▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

KOSELUGO ®
(selumetinib sulfate) capsules

1 NAME OF THE MEDICINE

Selumetinib sulfate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mg hard capsule contains 10 mg of selumetinib (as sulfate).

Each 25 mg hard capsule contains 25 mg of selumetinib (as sulfate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule, hard.

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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.

The recommended dose of KOSELUGO is based on body surface area (BSA) and 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	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.

Method of Administration

KOSELUGO can be taken with or without food.

KOSELUGO capsules should be swallowed whole with water, and should not be chewed, dissolved, or opened.

Do not administer to patients who are unable or unwilling to swallow a whole capsule. Patients should be assessed for their ability to swallow a capsule before starting treatment. Standard medicine swallowing techniques are expected to be sufficient to swallow selumetinib capsules. For patients who have difficulties swallowing the capsule, referral to an appropriate health care professional such as a speech and language therapist could be considered to identify suitable methods that can be tailored to the particular patient.

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.

Vomiting

Do not take an additional dose if vomiting occurs after KOSELUGO administration but continue with the next scheduled dose.

Dose adjustments

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

Body Surface Area	First Dose Reduction (mg/dose)		Second Dose Reduction* (mg/dose)	
	Morning	Evening	Morning	Evening
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
LVEF Reduction (see section 4.4 Special warnings and precautions for use)	
Asymptomatic decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline and less than lower level of normal	Withhold until resolution. Resume at reduced dose.
Symptomatic decreased LVEF Grade 3 or 4 decreased LVEF	Permanently discontinue.
Ocular Toxicity (see section 4.4 Special warnings and precautions for use)	
Retinal Pigment Epithelial Detachment (RPED) or Central Serous Retinopathy (CSR)	Withhold until resolution. Resume at reduced dose.
Retinal vein occlusion (RVO)	Permanently discontinue.
Gastrointestinal Toxicity (see section 4.4 Special warnings and precautions for use)	
Grade 3 Diarrhoea	Withhold until improved to Grade 0 or 1. Resume at same dose. Permanently discontinue if no improvement within 3 days.
Grade 4 Diarrhoea	Permanently discontinue.
Grade 3 or 4 Colitis	Permanently discontinue.
Skin Toxicity (see section 4.4 Special warnings and precautions for use)	
Grade 3 or 4	Withhold until improvement. Resume at reduced dose.
Increased Creatine Phosphokinase (CPK) (see section 4.4 Special warnings and precautions for use)	
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 CTCAE Grade (see section 4.8 Adverse effects (Undesirable effects))*	
Grade 1 Tolerable Grade 2	Continue treatment and monitor as clinically indicated
Intolerable Grade 2 Grade 3	Withhold KOSELUGO until improve 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

For drug interactions

Co-administration with CYP3A4 or CYP2C19 inhibitors

Concomitant use of strong or moderate CYP3A4 or CYP2C19 inhibitors is not recommended and alternative agents should be considered. If a strong or moderate CYP3A4 or CYP2C19 inhibitor must be co-administered, the recommended KOSELUGO dose reduction is as follows:

- If a patient is currently taking 25 mg/m^2 twice daily, dose reduce to 20 mg/m^2 twice daily.
- If a patient is currently taking 20 mg/m^2 twice daily, dose reduce to 15 mg/m^2 twice daily (see Table 4 and section 4.5).

Table 4 Recommended dosage to achieve 20 mg/m^2 or 15 mg/m^2 twice daily dose level

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

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 section 5.2 Pharmacokinetic properties*).

Hepatic Impairment

Based on clinical studies, no dose adjustment is recommended in patients with mild hepatic impairment. The starting dose should be reduced in patients with moderate hepatic impairment to 20 mg/m^2 BSA, twice daily (see Table 4). KOSELUGO is not recommended for use in patients with severe hepatic impairment (*see section 5.2 Pharmacokinetic properties*).

