1 NAME OF THE MEDICINAL PRODUCT

Koselugo 10 mg
Koselugo 25 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Selumetinib (As Hyd-Sulfate) 10 mg/capsule
Selumetinib (As Hyd-Sulfate) 25 mg/capsule

3 PHARMACEUTICAL FORM

Hard Capsules

4 THERAPEUTIC INDICATIONS

KOSELUGO is indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

The recommended dosage of KOSELUGO is 25 mg/m^2 orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.

Koselugo can be taken with or without food The recommended dose of KOSELUGO based on body surface area (BSA) is shown in Table 1.

Table 1 Recommended Dosage Based on Body Surface Area

Body Surface Area*	Recommended Dosage
0.55 – 0.69 m^2	20 mg in the morning and 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

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

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

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

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

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

For opening and closing of the bottle, press the cap and turn simultaneously.

5.2 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 2.

Table 2 Recommended Dose Reductions for KOSELUGO for Adverse Reactions

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

* Permanently discontinue KOSELUGO in patients unable to tolerate KOSELUGO after two dose reductions.

Dosage modifications for adverse reactions are in Table 3.

Table 3 Recommended Dosage Modifications for KOSELUGO for Adverse Reactions

Severity of Adverse Reaction	Recommended Dosage Modifications for KOSELUGO
Cardiomyopathy [see Warnings and Precautions (8.1)]	
• Asymptomatic decrease in left ventricular ejection fraction (LVEF) of10% or greater from baseline and less than lower level of normal	Withhold until resolution. Resume at reduced dose.
• Symptomatic decreased LVEF • Grade 3 or 4 decreased LVEF	Permanently discontinue.
Ocular Toxicity [see Warnings and Precautions (8.2)]	
• Retinal Pigment Epithelial Detachment (RPED)	Withhold until resolution. Resume at reduced dose.
• Retinal vein occlusion (RVO)	Permanently discontinue.
Gastrointestinal Toxicity [see Warnings and Precautions (8.3)]	
• Grade 3 Diarrhea	Withhold until improved to Grade 0 or 1. Resume at same dose. Permanently discontinue if no improvement within 3 days.
• Grade 4 Diarrhea	Permanently discontinue.
• Grade 3 or 4 Colitis	Permanently discontinue.
Skin Toxicity [see Warnings and Precautions (8.4)]	
• Grade 3 or 4	Withhold until improvement. Resume at reduced dose.
Increased Creatine Phosphokinase (CPK) [see Warnings and Precautions (8.5)]	

Severity of Adverse Reaction	Recommended Dosage Modifications for KOSELUGO
• Grade 4 Increased CPK • Any Increased CPK and myalgia	Withhold until improved to Grade 0 or 1. Resume at reduced dose. Permanently discontinue if no improvement within 3 weeks.
• Rhabdomyolysis	Permanently discontinue.
Other Adverse Reactions [see Adverse Reactions (9)]	
• Intolerable Grade 2 • Grade 3	Withhold KOSELUGO until improved to Grade 0 or 1. Resume at reduced dose.
• Grade 4	Withhold KOSELUGO until improved to Grade 0 or 1. Resume at reduced dose. Consider discontinuation.

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

5.3 Dosage Modifications for Hepatic Impairment

Reduce the recommended dosage of KOSELUGO to 20 mg/m^2 orally twice daily in patients with moderate hepatic impairment (Child-Pugh B). The recommended dosage of KOSELUGO for use in patients with severe hepatic impairment (Child-Pugh C) has not been established *[see Use in Specific Populations (11)]*.

