

Proposed packaging material	
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Name & Date	FTA, 21 st January 2025

KOSELUGO
Selumetinib Sulfate
Capsules

1. NAME OF THE MEDICINAL PRODUCT

Koselugo 10 mg hard capsules
Koselugo 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Koselugo 10 mg hard capsules

Each hard capsule contains 12.1 mg of selumetinib sulfate (equivalent to 10 mg Selumetinib).

Koselugo 25 mg hard capsules

Each hard capsule contains 30.25 mg of selumetinib sulfate (equivalent to 25 mg Selumetinib).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

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 physician experienced in the diagnosis and the treatment of patients with NF1 related tumours.

Posology

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

Dosing is individualised based on BSA (mg/m²) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of Koselugo capsules can be combined to attain the desired dose (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 m² 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 than 18, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician. 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 selumetinib 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 medicinal product 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), selumetinib treatment should be interrupted until resolution. Once resolved, selumetinib 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, selumetinib should be discontinued and a prompt cardiology referral should be carried out (see section 4.4).

Dose modification advice for ocular toxicities

Selumetinib 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 selumetinib

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 selumetinib 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/m² twice daily, dose reduce to 20 mg/m² twice daily.
- If a patient is currently taking 20 mg/m² twice daily, dose reduce to 15 mg/m² twice daily (see Table 4 and section 4.5).

Table 4. Recommended dose to achieve 20 mg/m² or 15 mg/m² 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/m² 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 drug release and affect the absorption of selumetinib.

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 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.

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 selumetinib 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 selumetinib 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 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).

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 section 4.2). If RVO is diagnosed, treatment with selumetinib should be permanently discontinued (see section 4.2).

Liver laboratory abnormalities

Liver laboratory abnormalities, specifically AST and ALT elevations, can occur with selumetinib (see section 4.8). Liver laboratory values should be monitored before initiation of selumetinib 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 medicinal products (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 medicinal products are warranted (see section 4.5).

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).

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 medicinal products and other forms of interaction

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

Active substances that may increase selumetinib plasma concentrations

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

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

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

Co-administration with 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 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).

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 selumetinib

In vitro, selumetinib 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 drug interactions with substrates of P-gp (e.g., digoxin or fexofenadine).

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 (see section 4.6).

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.

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 medicinal products (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 selumetinib 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 selumetinib in pregnant women. Studies in animals have shown reproductive toxicity including embryofetal 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.

Breast-feeding

It is not known whether selumetinib, or its metabolites, are excreted in human milk. Selumetinib 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. Selumetinib 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 selumetinib 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 selumetinib 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/m² twice daily). This paediatric 'pool' of patients comprised 50 patients in SPRINT Phase II Stratum 1, treated with selumetinib 25 mg/m² twice daily (the pivotal dataset) and 24 patients in SPRINT Phase I treated with 20 to 30 mg/m² selumetinib 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 selumetinib treatment in paediatric patients with NF1 who have PN was 55 months (range: < 1 to 97 months), 61% of patients were exposed to selumetinib treatment for > 48 months and 16% for >72 months.

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 selumetinib 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 (77%)	Common (3%)
	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%)

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)
	Hypoalbuminaemia	Very common (51%)	-
	AST increased	Very common (51%)	Common (1%)
	ALT increased	Very common (39%)	Common (3%)
	Blood creatinine increased	Very common (32%)	Common (1%)
	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 selumetinib (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 odema, 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 ($\geq 10\%$ 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 selumetinib 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, grade 1 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 selumetinib monotherapy (25 mg/m² 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 selumetinib 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 selumetinib 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 grade 1 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

PT AstraZeneca Indonesia

Apabila Anda ingin melaporkan dugaan efek samping produk AstraZeneca menanyakan/ meminta informasi medis terkait produk AstraZeneca mohon dikirimkan dengan mengisi form elektronik pada tautan berikut ini: <http://contactazmedical.astrazeneca.com>

Pusat Farmakovigilans

Reporting suspected adverse reactions after authorisation 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:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Telepon: +62-21-4244691 Ext.1079
Website: <https://e-meso.pom.go.id/ADR>

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/m² (BSA) twice daily, for 28 days (1 treatment cycle), on a continuous dosing schedule. Treatment was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity or PN progression, or at the discretion of the investigator.

The target PN, the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was 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 $\geq 20\%$ 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 $\geq 20\%$ 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 $\geq 20\%$ compared to baseline.

An independent centralized 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.

5.2 Pharmacokinetic properties

At the recommended dose of 25 mg/m² 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 (AUC₀₋₁₂) 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/m², 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/m² 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/m² 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 ¹⁴C-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.

Interactions

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 drug 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/m².

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 hemorrhage 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

Do not store above 30 °C.

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

Keep the bottle tightly closed.

In-Use stability has been demonstrated for up to 30 days at 25°C/60% RH and 30°C/75% RH from the time the packaged is opened

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.