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 paediatric Asian patients, however, these patients should be closely monitored for adverse events (*see section 5.2 Pharmacokinetic properties*).

Paediatric population

Safety and effectiveness have been established in paediatric patients 3 years of age and older with NF1 who have inoperable PN and information supporting this use is discussed throughout the Product Information. This indication was expanded to paediatric 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients (*see section 6.1 List of excipients)*
- Severe hepatic impairment

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

LVEF Reduction

Asymptomatic decreases in ejection fraction have been reported in 26% of paediatric patients in the pivotal clinical study (*see section 4.8 Adverse effects (Undesirable effects)*. Median time to initial onset of events was 232 days. A small number of serious reports of LVEF reduction associated with selumetinib have been reported in paediatric patients who participated in an expanded access program.

Paediatric patients with a history of impaired left ventricular function or a baseline LVEF below institutional LLN have not been studied. LVEF should be evaluated before initiation of treatment to establish baseline values. Prior to starting KOSELUGO treatment, patients should have an ejection fraction above the institutional LLN.

Evaluate LVEF 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 section 4.2 Dosage and Method of Administration*).

Ocular Toxicity

Advise patients to report any new visual disturbances. Adverse events of blurred vision have been reported in paediatric patients receiving selumetinib. Isolated cases of RPED, CSR and RVO in adult patients with multiple tumour types, receiving treatment with selumetinib monotherapy and in combination with other anti-cancer agents, and in a single paediatric patient with pilocytic astrocytoma on selumetinib monotherapy, have been observed (*see section 4.8 Adverse effects (Undesirable effects)*.

In line with clinical practice 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 selumetinib therapy should be interrupted and the dose reduced when treatment is resumed (see Table 2). If RVO is diagnosed, treatment with selumetinib should be permanently discontinued (*see section 4.2 Dosage and Method of Administration*).

Gastrointestinal Toxicity

Diarrhoea occurred in 81% of 74 paediatric patients who received KOSELUGO in SPRINT, including Grade 3 in 15% of patients. Diarrhoea resulting in permanent discontinuation occurred in 1.4% of patients. Diarrhoea resulting in dose interruption or dose reduction occurred in 15% and 1.4% of patients, respectively. The median time to first onset of diarrhoea was 20 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 tumour types who received KOSELUGO as a single agent or in combination with other anti-cancer agents. Colitis occurred in an unapproved population of paediatric patients with multiple tumour types who received KOSELUGO as a single agent.

Advise patients to start an anti-diarrhoeal agent (e.g., loperamide) immediately after the first episode of unformed, loose stool and to increase fluid intake during diarrhoea episodes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (*see section 4.2 Dosage and Method of Administration).*

Skin Toxicity

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

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 section 4.2 Dosage and Method of Administration).*

Increased Creatine Phosphokinase

Increased creatine phosphokinase (CPK) occurred in 77% of 74 paediatric 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 section 4.2 Dosage and Method of Administration).*

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 section 4.6 Fertility, pregnancy and lactation).*

Risk of Choking

Selumetinib is available as a capsule which must be swallowed whole. Some patients, in particular children < 6 years of age, may be at risk of choking on a capsule formulation due to developmental, anatomical or psychological reasons. Therefore, selumetinib should not be administered to patients who are unable or unwilling to swallow the capsule whole (*see section 4.2 Dosage and Method of Administration*).

Vitamin E Supplementation

Advise patients not to take any supplemental vitamin E.

KOSELUGO 10 mg capsules contain 32 mg vitamin E as the excipient, Tocofersolan (Australian Approved Name). KOSELUGO 25 mg capsules contain 36 mg vitamin E as Tocofersolan. High doses of vitamin E may increase the risk of bleeding in patients taking concomitant anticoagulant or antiplatelet medications (e.g., warfarin or aspirin). Perform anticoagulant assessments, including international normalized ratio (INR) or prothrombin time (PT) more frequently to detect when the dose adjustments of the anticoagulant or antiplatelet medications are warranted *(see Section 4.5 Interactions with other medicines and other forms of interaction).*

Use in the elderly

No data are available for use in elderly patients.

