Koselugo® (selumetinib)
10 mg & 25 mg capsules

SHRINK

NF1 Plexiform Neurofibromas (PN)

AND LET HIS **LOVE OF MUSIC**

GROW

KOSELUGO® (selumetinib) is the FIRST FDA-approved treatment for pediatric patients aged 2 years and older with neurofibromatosis type 1 (NF1) who have plexiform neurofibromas (PN) that cannot be completely removed by surgery.

Sam, age 10, living with NF1 PN. Sam is a Koselugo patient.

INDICATION & SELECT IMPORTANT SAFETY INFORMATION for KOSELUGO® (selumetinib)

INDICATION

Koselugo is a prescription medicine that is used to treat children 2 years of age and older with neurofibromatosis type 1 (NF1) who have plexiform neurofibromas that cannot be completely removed by surgery. It is not known if Koselugo is safe and effective in children under 2 years of age.

SELECT IMPORTANT SAFETY INFORMATION

Serious side effects include: heart problems, eye problems, severe diarrhea, skin rash, muscle problems (rhabdomyolysis), embryo-fetal toxicity.

Most common side effects include: vomiting, stomach-area pain, nausea, dry skin, muscle and bone pain, feeling of tiredness or lacking energy, fever, sores in your mouth, headache, redness around fingernails, itching.

Please see additional Important Safety Information throughout and scan the QR code or visit bit.ly/KoselugoPI to view Patient Information in the full Prescribing Information for Koselugo (selumetinib).

All families featured in this brochure have been compensated by Alexion, unless otherwise noted.

What are NF1 plexiform neurofibromas (PN)?

PN are noncancerous tumors that can grow along nerves in the body. Regardless of size, any PN may cause symptoms, depending on where it's located in the body.

PN are commonly seen in people living with NF1.

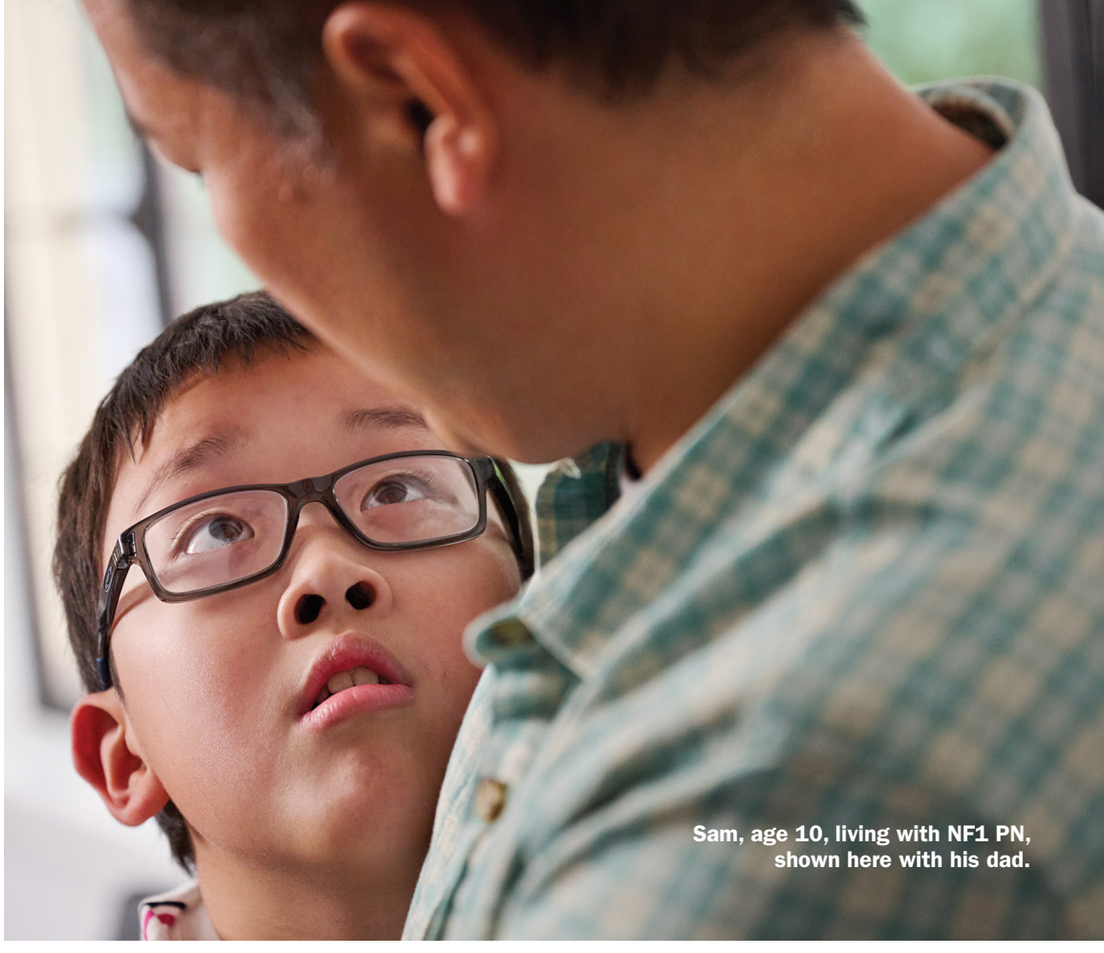
Up to **50%*** of children with NF1 **have PN**