Table 4 Recommended Dosage of KOSELUGO for Moderate Hepatic Impairment

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

5.4 Dosage Modifications for Drug Interactions

Strong or Moderate CYP3A4 Inhibitors or Fluconazole

Avoid coadministration of strong or moderate CYP3A4 inhibitors or fluconazole with KOSELUGO. If coadministration with strong or moderate CYP3A4 inhibitors or fluconazole cannot be avoided, reduce the KOSELUGO dosage as recommended in Table 5. After discontinuation of the strong or moderate

CYP3A4 inhibitor or fluconazole for 3 elimination half-lives, resume the KOSELUGO dose that was taken prior to initiating the inhibitor or fluconazole *[see Drug Interactions (10)]*.

Table 5 Recommended Dosage of KOSELUGO for Coadministration with Strong or Moderate CYP3A4 Inhibitors or Fluconazole

Body Surface Area	If the current dosage is 25 mg/m^2 twice daily, reduce to 20 mg/m^2 twice daily (mg/dose)		If the current dosage is 20 mg/m^2 twice daily, reduce to 15 mg/m^2 twice daily (mg/dose)	
	Morning	Evening	Morning	Evening
0.55 – 0.69 m^2	10	10	10 mg once daily	
0.70 – 0.89 m^2	20	10	10	10
0.90 – 1.09 m^2	20	20	20	10
1.10 – 1.29 m^2	25	25	25	10
1.30 – 1.49 m^2	30	25	25	20
1.50 – 1.69 m^2	35	30	25	25
1.70 – 1.89 m^2	35	35	30	25
≥ 1.90 m^2	40	40	30	30

6 DOSAGE FORMS AND STRENGTHS

Capsules:

- 10 mg: white to off-white, hard capsule, banded and marked with “SEL 10” in black ink.
- 25 mg: blue, hard capsule, banded and marked with “SEL 25” in black ink.

7 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 10.

8 WARNINGS AND PRECAUTIONS

8.1 Cardiomyopathy

Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥ 10% below baseline, occurred in 23% of 74 pediatric patients who received KOSELUGO in SPRINT *[see Adverse Reactions (9)]*. Four percent of patients experienced decreased LVEF below the institutional lower limit of normal (LLN). Grade 3 decreased LVEF occurred in one patient and resulted in dose reduction. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in 71% of these patients.

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

The safety of KOSELUGO has not been established in patients with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN.

Assess ejection fraction by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction *[see Dosage and Administration (5)]*. 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.

8.2 Ocular Toxicity

Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving KOSELUGO in SPRINT. Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients.

Serious ocular toxicities including retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED), occurred in an unapproved population of adult patients with multiple tumor types who received KOSELUGO as a single agent 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.

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 RVO. Withhold KOSELUGO in patients with RPED, follow up with optical coherence tomography assessments every 3 weeks until resolution, and resume KOSELUGO at a reduced dose. For other ocular toxicities, withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of the adverse reaction *[see Dosage and Administration (5)]*.

8.3 Gastrointestinal Toxicity

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

Serious gastrointestinal toxicities, including perforation, colitis, ileus, and intestinal obstruction, occurred in an unapproved population of adult patients with multiple tumor types who received KOSELUGO as a single agent or in combination with other anti-cancer agents. Colitis occurred in an unapproved population of pediatric patients with multiple tumor types who received KOSELUGO as a single agent.

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 Dosage and Administration (5)]*.

8.4 Skin Toxicity

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

occurred in 8% of patients. Rash resulted in dose interruption in 11% of patients and dose reduction in 4% of patients.

Other skin toxicities, including severe palmar-plantar erythrodysesthesia syndrome, occurred in an unapproved population of adult patients with multiple tumor 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 Dosage and Administration (5)]*.

8.5 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.

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 Dosage and Administration (5)]*.

8.6 Increased Levels of Vitamin E and Risk of Bleeding

KOSELUGO capsules contain vitamin E (10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS); while KOSELUGO 25 mg capsules contain 36 mg vitamin E as TPGS). Vitamin E can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. Daily vitamin E intake that exceeds the recommended or safe limits may increase the risk of bleeding. Supplemental vitamin E is not recommended if daily vitamin E intake (including the amount of vitamin E in KOSELUGO and supplement) will exceed the recommended or safe limits.