Paediatric use

Safety and effectiveness have been established in paediatric patients 3 years of age and older with NF1 who have inoperable PN and information supporting this use is discussed throughout the Product Information. This indication was expanded to paediatric 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.

Effects on laboratory tests

Please refer to *section 4.8 Adverse effects (Undesirable effects).*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interactions

Interaction studies have only been performed in healthy adults (aged ≥18 years).

Active substances that may increase selumetinib plasma concentration

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

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

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

Co-administration with strong inhibitors of CYP3A4 (e.g., clarithromycin, grapefruit juice, oral ketoconazole) or CYP2C19 (e.g., ticlopidine) should be avoided. Co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin and fluconazole) or CYP2C19 (e.g., omeprazole) should be avoided. If co-administration is unavoidable, patients should be carefully monitored for adverse events and the selumetinib dose should be reduced (*see section 4.2 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 selumetinib

In vitro, selumetinib is an inhibitor of OAT3 and the potential for a clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 cannot be excluded.

The effect of selumetinib on the exposure of oral contraceptives has not been evaluated. Therefore, use of an additional barrier method should be recommended to women using hormonal contraceptives.

Interactions with Minimal Clinical Impact

In vitro, selumetinib is not an inhibitor of, CYP2A6, CYP2C8, CYP3A4 or CYP2E1, not an inducer of, CYP1A2 and CYP2B6, and did not cause time-dependent inhibition of CYP2C9, CYP2D6 or CYP3A4/5.

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

Interactions with transport proteins

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

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 section 4.4 Special warnings and precautions for use*).

Effect of food on KOSELUGO

In separate clinical studies, in healthy adult subjects and in adult patients with advanced solid malignancies at a dose of 75 mg, co-administration of KOSELUGO with a high-fat meal resulted in a mean decrease in C_{max} of 50% and 62%, respectively, compared to fasting administration. Selumetinib mean AUC was reduced by 16% and 19%, respectively, and the time to reach maximum concentration (t_{max}) was delayed by approximately 1.5 hours to 3 hours (*see section 4.2 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 t_{max} was delayed by approximately 0.9 hours (*see section 4.2 Dosage and Administration*).

In adolescent patients with NF1 and inoperable PN treated with multiple doses of 25 mg/m^2 bid, co-administration of selumetinib with a low-fat meal resulted in 24% lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 8%, and t_{max} was delayed by approximately 0.57 hours (*see section 4.2 Dosage and Administration*).

A population PK analysis including children and adolescent patients with NF1 and inoperable PN, adult patients with advanced solid malignancies and healthy adult subjects taken from 15 studies showed that concomitant administration of a low or high fat meal resulted in a mean decrease in the exposure (AUC) of selumetinib when compared to fasted administration (23.1% and 20.7%, respectively) which was not considered clinically relevant.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

In mice, selumetinib did not affect male mating performance after 10 weeks of dosing up to 20 mg/kg twice daily corresponding to approximately 28-times the human clinical exposure based on AUC at the MRHD. In female mice exposed to selumetinib at up to 37.5 mg/kg twice daily (approximately 90 times the human clinical exposure at the MRHD based on AUC), mating performance and fertility were not affected, but the number of live fetuses was slightly reduced at ≥ 12.5 mg/kg twice daily (27 times the human clinical exposure). 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 times the human clinical exposure).

Use in pregnancy– Category D

There are no data on the use of selumetinib in pregnant women.

In embryofetal development studies in mice, administration of selumetinib during organogenesis-caused a reduction in the number of live fetuses due to an increase in post-implantation loss, a reduction in mean fetal and litter weights, an increase in unossified or incompletely ossified bones, increased occurrence of open eye and cleft palate at dose levels that did not induce significant maternal toxicity. These effects were seen at ≥2.5 mg/kg twice daily (>4.5 times the clinical exposure at the MRHD based on AUC) and indicate that selumetinib may have potential to cause defects in the fetus in patients.

