PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

KOSELUGO 10 mg: 10 mg hard capsules

KOSELUGO 25 mg: 25 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KOSELUGO 10 mg hard capsules

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

KOSELUGO 25 mg hard capsules

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

Sugar free

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard capsules

KOSELUGO 10 mg hard capsules

White to off-white, opaque, size 4 (approximately 14 mm x 5 mm), hard capsule, which has a centre band and is marked with “SEL 10” in black ink.

KOSELUGO 25 mg hard capsules

Blue, opaque, size 4 (approximately 14 mm x 5 mm), hard capsule, which has a centre band and is marked with “SEL 25” in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

KOSELUGO as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

4.2 Posology and method of administration

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

Posology

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

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

Table 1. Recommended dose based on body surface area

Body surface area (BSA)[a]	**Recommended dose**
0,55 - 0,69 m^2	20 mg in the morning and 10 mg in the evening
0,70 - 0,89 m^2	20 mg twice daily
0,90 - 1,09 m^2	25 mg twice daily
1,10 - 1,29 m^2	30 mg twice daily
1,30 - 1,49 m^2	35 mg twice daily
1,50 - 1,69 m^2	40 mg twice daily
1,70 - 1,89 m^2	45 mg twice daily
≥1,90 m^2	50 mg twice daily
[a] The recommended dose for patients with a BSA less than 0,55 m^2 has not been established.	

Treatment with KOSELUGO should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. There is limited data in patients older than18, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the doctor. However, start of treatment with KOSELUGO in adults is not appropriate.

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

If vomiting occurs after KOSELUGO is administered, an additional dose is not to be taken. The patient should continue with the next scheduled dose.

Dose adjustments

Interruption and/or dose reduction or permanent discontinuation of KOSELUGO may be required based on individual safety and tolerability (see sections 4.4 and 4.8). Recommended dose reductions are given in Table 2 and may require the daily dose to be divided into two administrations of different strength or for treatment to be given as a once daily dose.

Table 2. Recommended dose reductions for adverse reactions

Body surface area (BSA)	**Initial KOSELUGO dose[a] (mg/twice daily)**	**First dose reduction (mg/dose)**		**Second dose reduction (mg/dose)[b]**	
		Morning	**Evening**	**Morning**	**Evening**

0,55 – 0,69 m^2	20 mg in the morning and 10 mg in the evening	10	10	10 mg once daily	
0,70 - 0,89 m^2	20	20	10	10	10
0,90 - 1,09 m^2	25	25	10	10	10
1,10 - 1,29 m^2	30	25	20	20	10
1,30 - 1,49 m^2	35	25	25	25	10
1,50 - 1,69 m^2	40	30	30	25	20
1,70 - 1,89 m^2	45	35	30	25	20
≥ 1,90 m^2	50	35	35	25	25
[a] Based on BSA as shown in Table 1. [b] Permanently discontinue treatment in patients unable to tolerate KOSELUGO after two dose reductions.					

Dose modifications for the management of adverse reactions associated with this medicine are presented in Table 3.

Table 3. Recommended dose modifications for adverse reactions

CTCAE Grade*	**Recommended dose modification**
Grade 1 or 2 (tolerable - can be managed with supportive care)	Continue treatment and monitor as clinically indicated
Grade 2 (intolerable - cannot be managed with supportive care) or **Grade 3**	Interrupt treatment until toxicity is grade 0 or 1 and reduce by one dose level when resuming therapy (see Table 2)
Grade 4	Interrupt treatment until toxicity is grade 0 or 1, reduce by one dose level when resuming therapy (see Table 2). Consider discontinuation
* Common Terminology Criteria for Adverse Events (CTCAE)	

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

In cases of asymptomatic LVEF reduction of ≥10 percentage points from baseline and below the institutional lower level of normal (LLN), KOSELUGO treatment should be interrupted until resolution. Once resolved, KOSELUGO should be reduced by one dose level when resuming therapy (see Table 2).