An increased risk of bleeding in patients may occur in patients who are coadministered vitamin-K antagonists or anti-platelet antagonists with KOSELUGO. Monitor for bleeding in these patients. Increase international normalized ratio (INR) monitoring, as appropriate, 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 Drug Interactions (10)]*.

8.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, KOSELUGO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of selumetinib to mice during organogenesis caused reduced fetal weight, adverse structural defects, and effects on embryo-fetal survival at approximate exposures > 5 times the human exposure at the clinical dose of 25 mg/m^2 twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose *[see Use in Specific Populations (11.1, 11.3)]*.

8.8 Effects on ability to drive and use machines

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 selumetinib and patients who experience these symptoms should observe caution when driving or using machines.

9 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cardiomyopathy *[see Warnings and Precautions (8.1)]*
- Ocular toxicity *[see Warnings and Precautions (8.2)]*
- Gastrointestinal toxicity *[see Warnings and Precautions (8.3)]*
- Skin toxicity *[see Warnings and Precautions (8.4)]*
- Increased creatine phosphokinase *[see Warnings and Precautions (8.5)]*

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflects exposure to KOSELUGO in 74 pediatric patients who received a dosage ranging from 20 mg/m^2 to 30 mg/m^2 orally twice daily in SPRINT. Among these patients, the duration of KOSELUGO exposure, including dose interruptions, was 12 months or longer (91%), more than 2 years (74%), or more than 4 years (23%). The WARNINGS AND PRECAUTIONS also includes additional data from adult and pediatric patients who received KOSELUGO administered at various doses across a range of tumors in other clinical trials.

Neurofibromatosis Type 1 (NF1) with Inoperable Plexiform Neurofibromas (PN)

The safety of KOSELUGO was evaluated in SPRINT Phase II Stratum 1 *[see Clinical Studies (16)]*. 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 ≥ 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. Patients received KOSELUGO 25 mg/m^2 orally twice daily (n=50). Among these patients, 88% were exposed for 12 months or longer and 66% were exposed for greater than 2 years.

Serious adverse reactions occurred in 24% of patients who received KOSELUGO. Serious adverse reactions that occurred in 2 or more patients were anemia, hypoxia and diarrhea.

Permanent discontinuation due to an adverse reaction occurred in 12% of patients who received KOSELUGO. Adverse reactions resulting in permanent discontinuation of KOSELUGO included increased blood creatinine, increased weight, diarrhea, paronychia, malignant peripheral nerve sheath tumor,acute kidney injury, and skin ulcer.

Dosage interruptions and dose reductions due to adverse reactions occurred in 80% and 24% of patients who received KOSELUGO, respectively. Adverse reactions requiring a dosage interruption or reduction in ≥5% of patients were vomiting, paronychia, diarrhea, nausea, abdominal pain, rash, skin infection, influenza-like illness, pyrexia and weight gain.

The most common adverse reactions (≥ 40%) were vomiting, rash (all), abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

Table 6 presents the adverse reactions in SPRINT Phase II Stratum 1.

Table 6 Adverse Reactions (≥ 20%) in Patients Who Received KOSELUGO in SPRINT Phase II Stratum 1

Adverse Reaction	KOSELUGO N=50	
	All Grades (%)	Grade ≥ 3 (%)*
Gastrointestinal		
Vomiting	82	6
Abdominal pain[1]	76	0
Diarrhea	70	16
Nausea	66	2
Stomatitis[2]	50	0
Constipation	34	0
Skin and Subcutaneous Tissue		
Rash (all) [3]	80	6
Dry skin	60	0
Rash acneiform[4]	50	4
Paronychia[5]	48	6
Pruritus	46	0
Dermatitis[6]	36	4
Hair changes[7]	32	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[8]	58	0
General		
Fatigue[9]	56	0
Pyrexia	56	8
Edema[10]	20	0
Nervous System		
Headache	48	2
Respiratory, Thoracic and Mediastinal		
Epistaxis	28	0
Renal and Urinary System		
Hematuria	22	2
Proteinuria	22	0
Metabolism and Nutrition		
Decreased appetite	22	0
Cardiac System		
Decreased ejection fraction	22	0
Sinus tachycardia	20	0

Adverse Reaction	KOSELUGO N=50	
	All Grades (%)	Grade ≥ 3 (%)*
Infections		
Skin infection[11]	20	2

* All events were Grade 3.