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 at 7.5 mg/kg twice daily (approximately 6 times the clinical exposure based on C_{max}). The incidence of malformations (prematurely open eye(s) and/ or cleft palate) was increased at all dose levels (0.5 -7.5 mg/kg twice daily). Malformations occurred at maternal exposure 0.6 times the mean clinical exposure at MRHD based on C_{max}.

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 selumetinib. 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.

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. It cannot be excluded that selumetinib may reduce the effectiveness of oral contraceptives, therefore women using hormonal contraceptives should be recommended to add a barrier method.

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

Use in lactation

Selumetinib and its active metabolite are excreted in the milk of lactating mice. It is not known whether selumetinib, or its metabolites, are excreted in human milk. A risk to the breast-fed infant cannot be excluded, therefore breast-feeding mothers are advised not to breast-feed during treatment with KOSELUGO.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event 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 safety of selumetinib monotherapy has been evaluated in a combined safety population of 74 paediatric patients (20-30 mg/m^2 twice daily) with NF1 PN and 347 adult patients (75-100 mg twice daily) with multiple tumour types.

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

The safety of KOSELUGO was evaluated in SPRINT Phase II Stratum 1 *(see section 5.1 Pharmacodynamic properties, Clinical Trials)*. 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, 70% were exposed for more than 2 years and 56% were exposed for more than 4 years.

Serious adverse reactions occurred in 30% of patients who received KOSELUGO. Serious adverse reactions that occurred in 2 or more patients were anaemia, hypoxia, diarrhoea, skin infection and fracture.

Permanent discontinuation due to an adverse event occurred in 12% of patients who received KOSELUGO. Adverse events resulting in permanent discontinuation of KOSELUGO included increased blood creatine phosphokinase, increased weight, diarrhoea, paronychia, malignant peripheral nerve sheath tumour, acute kidney injury, and skin ulcer.

Dosage interruptions and dose reductions due to adverse events occurred in 86% and 32% of patients who received KOSELUGO, respectively. Adverse events requiring a dosage interruption or reduction in ≥ 5% of patients were vomiting, nausea, paronychia, influenza-like illness, diarrhoea, pyrexia, fracture, skin infection, abdominal pain and weight gain.

The most common adverse events (≥ 40%) were vomiting, abdominal pain, diarrhoea, nausea, dry skin, pyrexia, rash (non-acneiform), musculoskeletal pain, paronychia, fatigue, dermatitis acneiform, headache, stomatitis, pruritus and constipation.

Table 5 presents the adverse events in SPRINT Phase II Stratum 1.

Table 5 Adverse Events (≥ 20%) in Patients Who Received KOSELUGO in SPRINT Phase II Stratum 1

Adverse Event	KOSELUGO N=50	
	All Grades (%)	Grade ≥ 3 (%)*
Gastrointestinal		
Vomiting	86	8
Abdominal pain[1]	76	0
Diarrhoea	74	16
Nausea	72	4
Stomatitis[2]	52	0
Constipation	42	0
Skin and Subcutaneous Tissue		
Dry skin	68	2

Adverse Event	KOSELUGO N=50	
	All Grades (%)	Grade ≥ 3 (%)*
Rash (non-acneiform)[3]	62	2
Paronchyia[4]	58	8
Dermatitis acneiform	56	6
Pruritus	52	0
Dermatitis[5]	36	4
Hair changes[6]	32	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[7]	60	0
General		
Pyrexia	62	8
Fatigue[8]	56	0
Oedema[9]	34	0
Nervous System		
Headache	56	2
Respiratory, Thoracic and Mediastinal		
Epistaxis	32	0
Renal and Urinary System		
Haematuria	30	2
Proteinuria	28	0
Metabolism and Nutrition		
Decreased appetite	26	0
Cardiac System		
Decreased ejection fraction	26	0
Sinus tachycardia	22	0
Infections		
Skin infection[10]	22	4
Vascular		
Hypertension[11]	20	0

* All events were Grade 3.