In patients who develop symptomatic LVEF reduction or a grade 3 or 4 LVEF reduction, KOSELUGO should be discontinued and a prompt cardiology referral should be carried out (see section 4.4).

Dose modification advice for ocular toxicities

KOSELUGO treatment should be interrupted in patients diagnosed with retinal pigment epithelial detachment (RPED) or central serous retinopathy (CSR) with reduced visual acuity until resolution; reduce KOSELUGO by one dose level when resuming therapy (see Table 2). In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmic assessment should be conducted every 3 weeks until resolution. In patients who are diagnosed with retinal vein occlusion (RVO), treatment with KOSELUGO should be permanently discontinued (see section 4.4).

Dose adjustments for 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 dose 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 Populations

Renal impairment

Based on clinical trials 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).

Hepatic impairment

Based on clinical trials, 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 contraindicated for use in patients with severe hepatic impairment (see sections 4.3 and 5.2).

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).

Paediatric population

The safety and efficacy of KOSELUGO in children less than 3 years of age has not been established. No data are available.

Method of administration

KOSELUGO is for oral use. It can be taken with or without food (see section 5.2).

The capsules should be swallowed whole with water. The capsules should not be chewed, dissolved, or opened, because this could impair medicine release and affect the absorption of KOSELUGO.

KOSELUGO should not be administered to patients who are unable or unwilling to swallow the capsule whole. 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 KOSELUGO 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe hepatic impairment (see sections 4.2 and 5.2).

4.4 Special warnings and precautions for use

Left ventricular ejection fraction (LVEF) reduction

Asymptomatic decreases in ejection fraction have been reported in 26 % of paediatric patients in the pivotal clinical trial. Median time to initial onset of these adverse reactions was 232 days. A small number of serious reports of LVEF reduction associated with KOSELUGO have been reported in paediatric patients who participated in an expanded access program (see section 4.8).

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 by echocardiogram before initiation of treatment to establish baseline values. Prior to starting KOSELUGO treatment, patients should have an ejection fraction above the institutional LLN.

LVEF should be evaluated 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).

Ocular toxicity

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

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, KOSELUGO therapy should be interrupted and the dose reduced when treatment is resumed (see section 4.2). If RVO is diagnosed, treatment with KOSELUGO

should be permanently discontinued (see section 4.2).

Liver laboratory abnormalities

Liver laboratory abnormalities, specifically AST and ALT elevations, can occur with KOSELUGO (see section 4.8). Liver laboratory values should be monitored before initiation of KOSELUGO and at least monthly during the first 6 months of treatment, and thereafter as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see Table 2 in section 4.2).

Skin and subcutaneous disorders

Skin rash (including maculopapular rash and acneiform rash), paronychia and hair changes have been reported very commonly in the pivotal clinical study (see section 4.8). Dry skin, hair colour changes, paronychia and rash maculo-papular were seen more frequently in younger children (age 3-11 years) and acneiform rash was seen more frequently in post-pubertal children (age 12-16 years).

Vitamin E supplementation

Patients should be advised not to take any supplemental vitamin E. KOSELUGO 10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). KOSELUGO 25 mg capsules contain 36 mg vitamin E as TPGS. High doses of vitamin E may increase the risk of bleeding in patients taking concomitant anticoagulant or antiplatelet medicines (e.g., warfarin or acetylsalicylic acid). Anticoagulant assessments, including international normalised ratio or prothrombin time, should be conducted more frequently to detect when dose adjustments of the anticoagulant or antiplatelet medicines are warranted (see section 4.5).

Risk of choking

KOSELUGO 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, KOSELUGO should not be administered to patients who are unable or unwilling to swallow the capsule whole (see section 4.2).

Women of child bearing potential

KOSELUGO is not recommended in women of child bearing potential who are not using contraception (see section 4.6).

