

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **KOSELUGO™**

Selumetinib capsules

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

Antineoplastic Agent

AstraZeneca Canada Inc.
1004 Middlegate Road, Suite 5000
Mississauga, Ontario
L4Y 1M4
www.astrazeneca.ca

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RECENT MAJOR LABEL CHANGES

Not Applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KOSELUGO™ (selumetinib) is indicated for:

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

1.1 Pediatrics

Safety and effectiveness have been established in pediatric patients 3 years of age and older with NF1 who have inoperable PN and information supporting this use is discussed throughout the Product Monograph. This indication was expanded to pediatric patients who are 2 years of age and older, because the safety, efficacy and pharmacokinetics of KOSELUGO in patients who are 2 years of age is expected to be similar to patients at 3 years of age and older.

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 is 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 should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours.

Do not administer to patients who are unable to swallow a whole capsule.

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

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of KOSELUGO is 25 mg/m² based on body surface area (BSA), taken orally twice daily (approximately every 12 hours).

Dosing is individualized based on BSA (mg/m²) 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 Recommended Dosage Based on Body Surface Area

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

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

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

Dose Adjustments

Interruption and/or dose reduction or permanent discontinuation of KOSELUGO 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 2**.

Table 2 - KOSELUGO Recommended Dose Reductions for Adverse Reactions

Body Surface Area (BSA)	Initial KOSELUGO 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 3 - Recommended KOSELUGO 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 2)
Grade 4	Interrupt treatment until toxicity is grade 0 or 1, reduce by one dose level when resuming therapy (see Table 2). 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 treatment should be interrupted until resolution. Once resolved, reduce KOSELUGO by one dose level when resuming therapy (see **Table 2**).

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

Dose modification advice for retinal toxicities

KOSELUGO 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 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 should be permanently discontinued (see 7 WARNINGS AND PRECAUTIONS).

Dose adjustments for co-administration with CYP3A4 and CYP 2C19 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 dose reduction is as follows: If a patient is currently taking 25 mg/m² twice daily, dose reduce to 20 mg/m² twice daily. If a patient is currently taking 20 mg/m² twice daily, dose reduce to 15 mg/m² twice daily (see Table 4 and 9 DRUG INTERACTIONS).

Table 4. Recommended dosage to achieve 20 mg/m² or 15 mg/m² twice daily dose level

Body Surface Area	20 mg/m² twice daily (mg/dose)		15 mg/m² 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

Dose modifications for special patient populations

Renal impairment

Based on clinical studies no dose adjustment is recommended in patients with mild, moderate, 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/m² BSA, twice daily (See Table 4). KOSELUGO is not recommended for use in patients with severe hepatic impairment (see 10.3 Pharmacokinetics).

Ethnicity

Increased systemic exposure has been seen in adult 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 pediatric Asian patients, however, these patients should be closely monitored for adverse events (see 10.3 Pharmacokinetics).

4.4 Administration

KOSELUGO should be taken on an empty stomach with no food or drink other than water. Do not consume food 2 hours prior to dosing and 1 hour after dosing (see 9.5 Drug-Food Interactions and 10 CLINICAL PHARMACOLOGY).

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

4.5 Missed Dose

If a dose of KOSELUGO 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 5 - 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

KOSELUGO is sold in a 60 capsule HDPE plastic bottle with child-resistant closure and silica gel desiccant.

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.

7 WARNINGS AND PRECAUTIONS**General****Vitamin E Supplementation**

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**

Cardiomyopathy, defined as reduction in left ventricular ejection fraction (LVEF) $\geq 10\%$ below baseline, occurred in 23% 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 75.0 days. Decreased LVEF resolved in 71% of these patients.

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.

Pediatric patients with a history of impaired left ventricular function or a baseline LVEF below institutional lower limit of normal (LLN) have not been studied (see 14.1 Clinical Trials by Indication). Prior to starting KOSELUGO treatment, patients should have an ejection fraction above the institutional LLN.