*Using whole-body magnetic resonance imaging (MRI).

NF1 PN growth may be unpredictable and should not be ignored.

**Not an all-inclusive list.

This image is for illustration only, not an actual patient.



Sam, age 10, living with NF1 PN, shown here with his dad.

Which doctors treat NF1 PN?

Children with NF1 PN are usually seen by specialists who focus on treating symptoms caused by this disease. **The location of your child's PN in the body will help determine which doctors are best to see for treatment.**

By spotting PN early and communicating new or worsening symptoms with your child's doctor, you can help your child get the treatment they need.

Can NF1 PN be removed with surgery?

Surgery can be an effective option for removing NF1 PN. If your child's doctor determines that surgery is not possible, Koselugo may be able to help.

How can Koselugo help?

Koselugo is the first FDA-approved oral medication proven to shrink NF1 PN when PN cannot be completely removed by surgery.†

†66% (33 of 50) of patients in the clinical study saw a 20% or more decrease in the size of their PN, confirmed by 3D MRI scan.

IMPORTANT SAFETY INFORMATION

What are the possible side effects of Koselugo?

Koselugo may cause serious side effects, including:

- **Heart problems.** Koselugo can lower the amount of blood pumped by your heart, which is common and can also be severe. Your healthcare provider will do tests before and during treatment to check how well your heart is working. Tell your healthcare provider right away if you get any of the following signs or symptoms: persistent coughing or wheezing, shortness of breath, swelling of your ankles and feet, tiredness, increased heart rate.

Please see additional Important Safety Information throughout and scan the QR code or visit bit.ly/KoselugoPI to view Patient Information in the full Prescribing Information for Koselugo (selumetinib).

Kassidy, age 11, living with NF1 PN, shown here with her mom. Kassidy is not a Koselugo patient.

IMPORTANT SAFETY INFORMATION (CONT'D)

Koselugo may cause serious side effects, including:

- **Eye problems.** Koselugo can cause eye problems that can lead to blindness. Your healthcare provider will check your vision before and during treatment. Tell your healthcare provider right away if you get any of the following signs or symptoms: blurred vision, loss of vision, dark spots in your vision (floaters), other changes to your vision.

Please see additional Important Safety Information throughout and scan the QR code or visit bit.ly/KoselugoPI to view Patient Information in the full Prescribing Information for Koselugo (selumetinib).

How well does KOSELUGO® (selumetinib) work?