1 Abdominal pain includes abdominal pain; abdominal pain upper

2 Stomatitis includes stomatitis; mouth ulceration

3 Rash (non-acneiform) includes rash maculo-papular; erythema; rash pustular; rash; urticaria; exfoliative rash; rash pruritic; rash erythematous

4 Paronychia includes paronychia; nail infection

5 Dermatitis includes dermatitis; dermatitis atopic; dermatitis diaper; eczema; seborrheic dermatitis; skin irritation

6 Hair changes include alopecia, hair colour change

7 Musculoskeletal pain includes pain in extremity; back pain; neck pain; musculoskeletal pain

8 Fatigue includes fatigue, malaise

9 Oedema includes peripheral swelling, oedema, localised oedema; oedema peripheral

10 Skin infection includes skin infection; abscess; cellulitis; impetigo; staphylococcal skin infection

11 Hypertension includes hypertension, blood pressure increased

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

- *Eye*: vision blurred
- *Gastrointestinal Disorders*: dry mouth
- *General Disorders*: facial oedema, including periorbital oedema and face oedema
- *Respiratory, Thoracic & Mediastinal*: dyspnoea, including exertional dyspnoea and dyspnoea at rest

Table 6 presents the laboratory abnormalities in SPRINT Phase II Stratum 1.

Table 6 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	53	0
Increased aspartate aminotransferase (AST)	43	2
Increased alanine aminotransferase (ALT)	41	4
Increased lipase	39	12
Increased potassium	29	4§
Increased amylase	26	0
Increased alkaline phosphatase	22	0
Increased creatinine	22	2§
Decreased potassium	22	4§
Decreased sodium	20	0
Increased sodium	16	0
Haematology		
Decreased haemoglobin	51	4
Decreased neutrophils	40	4
Decreased lymphocytes	27	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. Change from baseline was derived from laboratory data collected at protocol-scheduled assessments.
§ Includes one Grade 4 increased CPK, one Grade 4 increased creatinine, one Grade 4 decreased potassium and one Grade 4 increased potassium.

Adverse Drug Reactions Identified in Other Clinical Trials

Table 7 presents the adverse drug reactions identified from other clinical trial experience in adult patients (N=347), with multiple tumour types, receiving treatment with selumetinib (75 mg twice daily):

Table 7 Adverse Drug Reactions Reported in Adult Patients with multiple tumour types but not Reported in SPRINT Phase II Stratum I

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE Grades)	Frequency of CTCAE Grade 3 and Above[†]
Eye disorders	Retinal Pigment Epithelial Detachment (RPED)/Central Serous Retinopathy (CSR)*	Uncommon (0.6%)	-
	Retinal Vein Occlusion (RVO)*	Uncommon (0.3%)	-

* ADRs based on grouping of individual Preferred Terms (PT):
CSR/RPED: Detachment of macular retinal pigment epithelium, Chorioretinopathy
RVO: Retinal vein occlusion, Retinal vein thrombosis, Retinal vascular disorder

In addition, a single event of RPED was reported in a paediatric patient receiving selumetinib monotherapy (25 mg/m^2 twice daily) for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study, see *sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions.*

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Selumetinib is an orally available, inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) that is not competitive with respect to ATP. MEK1/2 proteins are critical components of the *RAS*-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. Selumetinib blocks MEK activity and inhibits growth of RAF-MEK-ERK pathway activated cell lines. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.

Pharmacodynamics

In genetically modified mouse models of NF1 that generate neurofibromas that recapitulate the genotype and phenotype of human type 1 neurofibromas, oral dosing of selumetinib inhibits ERK phosphorylation, reduces neurofibroma volume, proliferation, number and growth.