4.5 Interaction with other medicines and other forms of interaction

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

Active substances that may increase KOSELUGO *plasma concentrations*

Co-administration with a strong CYP3A4 inhibitor (200 mg itraconazole twice daily for 4 days) increased KOSELUGO C_{max} by 19 % (90 % CI 4, 35) and AUC by 49 % (90 % CI 40, 59) in healthy adult subjects.

Co-administration with a strong CYP2C19/moderate CYP3A4 inhibitor (200 mg fluconazole once daily for 4 days) increased KOSELUGO C_{max} by 26 % (90 % CI 10, 43) and AUC by 53 % (90 % CI 44, 63) in healthy adult subjects, respectively.

Concomitant use of erythromycin (moderate CYP3A4 inhibitor) or fluoxetine (strong CYP2C19/CYP2D6 inhibitor) is predicted to increase KOSELUGO 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) and CYP2C19 (e.g., omeprazole) should be avoided.

If co-administration is unavoidable, patients should be carefully monitored for adverse events and the KOSELUGO dose should be reduced (see section 4.2 and Table 4).

Active substances that may decrease KOSELUGO *plasma concentrations*

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

Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St.John's Wort) or moderate CYP3A4 inducers with KOSELUGO should be avoided.

Active substances whose plasma concentrations may be altered by -KOSELUGO

In vitro, KOSELUGO is an inhibitor of OAT3. The potential for a clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 (e.g., methotrexate and furosemide) cannot be excluded (see section 5.2).

TPGS is a P-gp inhibitor *in vitro* and it cannot be excluded that it may cause clinically relevant medicine interactions with substrates of P-gp (e.g., digoxin or fexofenadine).

The effect of KOSELUGO 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 (see section 4.6).

Effect of gastric acid reducing agents on KOSELUGO

KOSELUGO capsules do not exhibit pH dependent dissolution. KOSELUGO can be used concomitantly with gastric pH modifying agents (i.e.,H2-receptor antagonists and proton pump inhibitors) without restrictions, except for omeprazole which is a CYP2C19 inhibitor.

Vitamin E

KOSELUGO capsules contain vitamin E as the excipient TPGS. Therefore, patients should avoid taking supplemental vitamin E and anticoagulant assessments should be performed more frequently in patients taking concomitant anticoagulant or antiplatelet medicines (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving KOSELUGO. It is recommended that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment.

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 KOSELUGO may reduce the effectiveness of oral contraceptives, therefore women using hormonal contraceptives should be recommended to add a barrier method (see section 4.5).

Pregnancy

There are no data on the use of KOSELUGO in pregnant women. Studies in animals have shown reproductive toxicity including embryofoetal death, structural defects and reduced foetal weights (see section 5.3). KOSELUGO is not recommended during pregnancy and in women of childbearing potential not using contraception (see section 4.4).

If a female patient or a female partner of a male patient receiving KOSELUGO becomes pregnant, she should be apprised of the potential risk to the foetus.

Breastfeeding

It is not known whether KOSELUGO, or its metabolites, are excreted in human milk. KOSELUGO and its

active metabolite are excreted in the milk of lactating mice (see section 5.3). A risk to the breast-fed child cannot be excluded, therefore breast-feeding should be discontinued during treatment with KOSELUGO.

Fertility

There are no data on the effect of KOSELUGO on human fertility. KOSELUGO had no impact on fertility and mating performance in male and female mice, although a reduction in embryonic survival was observed in female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

KOSELUGO may have a minor influence on the ability to drive and use machines. Fatigue, asthenia and visual disturbances have been reported during treatment with KOSELUGO and patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of KOSELUGO monotherapy in paediatric patients with NF1 who have inoperable PN has been determined following evaluation of a combined safety population of 74 paediatric patients (20-30 mg/m^2 twice daily). This paediatric 'pool' of patients comprised 50 patients in SPRINT Phase II Stratum 1, treated with KOSELUGO 25 mg/m^2 twice daily (the pivotal dataset) and 24 patients in SPRINT Phase I treated with 20 to 30 mg/m^2 KOSELUGO twice daily (the dose finding study). There were no clinically relevant differences in the safety profile between SPRINT Phase I and SPRINT Phase II Stratum 1. This safety profile was also substantiated by a pool of safety data from 7 AstraZeneca sponsored studies in adult patients with multiple tumour types (N=347) who received 75 to 100 mg twice daily).