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. 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

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

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

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

Increased creatine phosphokinase (CPK) occurred in 76% of 74 pediatric patients who received KOSELUGO in SPRINT, including Grade 3 or 4 in 9% of patients. Increased CPK resulted in dose reduction in 7% of patients. Increased CPK concurrent with myalgia occurred in 8% of patients, including one patient who permanently discontinued KOSELUGO for myalgia.

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

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

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 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, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue KOSELUGO in patients with retinal vein occlusion (RVO). Withhold KOSELUGO in patients with retinal pigment epithelial detachment (RPED), follow up with optical coherence tomography assessments every 3 weeks until resolution, and resume KOSELUGO 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 based on severity of adverse reaction (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Ophthalmologic

Visual Impairment

Advise patients to report any new visual disturbances. Adverse events of blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving KOSELUGO. Blurred vision resulted in dose interruption in 2.7% of patients. 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 is recommended. 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 therapy should be interrupted and the dose reduced when treatment is resumed (see Table 2). If RVO is diagnosed, treatment with KOSELUGO 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/m² 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 \geq 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

Rash occurred in 91% of 74 pediatric patients who received KOSELUGO in SPRINT. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred in 8% of patients. Rash resulted in dose interruption in 11% of

patients and dose reduction in 4% of patients.

Paronychia was reported in 45% of patients with Grade ≥ 3 events reported in 9.5% of patients. Paronychia resulted in dose interruption in 11 (13.9%) patients, and dose reduction in 4 (5.4%) patients, with discontinuation of KOSELUGO reported in 1 (1.4%) patient.

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.

Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION).

7.1 Special Populations

7.1.1 Pregnant Women

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 are no data 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/m² 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/m² twice daily clinical dose (see Reproductive and Developmental Toxicology). KOSELUGO is not recommended during pregnancy.

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

Advise women of childbearing potential to avoid becoming pregnant while receiving KOSELUGO. 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.

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

The safety and effectiveness of KOSELUGO have not been established in pediatric patients younger than 2 years 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/m² twice daily) with NF1 who had inoperable PN that was causing significant morbidity and 347 adult patients (75-100 mg/m² twice daily) with multiple tumour types.

The median total duration of KOSELUGO treatment in pediatric patients with NF1 PN was 28 months (range: <1 – 71 months), 23% of patients were exposed to KOSELUGO treatment for >48 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/m² twice daily (see 14.1 Clinical Trials by Indication). The most common adverse reactions of any grade (incidence ≥20%) were vomiting, rash, blood creatine phosphokinase increased, diarrhea, nausea, dry skin, asthenic events, pyrexia, acneiform rash, hypoalbuminemia, stomatitis, aspartate aminotransferase increased, paronychia, hemoglobin decreased, ALT increased, hair changes, blood creatinine increased and ejection fraction decreased.

In the Pediatric pool of 74 patients, the most commonly reported SAEs by preferred term (PT) were anemia, blood creatine phosphokinase increased, diarrhea, hypoxia, and pyrexia (2 [2.7%] patients each), all other SAEs were reported in 1 (1.4%) patient, each.

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/m² twice daily) for pilocytic astrocytoma involving the optic pathway in an externally sponsored pediatric study.

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 SPRINT Phase II Stratum 1 (14.1 Clinical Trials by Indication). Eligible 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 \geq 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/m² orally twice daily. Among these patients, 88% were exposed for 12 months or longer and 66% were exposed for greater than 2 years.

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 \geq 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.