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.

Clinical trials

SPRINT

The efficacy of KOSELUGO was evaluated in an open-label, multi-centre, single-arm study [SPRINT Phase II Stratum 1 (NCT01362803)] of 50 paediatric 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 25 mg/m^2 (BSA) twice daily, for 28 days (1 treatment cycle), on a continuous dosing schedule. Treatment was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity or PN progression, or at the discretion of the investigator.

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

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

At enrolment, the median age of the patients was 10.2 years (range: 3.5 - 17.4 years), 60% were male, 84% were Caucasian.

Disease characteristics at baseline are provided in Table 8.

Table 8 Baseline disease characteristics

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

The primary efficacy endpoint was Objective Response Rate (ORR), defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as ≥20% reduction in PN volume, confirmed at a subsequent tumour assessment

within 3-6 months), based on National Cancer Institute (NCI) centralised review. Duration of Response (DoR) was also evaluated.

Efficacy results are provided based on a data cut-off of March 2021, unless stated otherwise.

The primary endpoint, ORR was 68% (95% CI, 53.3 – 80.5). Time to onset of response for the majority of patients (24/34 [70.6%]) was within 8 cycles (range 4 – 42 cycles). The median time to onset of response was 7.2 months (range 3.3 months to 3.2 years).

The median DoR from onset of response was not reached; at the time of data cut-off the median follow-up time was 41.3 months from first dose. Of the 34 patients who had confirmed partial responses, 31 (91.2%) remained in response after 12 months; 26 (76.5%) remained in response after 24 months and 21 (61.8%) remained in response after 36 months . The probability to remain in response after 12, 24 and 36 months, estimated using the Kaplan-Meier method, was 100% (95% CI not estimated), 90.0% (95% CI 72.1 – 96.7) and 86.3% (95% CI 67.3 – 94.6), respectively. The median time from treatment initiation to disease progression while on treatment was not reached.

Table 9 NF1 PN efficacy results from SPRINT Phase II Stratum 1

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

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

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

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

c Two patients were not evaluable.

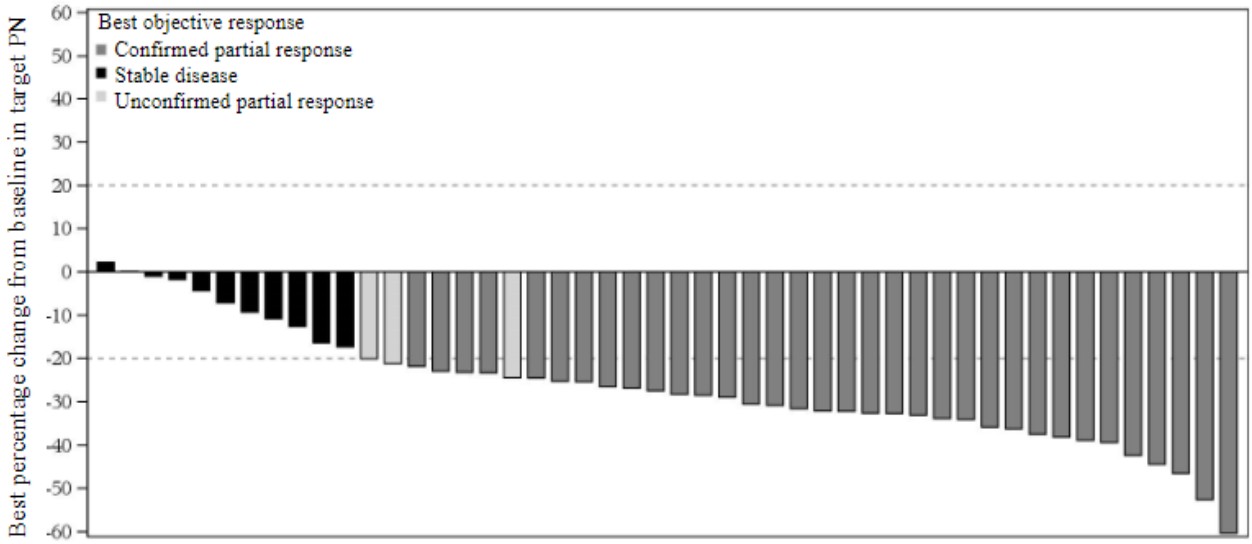
d Duration of Response from onset of response in patients with confirmed partial response.