[1] Abdominal pain includes abdominal pain; abdominal pain upper

[2] Stomatitis includes stomatitis; mouth ulceration

[3] Rash (all) includes dermatitis acneiform; rash maculo-papular; erythema; rash pustular; rash; urticaria; exfoliative rash; rash pruritic; rash erythematous

[4] Rash (acneiform) includes dermatitis acneiform

[5] Paronychia includes paronychia, nail infection

[6] Dermatitis includes dermatitis; dermatitis atopic; dermatitis diaper; eczema; seborrheic dermatitis; skin irritation

[7] Hair changes include alopecia, hair color change

[8] Musculoskeletal pain includes pain in extremity; back pain; neck pain; musculoskeletal pain

[9] Fatigue includes fatigue, malaise

[10] Edema includes peripheral swelling, edema, localized edema

[11] Skin infection includes skin infection; abscess; cellulitis; impetigo; staphylococcal skin infection

Clinically relevant adverse reactions that occurred < 20% of patients include:

- *Eye*: visual impairment
- *Gastrointestinal Disorders*: dry mouth
- *General Disorders*: facial edema, including periorbital edema and face edema
- *Metabolism and Nutrition*: increased weight
- *Renal and Urinary System*: acute kidney injury
- *Respiratory, Thoracic & Mediastinal*: dyspnea, including exertional dyspnea and dyspnea at rest
- *Vascular*: hypertension

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

Table 7 Select Laboratory Abnormalities (≥ 15%) Worsening from Baseline in Patients Who Received KOSELUGO in SPRINT Phase II Stratum 1

Laboratory Abnormality	KOSELUGO	
	All Grades (%)*	Grade ≥ 3 (%)
Chemistry		
Increased creatine phosphokinase (CPK)	79	7§
Decreased albumin	51	0
Increased aspartate aminotransferase (AST)	41	2
Increased alanine aminotransferase (ALT)	35	4
Increased lipase	32	5
Increased potassium	27	4
Decreased potassium	18	2§
Increased alkaline phosphatase	18	0
Increased amylase	18	0

Laboratory Abnormality	KOSELUGO	
	All Grades (%)*	Grade ≥ 3 (%)
Increased sodium	18	0
Decreased sodium	16	0
Hematology		
Decreased hemoglobin	41	4
Decreased neutrophils	33	4
Decreased lymphocytes	20	2

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

§ Includes one Grade 4 increased CPK and one Grade 4 increased potassium.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

10 DRUG INTERACTIONS

10.1 Effect of Other Drugs on KOSELUGO

Strong or Moderate CYP3A4 Inhibitors or Fluconazole	
Clinical Impact	• Concomitant use of KOSELUGO with a strong or moderate CYP3A4 inhibitor or fluconazole increased selumetinib plasma concentrations *[see Clinical Pharmacology (14)]*, which may increase the risk of adverse reactions.
Management	• Avoid coadministration of strong or moderate CYP3A4 inhibitors or fluconazole with KOSELUGO. If coadministration with strong or moderate CYP3A4 inhibitors or fluconazole cannot be avoided, reduce KOSELUGO dosage *[see Dosage and Administration (5)]*.
Strong or Moderate CYP3A4 Inducers	
Clinical Impact	• Concomitant use of KOSELUGO with a strong or moderate CYP3A4 inducer decreased selumetinib plasma concentrations *[see Clinical Pharmacology (14)]*, which may reduce KOSELUGO efficacy.
Management	• Avoid concomitant use of strong or moderate CYP3A4 inducers with KOSELUGO.
Vitamin E	
Clinical Impact	• 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.