Table 6 - 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 6 - 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 \geq 3 ^a N=50 n (%)
Cardiac Disorders		
Decreased Ejection Fraction	11 (22.0%)	0 (0%)
Sinus Tachycardia	10 (20.0%)	0 (0%)
Eye Disorders		
Vision Blurred	4 (8.0%)	0 (0%)
Gastrointestinal Disorders		
Vomiting	41 (82.0%)	3 (6.0%)
Abdominal Pain	38 (76.0%)	0 (0%)
Diarrhea	35 (70.0%)	8 (16.0%)
Nausea	33 (66.0%)	1 (2.0%)
Stomatitis	25 (50.0%)	0 (0%)

MedDRA System Organ Class MedDRA Term	All CTCAE Grades N=50 n (%)	CTCAE Grade ≥ 3 ^a N=50 n (%)
Dry Mouth	2 (4.0%)	0 (0%)
Skin and Subcutaneous Tissue Disorders		
Rash (all) ^b	39 (78.0%)	3 (6.0%)
Dry Skin	30 (60.0%)	0 (0%)
Rash Acneiform ^b	25 (50.0%)	2 (4.0%)
Paronychia	23 (46.0%)	3 (6.0%)
Pruritis	23 (46.0%)	0 (0%)
Dermatitis	18 (36.0%)	2 (4.0%)
Hair Changes	16 (32.0%)	0 (0%)
General Disorders		
Asthenic Events ^b	28 (56.0%)	0 (0%)
Pyrexia	28 (56.0%)	4 (8.0%)
Peripheral edema ^b	6 (12.0%)	0 (0%)
Facial edema ^b	2 (4.0%)	0 (0%)
Infections		
Skin Infection	10 (20.0%)	1 (2.0%)
Investigations		
Blood CPK increased	38 (76.0%)	3 (6.0%)
Hypoalbuminemia	25 (50.0%)	0 (0%)
AST increased	23 (46.0%)	1 (2.0%)
Hemoglobin decreased ^b	21 (42.0%)	2 (4.0%)
ALT increased	17 (34.0%)	2 (4.0%)
Blood creatinine increased	14 (28.0%)	1 (2.0%)
Ejection fraction decreased	11 (22.0%)	0 (0%)
Increased blood pressure ^b	9 (18.0%)	0 (0%)
Nervous System Disorders		
Headache	24 (48.0%)	1 (2.0%)
Renal and Urinary System Disorders		

MedDRA System Organ Class MedDRA Term	All CTCAE Grades N=50 n (%)	CTCAE Grade ≥ 3 ^a N=50 n (%)
Hematuria	11 (22%)	1 (2.0%)
Respiratory, Thoracic & Mediastinal Disorders		
Epistaxis	14 (28%)	0 (0%)
Dyspnea ^b	2 (4.0%)	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):

Rash (all): Dermatitis acneiform, Rash maculo-papular, Rash papular, Rash, Rash erythematous, Rash macular

Rash (acneiform): Dermatitis acneiform

Hair changes: Alopecia, Hair colour change

Asthenic events: Fatigue, Asthenia

Peripheral edema: Edema peripheral, Edema

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.

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

Table 7 presents the laboratory abnormalities in SPRINT Phase II Stratum 1.

Table 7 - Select Laboratory Abnormalities ($\geq 15\%$) 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	51	0
Increased aspartate aminotransferase (AST)	41	2
Increased alanine aminotransferase (ALT)	35	4

Laboratory Abnormality	KOSELUGO	
	All Grades (%) ^a	Grade ≥ 3 (%)
Increased lipase	32	5
Increased potassium	27	4
Decreased potassium	18	2 ^b
Increased alkaline phosphatase	18	0
Increased amylase	18	0
Increased sodium	18	0
Decreased sodium	16	0
Hematology		
Decreased hemoglobin	41	4
Decreased neutrophils	33	4
Decreased lymphocytes	20	2

^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.

^b Includes one Grade 4 increased CPK and one Grade 4 increased potassium.

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

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.

Active substances that may increase selumetinib plasma concentrations

Co-administration with a strong CYP3A4 inhibitor (200 mg itraconazole twice daily for 4 days) 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 (200 mg fluconazole once daily for 4 days) increased selumetinib C_{max} by 26% (90% CI 10, 43) and AUC by 53% (90% CI 44, 63) in healthy adult volunteers, respectively.

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

Co-administration with medicinal products that are strong inhibitors of CYP3A4 (e.g., clarithromycin, grapefruit and grapefruit products, oral ketoconazole) or CYP2C19 (e.g., ticlopidine) should be avoided. Co-administration with medicinal products that are 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 4).