e Calculated using Kaplan-Meier method.

At the time of data cut-off or last scan on treatment for patients who had discontinued treatment, 25 (50%) patients remained in confirmed partial response, 1 (2%) had unconfirmed partial responses, 12 (24%) had stable disease and 10 (20%) had progressive disease.

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

Figure 1 Waterfall plot of best percentage change from baseline in target PN volume[a]



[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.

An independent centralized review of tumor response per REiNS criteria (data cut-off June 2018) resulted in an ORR of 44% (95% CI: 30.0, 58.7).

5.2 PHARMACOKINETIC PROPERTIES

At the recommended dosage of 25 mg/m^2 twice daily in paediatric patients (3 to ≤18 years old), the geometric mean (coefficient of variation [CV%]) maximum plasma concentration (C_{max}) was 731 (62%) ng/mL and that of the area under the plasma drug concentration curve (AUC_{0-12}) following the first dose was 2009 (35%) ng·h/mL. Minimal accumulation of ~1.1 fold was observed at steady state upon twice daily dosing.

In paediatric patients, at a dose level of 25 mg/m^2, selumetinib has an apparent oral clearance of 8.8 L/h, mean apparent volume of distribution at steady state of 78 L and mean elimination half-life of ~6.2 hours.

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.

Effect of gastric acid reducing agents on selumetinib

Selumetinib 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 restrictions, except for omeprazole which is a CYP2C19 inhibitor.

Distribution

The mean apparent volume of distribution at steady state of selumetinib across 20 to 30 mg/m^2 ranged from 78 to 171 L in paediatric patients, indicating moderate distribution into tissue.

In vitro plasma protein binding is 98.4% in humans. Selumetinib mostly binds to serum albumin (96.1%) than 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. Glucuronidation is a significant route of elimination for selumetinib Phase 1 metabolites involving several UGT isoforms.

Following oral dosing of ^{14}C-selumetinib to healthy male subjects, unchanged selumetinib (~40% of the radioactivity) with other metabolites including glucuronide of imidazoindazole metabolite (M2; 22%), selumetinib glucuronide (M4; 7%), N-desmethyl selumetinib (M8; 3%), and N-desmethyl carboxylic acid (M11; 4%) accounted for the majority of the circulating radioactivity in human plasma. The active metabolite, 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. N-desmethyl selumetinib is mainly generated by CYP2C19 and catabolised by CYP3A4.

Excretion

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

Special populations

Renal impairment

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 section 4.2 Dose and method of administration*).

Hepatic impairment

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 normalised 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 section 4.2 Dose and method of administration*).

Ethnicity

Following a single-dose, 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 section 4.2 Dose and method of administration*).

Adult patients (>18 years old)

The PK parameters in adult healthy volunteers and adult patients with advanced solid malignancies, are similar to those in paediatric patients (3 to ≤18 years old) with NF1.