In a clinical study, **Koselugo was proven to shrink PN** in children 2 years and older with NF1 PN that couldn't be completely removed by surgery.

66%
(33/50) **of children** treated with Koselugo saw their **NF1 PN shrink by at least 20%***

Of these children who responded to treatment with Koselugo,

97%
(32/33) **saw results within 1 year,** while some saw results ranging from **3.3 months to 1.6 years****

For most children who saw their PN shrink, **Koselugo kept working for at least 3 years.**†

Of the children whose NF1 PN shrank 20% or more with Koselugo:

79% (26/33) maintained their results for **at least 2 years**†

64% (21/33) maintained their results for **at least 3 years**†

Some children maintained their results for **more than 4.5 years.**†

*Confirmed by 3D magnetic resonance imaging scan (MRI). Data cutoff June 2018.

**Data cutoff June 2018. Onset of response ranged from 3.3 months to 1.6 years. The median time to onset of response was 7.2 months.

†Data cutoff March 2021.

†Data cutoff February 2021. This information is from the SPRINT long-term follow-up study.

IMPORTANT SAFETY INFORMATION (CONT'D)

Koselugo may cause serious side effects, including:

- **Severe diarrhea.** Diarrhea is common with Koselugo and can also be severe. Tell your healthcare provider right away the first time that you get diarrhea during treatment. Your healthcare provider may give you medicine to help control your diarrhea and may tell you to drink more fluids.
- **Skin rash.** Skin rashes are common with Koselugo and can also be severe. Tell your healthcare provider if you get any of the following signs or symptoms: rash that covers a large area of your body, peeling skin, blisters.

How is KOSELUGO® (selumetinib) taken?

Koselugo is an oral medication **taken twice daily**, about 12 hours apart.

Koselugo can be taken on an empty stomach or with food.

Consult with your child's doctor about meal options that can work for your child.

Your child's doctor will determine the best time for starting, suspending, or stopping treatment with Koselugo.

Tic Tac® Breath Mint

Koselugo capsule

Similar in size to a Tic Tac®, Koselugo can be easy to take.

Tic Tac® and the three-dimensional design are registered trademarks of Ferrero S.A.

Images shown are actual size.

Koselugo capsules must be swallowed whole with water.
They must not be chewed, dissolved, or opened.

Taking Koselugo in a different way than instructed may affect how it works.

IMPORTANT SAFETY INFORMATION (CONT'D)

Koselugo may cause serious side effects, including:

- **Muscle problems (rhabdomyolysis).** Muscle problems are common with Koselugo and can also be severe. Treatment with Koselugo may increase the level of a muscle enzyme in your blood called creatine phosphokinase (CPK) and may be a sign of muscle damage. Your healthcare provider should do a blood test to check your muscle enzyme levels of CPK before you start taking Koselugo and during treatment. Tell your healthcare provider right away if you get any of the following signs or symptoms: muscle aches or pain; muscle spasms and weakness; dark, reddish urine.

Please see additional Important Safety Information throughout and scan the QR code or visit bit.ly/KoselugoPI to view Patient Information in the full Prescribing Information for Koselugo (selumetinib).

If your child misses a dose, they should take it as soon as you remember.
If it is less than 6 hours before the next scheduled dose, give the next dose at the regular time. Do not make up for the missed dose.

If your child vomits at any time after taking Koselugo, they should not take an additional dose. The next dose should be taken at the regular time.

IMPORTANT SAFETY INFORMATION (CONT'D)

Before taking Koselugo, tell your healthcare provider about all your medical conditions, including if you:

- have heart problems.
- have eye problems.
- have liver problems.
- are pregnant or plan to become pregnant. Koselugo can harm your unborn baby. Your healthcare provider should verify if you/your partner are pregnant before beginning treatment. Ensure you/your partner use effective birth control (contraception) during treatment and for 1 week after your last dose if there is possibility pregnancy could occur. Tell your healthcare provider right away if you/your partner think you may be pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Koselugo passes into your breast milk. Do not breastfeed during treatment and for 1 week after your last dose. Talk to your healthcare provider about the best way to feed your baby during this time.