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.

Active substances whose plasma concentrations may be altered by KOSELUGO

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 capsules do 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

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 8 - 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. If coadministration with strong or moderate CYP3A4 or CYP2C19 inhibitors cannot be avoided, reduce KOSELUGO 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.

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

9.5 Drug-Food Interactions

In healthy adult subjects, a single 75 mg dose (3 x 25 mg capsules) co-administration of KOSELUGO 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 (see 4 DOSAGE AND ADMINISTRATION).

In healthy adult subjects at a dose of 50 mg, co-administration of KOSELUGO with a low-fat meal resulted in 60% lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 38%, and the time to reach maximum concentration (T_{max}) was delayed by approximately 0.9 hours (see 4 DOSAGE AND ADMINISTRATION).

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

Table 9 - 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. AUC₀₋₁₂

e. AUC₀₋₆

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/m² to 30 mg/m² (0.8 to 1.2 times the recommended dose). Minimal accumulation of ~1.1 fold was observed at steady state upon twice daily dosing.

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}) between 1-1.5 hours post-dose.

Distribution:

The mean apparent volume of distribution at steady state of selumetinib across 20 to 30 mg/m² ranged from 78 to 171 L in pediatric patients, indicating 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 does not have clinically significant inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 or CYP2E1. Selumetinib does not induce CYP3A4, CYP1A2 or CYP2B6 at the recommended dose.

Based on *in vitro* studies, selumetinib is a substrate for BCRP and P-gp transporters but is unlikely to be subjected to clinically relevant drug interactions at the recommended pediatric dose. *In vitro* studies suggest that selumetinib does not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, MATE1 or MATE2K at the recommended pediatric dose. 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

Adult patients (>18 years old):

The PK parameters in adult subjects are similar to those in pediatric patients (3 to \leq 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

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

Store in the original bottle to protect from moisture and light. Do not remove desiccant.

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

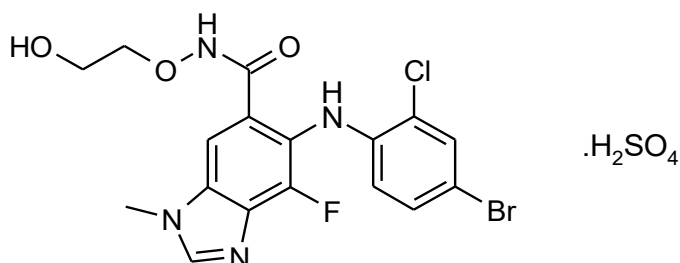
13 PHARMACEUTICAL INFORMATION

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: $\text{C}_{17}\text{H}_{17}\text{BrClFN}_4\text{O}_7\text{S}$

Selumetinib free base: $\text{C}_{17}\text{H}_{15}\text{BrClFN}_4\text{O}_3$

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 $\text{pK}_{\text{a}1}$ of 2.8 and a $\text{pK}_{\text{a}2}$ of 8.4

Solubility:	Media	Solubility ($\mu\text{g/mL}$)	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

Neurofibromatosis Type 1 with Inoperable Plexiform Neurofibromas

Table 10 - 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

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/m² (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 11 - 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%

Disease Characteristics	SPRINT (N = 50)
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 $\geq 20\%$ 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.

The primary endpoint, ORR was 66% (95% CI, 51.2 – 78.8). The median time to onset of response was 7.2 months (range 3.3 months to 1.6 years). The median (min-max) time to the maximal PN shrinkage from baseline was 14.6 months (3.3 months to 2.7 years).

The probability to remain in response after 12 and 16 cycles, estimated using the Kaplan-Meier method, was 100% (95% CI not estimated) and 96.2% (95% CI 75.7 – 99.4), respectively.