In the paediatric pool, the median total duration of KOSELUGO treatment in paediatric patients with NF1 who have PN was 55 months (range: <1 to 97 months), 61 % of patients were exposed to KOSELUGO treatment for >48 months and 16 % for >72 months. Patients aged ≥2 to 11 years (N=45) had a higher incidence of the following adverse drug reactions (ADRs) compared to patients aged 12 to 18 years (N=29):

hypoalbuminaemia, dry skin, pyrexia, hair colour changes, rash maculo-papular and paronychia.

In the paediatric pool (N=74; comprising 50 patients from the pivotal SPRINT Phase II Stratum 1 dataset and 24 patients from the supportive SPRINT Phase I dataset), the most common adverse reactions of any grade (incidence ≥45 %) were vomiting (86 %), diarrhoea (81%), blood creatine phosphokinase increased (77 %), nausea (77 %), dry skin (65 %), pyrexia (61 %), dermatitis acneiform (61%), asthenic events (59 %), paronychia (57 %), stomatitis (55 %), haemoglobin decreased (54 %), non-acneiform rashes (53 %), hypoalbuminaemia (51 %), and aspartate aminotransferase increased (51 %). Dose interruptions and reductions due to adverse events were reported in 82 % and 39 % of patients, respectively. The most commonly reported ADRs leading to dose modification (dose interrupted or dose reduced) of KOSELUGO were vomiting (32 %), paronychia (23 %), nausea (19 %), diarrhoea (15 %) and pyrexia (11 %). Permanent discontinuation due to adverse events was reported in 12 % of the patients. The following serious adverse reactions were reported: diarrhoea (3 %), anaemia (3 %), pyrexia (3 %), blood CPK increased (3 %), blood creatinine increased (1 %), oedema peripheral (1 %) and vomiting (1 %).

Tabulated list of adverse reactions

Table 5 presents the adverse reactions identified in the paediatric population with NF1 who have inoperable PN and in adult patients (see footnote to Table 5). The frequency is determined from the paediatric pool (N=74); comprising 50 patients from the pivotal SPRINT Phase II Stratum 1 dataset and 24 patients from the supportive SPRINT Phase I dataset. Adverse drug reactions (ADRs) are organised by MedDRA system organ class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data), including isolated reports.

Table 5. Adverse drug reactions reported in the paediatric pool (pivotal SPRINT Phase II Stratum 1 [N=50] and supportive SPRINT Phase I [N=24]) and in other identified clinical trials in adult patients (N= 347)††

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE grades) NF1 paediatric pool‡ (N= 74)	Frequency of CTCAE grade 3 and Above† NF1 paediatric pool‡ (N= 74)
Eye disorders	Vision blurred^	Very common (15 %)	-
	Retinal pigment epithelial detachment (RPED)/Central serous retinopathy (CSR)* ††	Uncommon (0,6 %)	-
	Retinal vein occlusion (RVO)* ††	Uncommon (0,3 %)	-
Respiratory, thoracic & mediastinal disorders	Dyspnoea*	Common (8 %)	-
Gastrointestinal disorders	Vomiting^	Very common (86 %)	Common (9 %)
	Diarrhoea^	Very common (81 %)	Very common (15 %)
	Nausea^	Very common	Common (3 %)