Is KOSELUGO® (selumetinib) safe?

The safety of Koselugo has been studied for up to 7.7 years*†

Side effects are well-known, can be manageable, and may not require stopping or delaying treatment with Koselugo.

In the SPRINT Phase 1 and 2 studies,* half of patients took Koselugo for more than 4.4 years.† Some patients in the study are still taking Koselugo and the longest treatment period is yet to be determined.

In the SPRINT Phase 2 Stratum 1 study, as of June 2018, children experienced mostly mild or moderate side effects while taking Koselugo.

76% (38/50)
of patients were able to stay on a full dose of Koselugo **without having to reduce their dose**

80% (40/50)
of patients required a dosing pause but **were able to avoid stopping treatment**

12% (6/50)
of children permanently **stopped treatment due to side effects**

For more information, ask your doctor or pharmacist. Call your child's doctor for medical advice about side effects. You may report side effects to AstraZeneca at **1-800-236-9933** or the FDA at **1-800-FDA-1088**.

*Data cutoff February 2021. Based on the long-term follow-up of the SPRINT studies, the evaluation of Koselugo is run by the National Cancer Institute and is designed to test the efficacy and safety of Koselugo. These data reflect exposure to Koselugo in 74 pediatric patients with NF1 PN that could not be removed by surgery without risk of issues because of their location or size. These patients received a dosage ranging from 20 mg/m^2 to 30 mg/m^2 orally twice daily in SPRINT.

†The median duration of Koselugo treatment is 4.4 years (range: 28 days to 7.7 years). Median is defined as the middlemost point in a dataset. In this case, 50% of patients received Koselugo treatment for less than 4.4 years, while the other 50% received Koselugo treatment for more than 4.4 years.

IMPORTANT SAFETY INFORMATION (CONT'D)

Tell your healthcare provider about all the medicines you take, including prescription, over-the-counter medicines, vitamins, or herbal supplements. Especially tell your healthcare provider if you are taking aspirin, blood thinners, or other medicines to treat blood clots. Koselugo contains vitamin E, which may increase risk of bleeding.

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Caleb, age 7, living with NF1 PN, shown here with his mom. Caleb is not a Koselugo patient.

Your child's healthcare provider may change the dose or ask your child to temporarily or permanently stop taking Koselugo if they have side effects.

The most common side effects include:

- vomiting
- stomach-area pain
- nausea
- dry skin
- muscle and bone pain
- feeling of tiredness or lacking energy
- fever
- sores in your mouth
- headache
- redness around the fingernails
- itching

These are not all the possible side effects of Koselugo.

IMPORTANT SAFETY INFORMATION (CONT'D)

What should I avoid while taking Koselugo?

Do not drink grapefruit juice, eat grapefruit, or take supplements with grapefruit or St. John's Wort during treatment.

Your local PEM is your partner

Your dedicated local **Patient Education Manager (PEM)** is available to meet in person or virtually to help you with what you need. Whether you have questions about NF1 PN or how Koselugo works, or just need someone to listen, your PEM is here for you.

PEMs engage with the community by:

- Hosting national educational webinars
- Partnering with patient advocacy groups
- Coordinating one-on-one or group interactions

You can get in touch with your PEM by:

- Asking your doctor for the PEM's business card
- Attending a community event
- Using the PEM finder at **bit.ly/NF1-PEM-Finder** or scanning the QR code

IMPORTANT SAFETY INFORMATION (CONT'D)

Most common side effects include: vomiting, stomach-area pain, nausea, dry skin, muscle and bone pain, feeling of tiredness or lacking energy, fever, sores in your mouth, headache, redness around the fingernails, itching.