Table 12 - NF1 PN Efficacy Results from SPRINT (Phase II; Stratum I)

Efficacy Parameter	SPRINT (N=50)
Objective Response Rate ^a	
Objective Response Rate, % (95% CI)	66.0 (51.2 – 78.8)
Best objective response, n (%) ^{b, c}	
Complete Response	0
Confirmed Partial Response	33 (66%)
Unconfirmed Partial Response	4 (8%)
Stable Disease	11 (22%)
Progressive Disease	0
Duration of Response	
DoR ≥ 12 months, n (%)	27 (82%)

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.

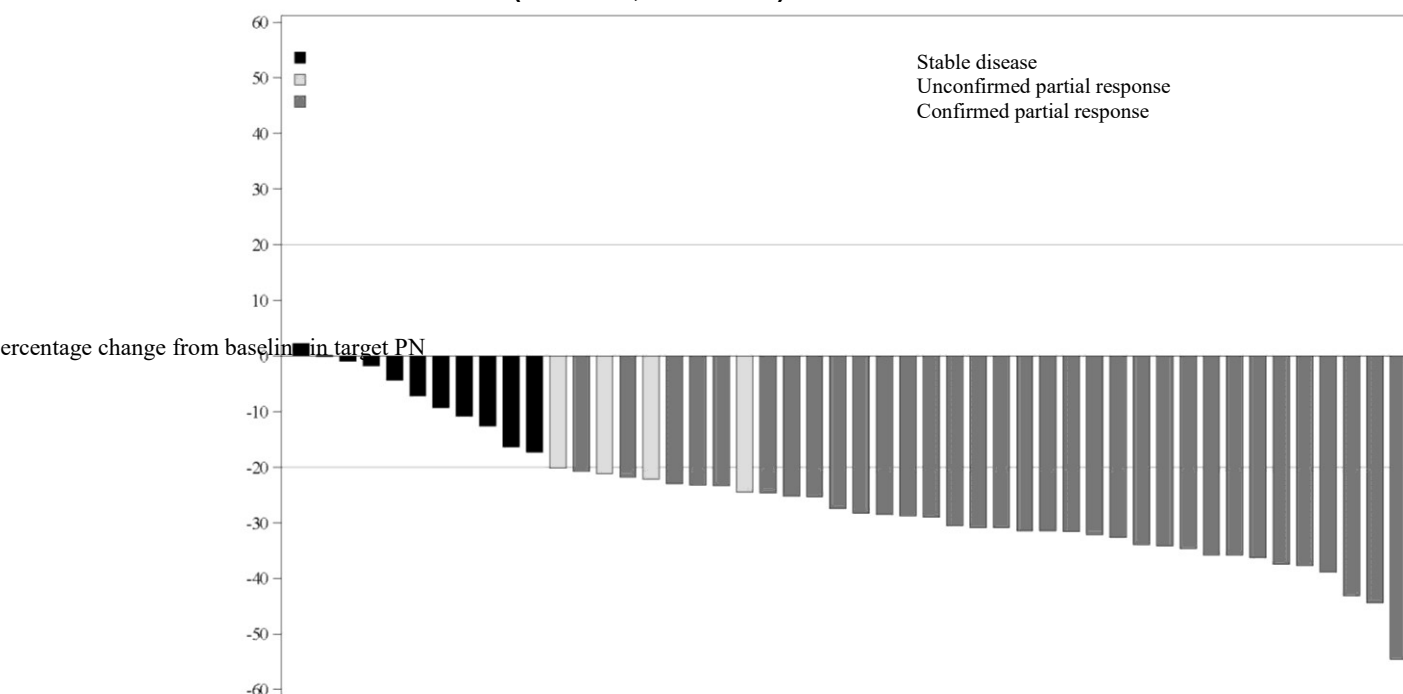
^b Complete response: disappearance of the target lesion; Partial Response: decrease in target PN volume by $\geq 20\%$ compared to baseline; Stable Disease: insufficient volume change from baseline to qualify for either partial response or progressive disease; Progressive Disease: increase in target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

^c Two patients were not evaluable.