		(77 %)	
	Stomatitis^	Very common (55 %)	Common (1 %)
	Dry mouth	Common (5 %)	-
Skin and subcutaneous tissue disorders	Dry skin	Very common (65 %)	Common (1 %)
	Dermatitis acneiform^	Very common (61 %)	Common (4 %)
	Paronychia^	Very common (57 %)	Very common (14 %)
	Rashes (non-acneiform)^*	Very common (53 %)	Common (3 %)
	Hair changes^*	Very common (39 %)	-
General disorders	Pyrexia	Very common (61 %)	Common (8 %)
	Asthenic events*	Very common (59 %)	-
	Peripheral oedema*	Very common (31 %)	-
	Facial oedema*	Common (8 %)	-
Investigations	Blood CPK increased^	Very common (77 %)	Common (9 %)
	Haemoglobin decreased*	Very common (54 %)	Common (3 %)
	Hypoalbuminaemia	Very common (51 %)	-
	AST increased	Very common (51 %)	Common (1 %)
	ALT increased	Very common (39 %)	Common (3 %)
	Blood creatinine	Very common	Common (1 %)

	increased	(32 %)	
	Ejection fraction decreased^	Very common (28 %)	Common (1 %)
	Increased blood pressure*	Very common (18 %)	-

Per National Cancer Institute CTCAE version 4,03

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

^See Description of selected adverse reactions

†All reactions were CTCAE grade 3, except for one CTCAE grade 4 event of blood CPK increased and one CTCAE grade 4 event of blood creatinine increased. There were no deaths.

†† Identified ADRs from other clinical trial experience in adult patients (N = 347), with multiple tumour types, receiving treatment with KOSELUGO (75 mg twice daily). These ADRs have not been reported in paediatric population with NF1 who have inoperable PN.

‡Paediatric pool (N=74) percentage rounded to the nearest decimal.

*ADRs based on grouping of individual preferred terms (PT):

Asthenic events: asthenia, fatigue

CSR/RPED: Detachment of macular retinal pigment epithelium, chorioretinopathy

Dyspnoea: dyspnoea exertional, dyspnoea, dyspnoea at rest

Facial oedema: face oedema, periorbital oedema

Haemoglobin decreased: anaemia, haemoglobin decreased

Hair changes: alopecia, hair colour change

Increased blood pressure: blood pressure increased, hypertension

Peripheral oedema: oedema peripheral, oedema, localised oedema, peripheral swelling

Rashes (non-acneiform): rash pruritic, rash maculo-papular, rash papular, rash, rash erythematous, rash macular

RVO: retinal vascular disorder, retinal vein occlusion, retinal vein thrombosis

Description of selected adverse reactions

Left ventricular ejection fraction (LVEF) reduction

In SPRINT, Phase II Stratum 1, LVEF reduction (PT: ejection fraction decreased) was reported in 13 (26 %) patients; all cases were grade 2, asymptomatic and did not lead to discontinuation; one (2 %) case led to dose interruption then reduction. Of the 13 patients, 11 patients recovered and for 2 patients the outcome was not reported. The median time to first occurrence of LVEF reduction was 232 days (median duration 252 days). The majority of LVEF reduction adverse reactions were reported as reductions from baseline (≥10 % reduction) but were considered to remain in the normal range. Patients with LVEF lower than the institutional LLN at baseline were not included in the pivotal study. In addition, a small number of serious cases of LVEF reduction associated with KOSELUGO have been reported in paediatric patients who participated in an expanded access program. For clinical management of LVEF reduction (see sections 4.2 and 4.4).

Ocular toxicity

In SPRINT, Phase II Stratum 1, grade1 and 2 adverse reactions of blurred vision were reported in 7 (14 %) patients. Two patients required dose interruption. All adverse reactions were managed without dose reduction. For clinical management of new visual disturbances (see sections 4.2 and 4.4).

In addition, a single event of RPED was reported in a paediatric patient receiving KOSELUGO monotherapy

(25 mg/m^2 twice daily) for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study (see sections 4.2 and 4.4).