ONESOURCE®
Personalized Patient Support from Alexion

OneSource™ is here to support patients and their caregivers

KOSELUGO® (selumetinib) has a free patient support program offered by Alexion complete with dedicated specialists ready to address your needs. Whether your child is newly diagnosed or has had NF1 PN for some time, our team of specialists is committed to helping your child start and stay on track with their treatment.

Our team can help you understand your health insurance coverage, answer questions about Koselugo, and connect you to community resources. We're committed to helping you and your family get the most out of Koselugo treatment.

If your doctor has prescribed Koselugo, you may have questions.

This program is designed to help you navigate access to Koselugo and get the most out of your child's treatment.

OneSource Support Services:

Once your child has been prescribed Koselugo, a dedicated Alexion **Case Manager** is ready to help your family navigate the logistics of starting and staying on treatment.

Case Managers can help by:

- Navigating insurance coverage
- Answering treatment questions
- Offering practical support
- Addressing financial concerns
- Assisting in avoiding treatment interruptions

To connect with your local PEM for educational support or your Case Manager for insurance and treatment-related support, call **1-888-765-4747**, Monday through Friday, 8:30 AM – 8:00 PM ET, or visit **www.AlexionOneSource.com**.

IMPORTANT SAFETY INFORMATION (CONT'D)

These are not all the possible side effects of Koselugo. Call your healthcare provider for medical advice about side effects. Your healthcare provider may change your dose, temporarily stop, or permanently ask you to stop taking Koselugo if you have any of these side effects. **You may report side effects to AstraZeneca at 1-800-236-9933 or at https://us-aereporting.astrazeneca.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.

Please see additional Important Safety Information throughout and scan the QR code or visit bit.ly/KoselugoPI to view Patient Information in the full Prescribing Information for Koselugo (selumetinib).

Ask your child's doctor if KOSELUGO® (selumetinib) is right for them.

To learn more or to contact your local PEM or a dedicated Case Manager, patients and caregivers can call **1-888-765-4747**, Monday through Friday, 8:30 AM – 8:00 PM ET, or visit **www.AlexionOneSource.com**.

You are encouraged to report negative side effects of Koselugo by calling **1-800-236-9933** or visiting **https://us-aereporting.astrazeneca.com**. If you prefer to report these to the FDA, either visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

INDICATION

What is Koselugo?

Koselugo is a prescription medicine that is used to treat children 2 years of age and older with neurofibromatosis type 1 (NF1) who have plexiform neurofibromas that cannot be completely removed by surgery. It is not known if Koselugo is safe and effective in children under 2 years of age.

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ALEXION®
AstraZeneca Rare Disease

8.4 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.

8.5 Geriatric Use

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

8.6 Renal Impairment

No dose adjustment is recommended in patients with renal impairment or those with End Stage Renal Disease *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Selumetinib exposures increased in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*. 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 (2.3)]*.

10 OVERDOSAGE

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

11 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 sulfate) and the excipient, vitamin E polyethylene glycol succinate. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, carnauba wax, and purified water. 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 sulfate) and the excipient, vitamin E polyethylene glycol succinate. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, FD&C blue 2, ferric oxide yellow, purified water, carnauba wax, and/or corn starch. The capsule is imprinted with black ink that contains ferric oxide red, ferric oxide yellow, FD&C Blue 2 aluminum lake, carnauba wax, shellac, and glyceryl monooleate.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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.

12.3 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 ($AUC_{0\text{-}12h}$) following the first dose was 2009 (35%) ng•h/mL and the $AUC_{0\text{-}6h}$ 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 by approximately 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 a-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.

13 NONCLINICAL TOXICOLOGY

13.1 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).

13.2 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.