Management	• 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 coadministered a vitamin-K antagonist or an anti-platelet agent with KOSELUGO. Increase INR monitoring, as appropriate, in patients taking a vitamin-K antagonist *[see Warnings and Precautions (8.3)]*.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (14)]*, KOSELUGO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of KOSELUGO in pregnant women to evaluate drug-associated risk. In animal reproduction studies, administration of selumetinib to mice during organogenesis caused reduced fetal weight, adverse structural defects, and effects on embryofetal survival at exposures approximately > 5 times the human exposure at the clinical dose of 25 mg/m^2 twice daily (*see Data*). Advise pregnant women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies in mice at doses > 2.5 mg/kg twice daily (~5 times the human exposure based on area under the curve [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.

Administration of selumetinib to pregnant mice from gestation Day 6 through 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).

11.2 Lactation

Risk Summary

There are no data on the presence of selumetinib or its active metabolite in human milk or their effects on the breastfed child or milk production. Selumetinib and its active metabolite were present in the milk of lactating mice (*see Data*). 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.

Data

Animal Data

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. Administration of selumetinib to dams during gestation and early lactation was associated with adverse events in pups, including reduced growth rates and incidence of malformations *[see Use in Specific Populations (11.1)]*.

11.3 Females and Males of Reproductive Potential

KOSELUGO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (11.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating KOSELUGO *[see Use in Specific Populations (11.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose.

11.4 Pediatric Use

The safety and effectiveness have been established in pediatric patients 2 years of age and older with NF1 who have inoperable PN and the information on this use is discussed throughout the labeling. The safety and effectiveness of KOSELUGO have not been established in pediatric patients younger than 2 years of age.

Animal Toxicity Data

In 3-month general toxicology studies, male rats receiving selumetinib at doses ≥ 10 mg/kg daily (~60 times the human exposure based on AUC at the clinical dose of 25 mg/m^2 twice daily) showed growth plate dysplasia.

11.5 Geriatric Use

Clinical studies did not include patients 65 years of age and older.

11.6 Renal Impairment

No dose adjustment is recommended in patients with renal impairment or those with End Stage Renal Disease *[see Clinical Pharmacology (14.3)]*.

11.7 Hepatic Impairment

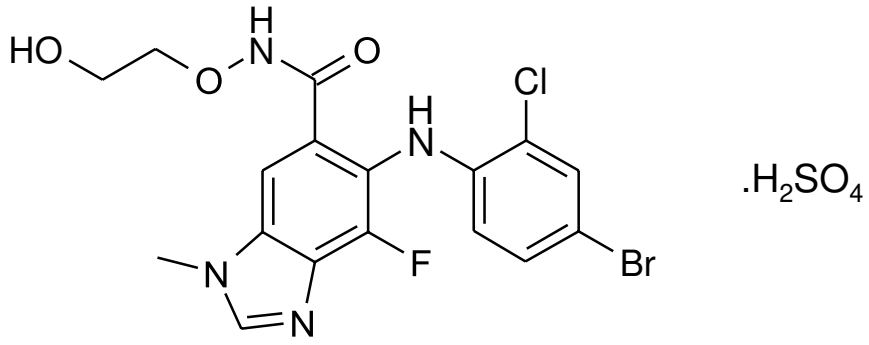
Selumetinib exposures increased in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (14)]*. Reduce the dose of KOSELUGO for patients with moderate hepatic impairment (Child-Pugh B). A recommended dosage of KOSELUGO for use in patients with severe hepatic impairment (Child-Pugh C) has not been established *[see Dosage and Administration (5.3)]*.

12 OVERDOSAGE

Dialysis is not helpful as KOSELUGO is highly protein bound and is extensively metabolized.