Paronychia

In SPRINT, Phase II Stratum 1, paronychia was reported in 28 (56 %) patients, the median time to first onset of maximum grade paronychia adverse reaction was 423 days and the median duration of adverse reactions was 51 days. The majority of these adverse reactions were grade 1 or 2 and were treated with supportive or symptomatic therapy and/or dose modification. Grade ≥3 events occurred in 4 (8 %) patients. Ten patients (3 with a maximum grade 3 adverse reaction and 7 with a maximum grade 2 adverse reaction) had a KOSELUGO dose interruption for adverse reactions of paronychia, of whom 5 had dose interruption followed by dose reduction (2 patients required a second dose reduction). In one patient (2 %) the event led to discontinuation.

Blood creatine phosphokinase (CPK) increase

Adverse reactions of blood CPK elevation occurred in 39 (78 %) of patients in SPRINT Phase II Stratum 1. The median time to first onset of the maximum grade CPK increase was 112 days and the median duration of adverse reactions was 153 days. The majority of adverse reactions were grade 1 or 2 and resolved with no change in KOSELUGO dose. Grade ≥3 adverse reactions occurred in 3 (6 %) patients. A grade 4 adverse reaction led to treatment interruption followed by dose reduction.

Gastrointestinal toxicities

In SPRINT, Phase II Stratum 1, vomiting (43 patients, 86 %, median duration 3 days), diarrhoea (37 patients, 74 %, median duration 6 days), nausea (36 patients, 72 %, median duration 15 days), and stomatitis (26 patients, 52 %, median duration 27 days) were the most commonly reported gastrointestinal (GI) reactions. The majority of these cases were grade 1 or 2 and did not require any dose interruptions or dose reductions.

Grade 3 adverse reactions were reported for diarrhoea (8 patients, 16 %), nausea (2 patients, 4 %), and vomiting (4 patients, 8 %). For one patient diarrhoea led to dose reduction and subsequent discontinuation. No dose reduction or discontinuation was required for adverse reactions of nausea, vomiting or stomatitis.

Skin toxicities

In SPRINT, Phase II Stratum 1, dermatitis acneiform was observed in 28 (56 %) patients (median time to onset 43 days; median duration of 202 days for the maximum CTCAE grade event). The majority of these cases were grade1 or 2, observed in post-pubertal patients (>12 years) and did not require any dose interruptions or reductions. Grade 3 adverse reactions were reported in 3 (6 %) patients.

Other (non-acneiform) rashes were observed in 27 (54 %) patients in the pivotal study and were predominantly grade 1 or 2.

Hair changes

In SPRINT, Phase II Stratum 1, 16 (32 %) of patients experienced hair changes (reported as hair lightening [PT: hair colour changes] in 12 patients (24 %) and hair thinning [PT: alopecia] in 12 patients (24 %)); in 8 patients (16 %) both alopecia and hair colour changes were reported during treatment. All cases were grade 1 and did not require dose interruption or dose reduction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no specific treatment for overdose. If overdose occurs, patients should be closely monitored for

signs and symptoms of adverse reactions and treated supportively with appropriate monitoring as necessary. Dialysis is ineffective in the treatment of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, ATC code: L01EE04

Mechanism of action

Selumetinib is a selective inhibitor of mitogen activated protein kinase kinases 1 and 2 (MEK 1/2). Selumetinib blocks MEK activity and the RAF-MEK-ERK pathway. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.

Clinical efficacy

The efficacy of KOSELUGO was evaluated in an open-label, multi-centre, single-arm study (SPRINT) Phase II Stratum 1 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 were excluded for the following ocular toxicities: any current or past history of CSR, current or past history of RVO, known intraocular pressure >21 mmHg (or upper limit of normal adjusted by age) or uncontrolled glaucoma. 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 to 17,4 years), 60 % were male and 84 % were Caucasian.