14 CLINICAL STUDIES

14.1 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 SPRINT investigator 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Strength	Description	Capsules per Bottle	NDC Number
10 mg	White to off-white, opaque, hard capsule sealed with a clear band and marked with “SEL 10” in black ink.	60	0310-0610-60
		28	0310-0610-28
25 mg	Blue, opaque, hard capsule sealed with a clear band and marked with “SEL 25” in black ink.	60	0310-0625-60
		28	0310-0625-28

Storage

Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Dispense in original bottle. Keep the bottle tightly closed. Do not remove desiccant. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Cardiomyopathy

Advise patients and caregivers that KOSELUGO can cause a reduction in LVEF and to immediately report any signs or symptoms of cardiomyopathy to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Ocular Toxicity

Advise patients and caregivers that KOSELUGO can cause ocular toxicity that can lead to blindness and to contact their healthcare provider if the patient experiences any changes in their vision *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Toxicity

Advise patients and caregivers that KOSELUGO can cause diarrhea and to contact their healthcare provider at the onset of diarrhea *[see Warnings and Precautions (5.3)]*.

Skin Toxicity

Advise patients and caregivers that KOSELUGO can cause serious skin toxicities and to contact their healthcare provider for severe skin changes *[see Warnings and Precautions (5.4)]*.

Increased Creatine Phosphokinase

Advise patients and caregivers that KOSELUGO can cause increased CPK and to report any signs and symptoms of muscle pain or weakness to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Increased Vitamin E Levels and Risk of Bleeding

Advise patients and caregivers to notify their healthcare provider if they are taking a supplement containing vitamin E, a vitamin-K antagonist or an anti-platelet agent *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with KOSELUGO and for at least 1 week after the last dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with KOSELUGO and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, grapefruit or grapefruit juice while taking KOSELUGO *[see Drug Interactions (7)]*.

Dosing and Administration

Inform patients and caregivers on how to take KOSELUGO and what to do for missed or vomited doses *[see Dosage and Administration (2.1)]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

US/KOS-NF1/0288 V2 01/2024

Patient Information
KOSELUGO™ (ko-SEL-u-go)
(selumetinib) capsules

What is KOSELUGO?

KOSELUGO is a prescription medicine that is used to treat children 2 years of age and older with neurofibromatosis type 1 (NF1) who have plexiform neurofibromas that cannot be completely removed by surgery.

It is not known if KOSELUGO is safe and effective in children under 2 years of age.

Before taking KOSELUGO, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have eye problems.
- have liver problems.
- are pregnant or plan to become pregnant. KOSELUGO can harm your unborn baby.
  - Your healthcare provider should check to see if you are pregnant before you begin treatment with KOSELUGO.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with KOSELUGO and for 1 week after your last dose.
  - Males with female partners who are able to become pregnant should use effective birth control (contraception) during treatment with KOSELUGO and for 1 week after your last dose.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with KOSELUGO.
- are breastfeeding or plan to breastfeed. It is not known if KOSELUGO passes into your breast milk.
  - Do not breastfeed during treatment with KOSELUGO and for 1 week after your last dose.
  - Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements. Especially tell your healthcare provider if you are taking aspirin, blood thinners, or other medicines to treat blood clots. KOSELUGO contains vitamin E which may increase your risk of bleeding.

How should I take KOSELUGO?

- Take KOSELUGO exactly as your healthcare provider tells you to.
- Do not change your dose or stop taking KOSELUGO unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with KOSELUGO if you have side effects.
- Your healthcare provider will decide on the right dose of KOSELUGO based on your weight or size (body surface area) and how many capsules of KOSELUGO to take.
- Take KOSELUGO around the same time each day, about 12 hours apart.
- Take KOSELUGO with or without food.
- Swallow KOSELUGO capsules whole with water. Do not chew, dissolve, or open the capsules.
- If you miss a dose of KOSELUGO, take it as soon as you remember. If it is less than 6 hours before your next scheduled dose, take your next dose at your regular time. Do not make up for the missed dose.
- If you vomit at any time after taking KOSELUGO, do not take an additional dose. Take your next dose at your regular time.

What should I avoid while taking KOSELUGO?