The median DoR from onset of response was not reached; at the time of data cut-off the median follow-up time was 22.1 months. The median time from treatment initiation to disease progression while on treatment was not reached. At the time of data cut-off, 28 (56%) patients remained in confirmed partial response, 2 (4%) had unconfirmed partial responses, 15 (30%) had stable disease and 3 (6%) had progressive disease.

The median best percentage change in PN volume from baseline was -27.85% (range: 2.2% to -54.5%). **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). A clinically meaningful reduction in pain (defined as, ≥ 2 -point decrease from baseline) was reported for 50% of patients (n=12) at pre-Cycle 13; 12 patients (50%) reported no change (10 of which had a baseline score of ≤ 1) and no patients showed deterioration.

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 11.9) was reported by parents at pre-Cycle 13 with a mean change from

baseline in Peds-QL total score of 12.7 (95% CI 8.91 - 16.55). Improvement in HRQoL was also reported by patients with a mean change from baseline of 6.68 (95% CI 1.34 - 12.02).

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/m² 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/m².

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/m².

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/m² 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/m² 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/m² 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/m² 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/m² twice daily).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KOSELUGO™ **selumetinib capsules**

Read this carefully before you/your child start taking **KOSELUGO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your/your child's medical condition and treatment and ask if there is any new information about **KOSELUGO**.

What is KOSELUGO used for?

KOSELUGO is used to treat **children aged 2 to 18 years old** with:

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

How does KOSELUGO work?

KOSELUGO 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 may reduce the size of PNs caused by NF1.

What are the ingredients in KOSELUGO?

Medicinal ingredients: selumetinib (as 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.

KOSELUGO comes in the following dosage forms:

Capsules: 10 mg and 25 mg selumetinib (as selumetinib sulfate).

Do not use KOSELUGO if:

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KOSELUGO. 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 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 can cause the following side effects, including

Eye problems

KOSELUGO 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.

Heart problems

KOSELUGO can lower the amount of blood pumped by your heart (cardiomyopathy).

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

Skin Problems: KOSELUGO 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 can also cause skin infections around fingernails or toenails (**paronychia**) and a severe skin problem called **palmar-plantar erythrodysesthesia syndrome**.

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

Birth Control

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

Children under 2 years old:

KOSELUGO should not be given to children under 2 years 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 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 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:

- 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
- 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

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:

- Always take KOSELUGO exactly as your healthcare professional has told you. You should check with your healthcare professional if you are not sure how to take KOSELUGO.
- Take KOSELUGO twice a day, about 12 hours apart
- Swallow KOSELUGO capsules whole with water. Do not chew, dissolve, or open the capsules
 - Do not take KOSELUGO if you are unable to swallow a whole capsule.
- Take on an empty stomach (at least 1 hour before a meal or 2 hours after a meal).
- Take KOSELUGO for as long as your healthcare professional prescribes it.

Usual dose:

- The healthcare professional will tell you which and how many capsules of KOSELUGO to take and when. 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, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of KOSELUGO 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, do not take another dose. Take the next dose at your usual time.

What are possible side effects from using KOSELUGO?

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

- | | |
|--|---|
| • Vomiting, feeling sick | • fingernails, itching, skin infection |
| • Diarrhea | • Hair thinning, hair colour change |
| • Mouth sores, redness or swelling inside of the mouth | • Headache |
| • Skin and nail problems: dry skin, rash, redness around the | • Nosebleeds |
| | • Tiredness, weakness or lacking energy |

- Fever
- Swelling of the hands or feet
- Blurred vision
- Dry mouth
- Swelling of the face
- Shortness of breath
- Stomach pain
- Weight gain

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking 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, Sinus Tachycardia (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.		✓	
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 vision, loss of vision, dark spots in your vision, 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		✓	

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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) 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 at room temperature between 15 to 30°C in the original bottle to protect from moisture and light. Do not remove the desiccant pack.

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.

If you want more information about KOSELUGO:

- 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/drugproduct-database.html>); the manufacturer's website www.astrazeneca.ca or by calling 1-800-668-6000.
- This patient medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

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