The median target PN volume at baseline was 487,5 mL (range: 5,6 - 3820 mL). PN-related morbidities that were present in ≥20 % of patients included disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction.

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.

Table 6. Efficacy results from SPRINT Phase II Stratum 1

Efficacy parameter	**SPRINT (N=50)**
Objective response rate [a, b]	
Objective response rate, % (95 % CI)	34 (68 %) (53,3 – 80,5)
Complete response	0
Confirmed partial response, n (%)[b]	34 (68 %)
Duration of response	

DoR ≥ 12 months, n (%)	31 (91,2 %)
DoR ≥ 24 months, n (%)	26 (76,5 %)
DoR ≥ 36 months, n (%)	21 (61,8 %)
CI –confidence interval, DoR –duration of response. [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.	

An independent centralised review of tumour response per REiNS criteria (data cut-off June 2018) resulted in an ORR of 44 % (95 % CI: 30,0; 58,7).

The median time to onset of response was 7,2 months (range: 3,3 months to 3,2 years). The median (min-max) time to the maximal PN shrinkage from baseline was 15,1 months (range: 3,3 months to 5,2 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. The median time from treatment initiation to disease progression while on treatment was not reached.

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

Paediatric population

The safety and efficacy of KOSELUGO in children less than 3 years of age has not been established. No data are available.

5.2 Pharmacokinetic properties

At the recommended dose 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 food

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 selumetinib 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 to 3 hours (see section 4.2).

In healthy adult subjects at a dose of 50 mg, co-administration of selumetinib with a low-fat meal resulted in 60 % lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 38 %, and the time to reach maximum concentration (t_{max}) was delayed by approximately 0,9 hours (see section 4.2).

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).

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.

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 %).

Biotransformation

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, 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. 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.

I*nteractions*

In vitro, selumetinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E1. *In vitro*, selumetinib is not an inducer of CYP1A2 and CYP2B6. Selumetinib is an inducer of CYP3A4 *in vitro*, this is however not expected to be clinically relevant.

In vitro, selumetinib inhibits UGT1A3, UGT1A4, UGT1A6 and UGT1A9 however these effects are not expected to be clinically relevant.

Interactions with transport proteins

Based on *in vitro* studies, selumetinib is a substrate for BCRP and P-gp transporters but is unlikely to be subjected to clinically relevant medicine interactions. *In vitro* studies suggest that selumetinib does not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, MATE1 and MATE2K at the recommended paediatric dose. A clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 cannot be excluded.

Elimination

In healthy adult subjects, 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).

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). There was a trend of lower protein binding in subjects with severe hepatic impairment although the protein binding remained >99 % (see section 4.3).

Ethnicity

Following a single-dose, selumetinib exposure appears to be higher in Japanese, non-Japanese-Asian and Indian healthy adult subjects compared to Western adult subjects, however, there is considerable overlap with Western subjects when corrected for body weight or BSA (see section 4.2).

Adult patients (>18 years old)

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

In adult patients, C_{max} and AUC increased dose proportionally over a 25 mg to 100 mg dose range.

5.3 Preclinical safety data

Genotoxicity

Selumetinib was positive in the mouse micronucleus study via an aneugenic mode of action. The free mean exposure (C_{max}) at the no observed effect level (NOEL) was approximately 27-times greater than clinical free exposure at the maximum recommended human dose (MRHD) of 25 mg/m^2.

Carcinogenicity

Selumetinib was not carcinogenic in rats or transgenic mice.