Do not drink grapefruit juice, eat grapefruit or take supplements that contain grapefruit or St. John's Wort during treatment with KOSELUGO.

What are the possible side effects of KOSELUGO?

KOSELUGO may cause serious side effects, including:

- **Heart problems.** KOSELUGO can lower the amount of blood pumped by your heart which is common and can also be severe. Your healthcare provider will do tests before and during treatment with KOSELUGO to check how well your heart is working. Tell your healthcare provider right away if you get any of the following signs or symptoms:
  - persistent coughing or wheezing
  - shortness of breath
  - swelling of your ankles and feet
  - tiredness
  - increased heart rate
- **Eye problems.** KOSELUGO can cause eye problems that can lead to blindness. Your healthcare provider will check your vision before and during treatment with KOSELUGO. Tell your healthcare provider right away if you get any of the following signs or symptoms:
  - blurred vision
  - loss of vision
  - dark spots in your vision (floaters)
  - other changes to your vision
- **Severe diarrhea.** Diarrhea is common with KOSELUGO and can also be severe. Tell your healthcare provider right away the first time that you get diarrhea during treatment with KOSELUGO. Your healthcare provider may give you medicine to help control your diarrhea and may tell you to drink more fluids.
- **Skin rash.** Skin rashes are common with KOSELUGO and can also be severe. Tell your healthcare provider if you get any of the following signs or symptoms:
  - rash that covers a large area of your body
  - peeling skin
  - blisters
- **Muscle problems (rhabdomyolysis).** Muscle problems are common with KOSELUGO and can also be severe. Treatment with KOSELUGO may increase the level of enzyme in your blood called creatine phosphokinase (CPK) and may be a sign of muscle damage. Your healthcare provider should do a blood test to check your blood levels of CPK before you start taking KOSELUGO and during treatment. Tell your healthcare provider right away if you get any of the following signs or symptoms:
  - muscle aches or pain
  - muscle spasms and weakness
  - dark, reddish urine

Your healthcare provider may change your dose, temporarily stop, or permanently ask you to stop taking KOSELUGO if you have any of these side effects.

The most common side effects of KOSELUGO are:

- vomiting
- stomach-area pain
- nausea
- dry skin
- muscle and bone pain
- feeling of tiredness or lacking energy
- fever
- sores in your mouth
- headache
- redness around the fingernails
- itching

These are not all of the possible side effects of KOSELUGO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KOSELUGO?

- Store KOSELUGO at room temperature between 68°F to 77°F (20°C to 25°C).
- The bottle of KOSELUGO contains a desiccant packet to reduce moisture. Do not throw away desiccant packet.
- Keep KOSELUGO in its original bottle. Keep the bottle tightly closed.

Keep KOSELUGO and all medicines out of the reach of children.

General information about the safe and effective use of KOSELUGO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KOSELUGO for a condition for which it was not prescribed. Do not give KOSELUGO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about KOSELUGO that is written for a healthcare professional.

What are the ingredients in KOSELUGO?

Active ingredient: selumetinib.

Inactive ingredients:

Capsule contains: vitamin E polyethylene glycol succinate.

The 10 mg capsule shell contains: hypromellose, carrageenan, potassium chloride, titanium dioxide, carnauba wax, and purified water.

The 10 mg capsule printing ink contains: shellac, iron oxide black, propylene glycol, and ammonium hydroxide.

The 25 mg capsule shell contains: hypromellose, carrageenan, potassium chloride, titanium dioxide, FD&C blue 2, ferric oxide yellow, purified water, carnauba wax and/or corn starch.

The 25 mg printing ink contains: ferric oxide red, ferric oxide yellow, FD&C Blue 2 aluminum lake, carnauba wax, shellac, glyceryl monooleate.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

For more information, go to website www.KOSELUGO.com or call 1-800-236-9933

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: Jan/2024 US/KOS-NF1/0288 V2 01/2024