In adult patients with solid malignancies, at a single dose of 75 mg selumetinib, geometric mean (%GCV) C_{max} and AUC were 1307 (76%) ng/mL and 4736 (37%) ng·h/mL, respectively. Peak plasma concentrations of selumetinib were achieved 1.5-hour post-dose with a mean elimination half-life of 7.8 hours. C_{max} and AUC increased dose proportionally over a 25 mg to 100 mg dose range, and administration of 75 mg selumetinib twice daily resulted in minimal accumulation of ~1.2 fold.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Selumetinib showed no mutagenic or clastogenic potential in *in vitro* bacterial reverse mutation [Ames] and mammalian mutagenesis [tk locus TK] assays, and in an in vitro micronucleus assay (in mouse lymphoma L5178Y cells) but produced an increase in micronucleated immature erythrocytes (chromosome aberrations) in in vivo micronucleus assays in mice at ≥121 mg/kg, predominantly via an aneugenic mode of action. The exposure at the No Observed Effect Level (NOEL) of 24 mg/kg was approximately 40 times the clinical exposure at the MRHD based on C_{max}. The weight of evidence indicates selumetinib has a low genotoxic potential.

Carcinogenicity

No evidence of tumourigenicity by selumetinib was observed in a 6-month study in transgenic (Tg.rasH2) mice and in a conventional 2-year study in rats. The highest doses tested (15 mg/kg BID in mice and 2.5 mg/kg once daily in male rats and 1 mg/kg once daily in female rats) yielded exposures 20 (male mice), 31 (female mice), 17 (male rat) and 13 (female rat) times the human clinical exposure at the MRHD based on AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

10 mg hard capsule

- Capsule content: Tocofersolan

- Capsule shell: Hypromellose, Carrageenan, Potassium chloride, Titanium dioxide, Carnauba wax and Purified water.

- Printing ink: Shellac, Iron oxide black, Propylene glycol, Strong ammonia solution.

25 mg hard capsule

- Capsule content: Tocofersolan

- Capsule shell: Hypromellose, Carrageenan, Potassium chloride, Titanium dioxide, Indigo carmine, Iron oxide yellow. Purified water, Carnauba wax and/or maize starch.

- Printing ink: Iron oxide red, Iron oxide yellow, Indigo carmine aluminium lake, Carnauba wax, Shellac, Glyceryl monooleate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Store in the original bottle to protect from moisture. Keep the bottle tightly closed

Do not remove desiccant.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE plastic bottle with child-resistant closure and silica gel desiccant, containing 60 hard capsules.

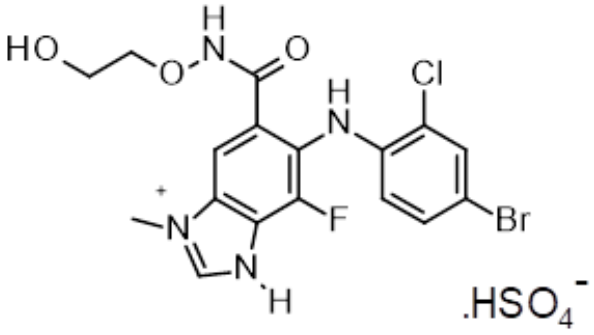
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Figure 2 Chemical structure of selumetinib (as sulfate)



CAS number

CAS 943332-08-9 (selumetinib sulfate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

Alexion Pharmaceuticals Australasia Pty Ltd
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 788 189

9 DATE OF FIRST APPROVAL

02 December 2021

10 DATE OF REVISION

14 November 2024

Summary table of changes

Section changed	Summary of new information
4.2	Update the posology statement, Koselugo can be taken with or without food supported by the results from Study 15

Section changed	Summary of new information
4.4	Updates to the frequency information in the LVEF Reduction, Gastrointestinal Toxicity, Skin Toxicity, and Increased Creatine Phosphokinase subsections based on data from SPRINT Phase II Stratum 1 and SPRINT Phase 1 DCO2
4.5	Effect of itraconazole and fluconazole on the pharmacokinetics of selumetinib and N desmethyl selumetinib and addition of results of the population PK analysis investigating the effect of food on the PK of Selumetinib.
4.8	Update to the duration of exposure and update the frequency and list of serious adverse reactions based on data from SPRINT Phase II Stratum 1 DCO2
5.1	Updated with results from the SPRINT CSR Addendum