13 DESCRIPTION

Selumetinib is a kinase inhibitor. The chemical name is 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1*H*-benzimidazol-3-ium hydrogen sulfate. The molecular formula for selumetinib sulfate is $C_{17}H_{17}BrClFN_4O_7S$ and the relative molecular mass is 555.76 g/mol. Selumetinib sulfate has the following structural formula:



Selumetinib sulfate is a white to yellow monomorphic crystalline powder that exhibits a pH dependent solubility. Selumetinib sulfate is freely soluble at pH < 1.5, sparingly soluble in the pH range at 1.5 to 3 and slightly soluble at pH > 3. Selumetinib sulfate has two ionizable functions with pKa values of 2.8 and 8.4.

KOSELUGO (selumetinib) 10 mg capsules for oral use, contain 10 mg selumetinib (equivalent to 12.1 mg selumetinib hyd-sulfate) and the excipient, vitamin E polyethylene glycol succinate. The capsule shell contains hypromellose, purified water, titanium dioxide, potassium chloride, and carrageenan. The capsule is imprinted with black ink that contains shellac, iron oxide black, propylene glycol and ammonium hydroxide.

KOSELUGO (selumetinib) 25 mg capsules for oral use, contain 25 mg selumetinib (equivalent to 30.25 mg selumetinib hyd-sulfate) and the excipient, vitamin E polyethylene glycol succinate. The capsule shell, body and cap contain hypromellose, purified water, titanium dioxide, potassium chloride, carrageenan, FD&C blue 2 and ferric oxide yellow. The capsule is imprinted with black ink that contains White shellac, FD&C Blue Aluminium lake, Ferric oxide yellow, Ferric oxide red, Carnauba wax and Glyceryl monooleate.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Selumetinib is an inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Both MEK and ERK are critical components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers.

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

14.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of KOSELUGO have not been fully characterized.

Cardiac Electrophysiology

At a dose 1.5 times the maximum recommended dose, KOSELUGO does not prolong the QT/QTc interval to any clinically relevant extent.

14.3 Pharmacokinetics

At the recommended dosage of 25 mg/m^2 twice daily in pediatric patients (2 to ≤ 18 years old), the mean maximum plasma concentration (C_{max}) (coefficient of variation [CV%]) following the first dose and at steady state was 731 (62%) ng/mL and 798 (52%) ng/mL, respectively. The mean area under the plasma drug concentration curve (AUC_{0-12h}) following the first dose was 2009 (35%) ng•h/mL and the AUC_{0-6h} at steady state was 1958 (41%) ng•h/mL. 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). The accumulation was 1.1-fold following administration of KOSELUGO 25 mg/m^2 twice daily.

Absorption

The mean absolute oral bioavailability of selumetinib was 62% in healthy adults. The median time to peak plasma concentrations (T_{max}) at steady-state in pediatric patients was 1 to 1.5 hours.

Effect of Food

Selumetinib C_{max} and AUC decreased by 24% and 8%, respectively, following a low-fat meal (400 calories, 25% fat) in adolescent patients with NF1 and inoperable PN administered multiple doses of 25 mg/m^2 twice daily and-. T_{max} was delayed byapproximately 0.6 hours.

A population PK analysis including children and adolescent patients with NF1 and inoperable PN, adult patients with cancers, and healthy adults showed that a low or high-fat meal had no clinically relevant effect on the AUC of selumetinib.

Distribution

The mean apparent volume of distribution at steady state (V_{ss}) of selumetinib across a dose range of 20 mg/m^2 to 30 mg/m^2 (0.8 to 1.2 times the recommended dosage) ranged from 78 L to 171 L in pediatric patients.

The plasma protein binding was 98.4% in humans in vitro. Selumetinib binds to serum albumin (96%) and α-1 acid glycoprotein (< 35%).

Elimination

In pediatric patients, selumetinib had an apparent oral clearance (CL/F) of 8.8 L/hr and a mean elimination half-life of approximately 6.2 hours following a dose of 25 mg/m^2.

