30°C.

- **Granules:**
  - Store in fridge or at room temperature (between 2°C to 25°C).
  - Do NOT store above 30°C. Granules may clump or stick to the capsule shell if exposed to high temperatures. This can lead to a wrong dose.
  - Keep KOSELUGO oral granules cold in a cooler bag with a cold pack if you need to take it anywhere.

If you want more information about KOSELUGO / KOSELUGO Granules:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://alexion.com/worldwide/canada or by calling 1-833-569-2435.
- This patient medication Information is current at the time of printing. The most up-to-date version can be found at https://alexion.com/worldwide/canada.

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