Repeat-dose toxicity

In repeat-dose toxicity studies in mice, rats and monkeys, the main effects seen after selumetinib exposure were in the skin, GI tract and bones. Scabs associated with microscopic erosions and ulceration at a free exposure similar to the clinical exposure (free AUC) at the MRHD were seen in rats. Inflammatory and ulcerative GI tract findings associated with secondary changes in the liver and lymphoreticular system at free exposures approximately 28 times the clinical free exposure at the MRHD were observed in mice. Growth plate (physeal) dysplasia was seen in male rats dosed for up to 3 months with selumetinib at a free exposure 11 times the clinical free exposure at the MRHD. GI findings showed evidence of reversibility following a recovery period. Reversibility for skin toxicities and physeal dysplasia was not evaluated. Vascular engorgement of the corpus cavernosum of the bulbocavernosus muscle were observed in male mice in a 26-week study at a dose of 40 mg/kg/day (28 times the free AUC in humans at the MRHD) leading to significant urinary tract obstruction as well as inflammation and luminal haemorrhage of the urethra leading to early death in male mice.

Reproductive toxicology

Developmental and reproduction toxicity studies were conducted in mice. Fertility was not affected in male mice at up to 40 mg/kg/day (corresponding to 22-fold the free AUC in humans at the MRHD). In females, mating performance and fertility were not affected at up to 75 mg/kg/day, but a reversible decrease in the number of live foetuses was observed at this dose level; the NOAEL for effects on reproductive performance was 5 mg/kg/day (approximately 3,5-fold the free AUC in humans at the MRHD). A treatment-related increase in the incidence of external malformations (open eye, cleft palate) was reported in absence of maternal toxicity in embryofoetal development studies at >5 mg/kg/day, and in the pre-and post-natal development study at ≥1 mg/kg/day (corresponding to 0,4-fold the free C_{max} in humans at the MRHD). The other treatment related effects observed at non-maternotoxic dose levels in these studies consisted of embryo-lethality and decreased foetal weight at ≥25 mg/kg/day (corresponding to 22-fold the free AUC in humans at the MRHD), reductions in post-natal pup growth and at weaning a lower number of pups met the pupil constriction criterion at 15 mg/kg/day (corresponding to 3.6-fold the free C_{max} in humans at the MRHD). Selumetinib and its active metabolite were excreted in the milk of lactating mice at concentrations

approximately the same as those in plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Tocofersolan (Vitamin E polyethylene glycol succinate /D α-tocopheryl polyethylene glycol succinate).

Capsule shell

KOSELUGO 10 mg hard capsules

Hypromellose (E464)

Carrageenan (E407)

Potassium chloride (E508)

Titanium dioxide (E171)

Carnauba wax (E903)

KOSELUGO 25 mg hard capsules

Hypromellose (E464)

Carrageenan (E407)

Potassium chloride (E508)

Titanium dioxide (E171)

Indigo carmine aluminium lake (E132)

Iron oxide yellow (E172)

Carnauba wax (E903)

Maize starch

Printing ink

KOSELUGO 10 mg hard capsules

Shellac glaze, standard (E904)

Iron oxide black (E172)

Propylene glycol (E1520)

Ammonium hydroxide (E527)

KOSELUGO 25 mg hard capsules

Iron oxide red (E172)

Iron oxide yellow (E172)

Indigo carmine aluminium lake (E132)

Carnauba wax (E903)

Shellac, standard (E904)

Glyceryl mono-oleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.

Store in the original bottle in order to protect from moisture and light.

Keep the bottle tightly closed.

6.5 Nature and contents of container

KOSELUGO 10 mg hard capsules

High-density polyethylene (HDPE) plastic bottle with white child-resistant polypropylene closure.

KOSELUGO 25 mg hard capsules

High-density polyethylene (HDPE) plastic bottle with blue child-resistant polypropylene closure.

Each bottle contains 60 hard capsules and a silica gel desiccant. Each carton contains one bottle.

6.6 Special precautions for disposal and other handling

Patients should be instructed not to remove the desiccant from the bottle.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

8 REGISTRATION NUMBERS

KOSELUGO 10 mg: 59/26/0679

KOSELUGO 25 mg: 59/26/0680

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 2024

10 DATE OF REVISION OF THE TEXT

Not applicable

SMPC date of first authorisation 17 June 2021; Renewal 31 May 2023