Metabolism

Selumetinib is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19, CYP1A2, CYP2C9, CYP2E1, and CYP3A5. Selumetinib also undergoes glucuronidation by UGT1A1 and UGT1A3. It is estimated that 56% of the observed intrinsic clearance of selumetinib could be attributed to

CYP metabolism and about 29% attributed to direct glucuronidation by UGT enzymes in vitro. The active metabolite, N-desmethyl selumetinib, is generated by CYP2C19 and CYP1A2 with additional contribution by CYP2C9 and CYP2A6, and metabolized through the same routes as selumetinib.

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.

Excretion

After a single oral dose of radiolabeled selumetinib 75 mg (1.5 times the recommended dose) to healthy adults, 59% of the dose was recovered in feces (19% as unchanged) and 33% in urine (< 1% as parent).

Specific Populations

Racial or Ethnic Groups

No clinically meaningful effect on the pharmacokinetics of selumetinib or N-desmethyl selumetinib were observed based on race (White, Asian, Black).

Patients with Renal Impairment

Following administration of a single dose of 50 mg, selumetinib exposures were similar in subjects with End Stage Renal Disease (CLcr < 15 mL/min) who required dialysis compared to subjects with normal renal function (CLcr ≥ 90 mL/min).

Patients with Hepatic Impairment

Following administration of a single-dose of selumetinib, dose normalized total $AUC_{0\text{-}INF}$ decreased by 14% in subjects with mild hepatic impairment (Child-Pugh A), and increased by 59% in subjects with moderate hepatic impairment (Child-Pugh B) and by 57% in subjects with severe hepatic impairment (Child-Pugh class C) compared to subjects with normal hepatic function. Selumetinib unbound $AUC_{0\text{-}INF}$ decreased by 31% in subjects with mild hepatic impairment (Child-Pugh A), and increased by 41% in subjects with moderate hepatic impairment (Child-Pugh B), and 3.2-fold in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Strong or Moderate CYP3A4 Inhibitors: Concomitant use of itraconazole (strong CYP3A4 inhibitor) increased selumetinib AUC by 49% and C_{max} by 19%. Concomitant use of erythromycin (moderate CYP3A4 inhibitor) is predicted to increase selumetinib AUC by 41% and C_{max} by 23%.

Effect of Fluconazole: Concomitant use of fluconazole (strong CYP2C19 inhibitor and moderate CYP3A4 inhibitor) increased selumetinib AUC by 53% and C_{max} by 26%.

Effect of Strong or Moderate CYP3A4 Inducers: Concomitant use of rifampicin (strong CYP3A4 inducer) decreased selumetinib AUC by 51% and C_{max} by 26%. Concomitant use of efavirenz (moderate CYP3A4 inducer) is predicted to decrease selumetinib AUC by 38% and C_{max} by 22%.

In Vitro Studies

CYP Enzymes: Selumetinib does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP2E1. Selumetinib does not induce CYP3A4, CYP1A2, or CYP2B6.

Transporter Systems: Selumetinib does not inhibit breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2K transporters.

Selumetinib is a substrate of BCRP and P-gp transporters.

15 NONCLINICAL TOXICOLOGY

15.1 12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Selumetinib was not carcinogenic in a 6-month study in rasH2 transgenic mice at exposures 24 times (males) and 36 times (females) and in 2-year carcinogenicity study in rats at exposures 20 times (male) and 15 times the human exposure (AUC) at the clinical dose of 25 mg/m^2.

Mutagenicity

Selumetinib was not mutagenic or clastogenic in vitro. Selumetinib did result in an increase in micronucleated immature erythrocytes (chromosome aberrations) in mouse micronucleus studies, predominantly via an aneugenic mode of action, but at doses > 160 mg/kg (~38 times the human C_{max} at the clinical dose of 25 mg/m^2).

Impairment of Fertility

In a 6-month mouse study, selumetinib did not affect male mating performance at any dose up to 20 mg/kg twice daily (approximately 33 times the human exposure based on AUC at the clinical dose of 25 mg/m^2 twice daily). In female mice exposed to selumetinib at 12.5 mg/kg twice daily, mating performance and fertility were not affected. The NOAEL for both maternal toxicity and effects on reproductive performance was 2.5 mg/kg twice daily (approximately 5 times the human exposure based on AUC at the clinical dose of 25 mg/m^2 twice daily).

15.2 Animal Toxicology and/or Pharmacology

In a 26-week repeat-dose toxicology study, selumetinib at a dose of 20 mg/kg (approximately 33 times the human exposure based on AUC at the clinical dose of 25 mg/m^2 twice daily) led to significant urinary tract obstruction as well as inflammation and luminal hemorrhage of the urethra leading to early death in male mice.

16 CLINICAL STUDIES

16.1 Neurofibromatosis Type 1 (NF1) with Inoperable Plexiform Neurofibromas (PN)

The efficacy of KOSELUGO was evaluated in SPRINT Phase II Stratum 1, an open-label, multicenter, single arm trial (NCT01362803). Eligible patients were required to have NF1 with inoperable PN, defined as a PN that could not be 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 were also required to have significant morbidity related to the target PN. Morbidities that were present in ≥ 20% of

patients included disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction. Patients received KOSELUGO 25 mg/m^2 orally twice daily until disease progression or unacceptable toxicity.

The major efficacy outcome measure was overall 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 tumor assessment within 3-6 months). The target PN, defined as the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was evaluated for response rate using centrally read volumetric magnetic resonance imaging (MRI) analysis per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. Tumor response was evaluated at baseline and while on treatment after every 4 cycles for 2 years, and then every 6 cycles. An additional efficacy outcome measure was duration of response (DoR).

A total of 50 pediatric patients received KOSELUGO. The median age was 10.2 years (range 3.5 to 17.4 years); 60% were male; and 84% were White, 8% were Black and 2% were Asian.

Efficacy results are provided in Table 8. The median time to onset of response was 7.2 months (range: 3.3 months to 1.6 years).

Table 8 Efficacy Results from SPRINT Phase II Stratum 1

Efficacy Parameter	**SPRINT N = 50**
Overall Response Rate [*, §]	
Overall Response Rate, n (%)	33 (66%)
95% CI	(51, 79)
Complete Response[†]	0
Confirmed Partial Response, n (%)[†]	33 (66%)
Duration of Response[‡]	
Median (95% CI) months	NR (41.2 – NE)
DoR ≥ 24 months, n (%)	26 (79%)
DoR ≥ 36 months, n (%)	21 (64%)

CI – confidence interval, DoR – duration of response, NE – not evaluable, NR – not reached.

§ The ORR assessment (data cut-off date [DCO]: June 2018) was conducted by a single National Cancer Institute reviewer who was a SPRINTinvestigator and who evaluated all PN imaging from patients enrolled at all trial sites.

* Responses required confirmation at least 3 months after the criteria for first response were met.

† Complete response: disappearance of the target lesion; Partial response: decrease in target PN volume by ≥ 20% compared to baseline.

‡ DCO: March 2021.

An independent centralized review of tumor response per REiNS criteria (data cut-off June 2018) resulted in an ORR of 44%(95% CI: 30, 59).

17 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Strength	Description	Capsules per Bottle	Registration Number
10 mg	White to off-white, hard capsule, banded and marked with “SEL10” in black ink.	60	167-72-36526-99
25 mg	Blue, hard capsule, banded and marked with “SEL25” in black ink.	60	167-75-36527-99

Storage

Do not store above 25°C. Store in the original bottle to protect from moisture and light.

Do not remove desiccant.

The expiry date of the product is indicated on the packaging materials.

18 MANUFACTURER

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