6.6 Special precautions for disposal and other handling

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

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

7. Pack Size

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

1 box, Bottle @ 60 hard Capsules Koselugo 10 mg (Reg No. DKI2459602801A1)

1 box, Bottle @ 60 hard Capsules Koselugo 25 mg (Reg No. DKI2459602801B1)

HARUS DENGAN RESEP DOKTER

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Proposed packaging material		
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Changes	CDS Update - Study 15	
Name	FTA, 21st of January 2025	

Leaflet Informasi Pasien

KOSELUGO

Selumetinib Sulfate

Kapsul Keras 10 mg dan 25 mg

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet berisi informasi penting untuk Anda.

- Simpan leaflet ini. Anda mungkin perlu membacanya lagi di kemudian hari.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini hanya diresepkan khusus hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, meskipun tanda-tanda penyakit yang mereka miliki sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat Anda. Hal ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Lihat bagian 4.

Leaflet ini berisi informasi mengenai

1. Tentang Koselugo dan kegunaannya
2. Hal yang perlu diketahui sebelum menggunakan Koselugo
3. Cara pemakaian Koselugo
4. Efek samping yang mungkin dialami
5. Cara penyimpanan Koselugo
6. Isi kemasan dan informasi lainnya

1. Tentang Koselugo dan kegunaannya

Tentang Koselugo dan cara kerjanya

Koselugo mengandung zat aktif selumetinib.

Selumetinib adalah jenis obat yang disebut penghambat protein MEK. Obat ini bekerja dengan memblokir protein tertentu yang terlibat dalam pertumbuhan sel tumor.

Koselugo diharapkan dapat mengecilkan tumor yang tumbuh di sepanjang saraf, yang disebut neurofibroma pleksiform.

Tumor ini disebabkan oleh kondisi genetik yang disebut neurofibromatosis tipe 1 (NF1).

Kegunaan Koselugo

Koselugo digunakan untuk mengobati anak-anak berusia 3 tahun ke atas dengan neurofibroma pleksiform yang tidak dapat diangkat sepenuhnya melalui pembedahan.

Jika Anda memiliki pertanyaan tentang cara kerja Koselugo atau mengapa obat ini diresepkan untuk Anda, tanyakan kepada dokter Anda.

2. Hal yang perlu diketahui sebelum menggunakan Koselugo

Jangan menggunakan Koselugo:

- jika Anda alergi terhadap selumetinib atau kandungan lain dari obat ini (tercantum dalam bagian 6)
- jika Anda memiliki penyakit hati parah

Jika Anda tidak yakin, konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan Koselugo.

Peringatan dan pencegahan

Konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum dan selama perawatan dengan Koselugo:

- jika Anda memiliki masalah pada organ mata
- jika Anda memiliki masalah pada organ jantung
- jika Anda memiliki masalah pada organ hati
- jika Anda menggunakan suplemen mengandung vitamin E
- jika Anda tidak dapat menelan kapsul utuh

Jika kondisi di atas berlaku untuk Anda (atau Anda tidak yakin), konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan obat ini.

Masalah pada organ mata

Koselugo dapat menyebabkan masalah pada organ mata (lihat bagian 4 'Efek samping yang mungkin dialami'). **Beritahu dokter Anda segera** jika penglihatan kabur atau perubahan lain pada penglihatan Anda selama perawatan. Dokter Anda harus memeriksa mata Anda jika mulai mengalami masalah penglihatan atau penglihatan Anda memburuk saat menggunakan obat ini.

Masalah jantung

Koselugo dapat menurunkan jumlah darah yang dipompa oleh jantung Anda (lihat bagian 4 'Efek samping yang mungkin dialami'). Dokter Anda akan memeriksa seberapa baik jantung Anda bekerja sebelum dan selama perawatan Anda dengan Koselugo.

Masalah hati

Koselugo dapat meningkatkan jumlah beberapa enzim hati dalam darah Anda (lihat bagian 4 'Efek samping yang mungkin dialami'). Dokter Anda akan melakukan tes darah sebelum dan selama perawatan untuk memeriksa seberapa baik hati Anda bekerja.

Suplemen vitamin E

Kapsul Koselugo mengandung vitamin E yang dapat meningkatkan risiko pendarahan. Anda harus memberi tahu dokter Anda jika menggunakan obat lain yang meningkatkan risiko pendarahan seperti:

- asam asetilsalisilat (juga dikenal sebagai aspirin) untuk mengatasi rasa sakit dan peradangan

- obat antikoagulan (pengencer darah) seperti warfarin atau obat lain yang digunakan untuk mencegah penggumpalan darah
- suplemen yang dapat meningkatkan risiko perdarahan, seperti vitamin E

Kesulitan menelan kapsul

Konsultasikan dengan dokter Anda jika Anda merasa kesulitan menelan kapsul secara utuh (lihat bagian 3 'Cara menggunakan Koselugo').

Masalah kulit, kuku dan rambut

Koselugo dapat menyebabkan ruam kulit, infeksi kuku atau penipisan rambut atau perubahan warna rambut (lihat bagian 4 'Efek samping yang mungkin dialami'). Beritahu dokter Anda jika ada gejala-gejala berikut yang mengganggu Anda selama perawatan.

Anak-anak di bawah 3 tahun

Jangan berikan Koselugo pada anak-anak di bawah usia 3 tahun karena obat ini belum pernah diteliti pada kelompok usia ini.

Obat-obatan lain dan Koselugo

Beritahu dokter atau apoteker Anda jika sedang, baru saja, atau mungkin akan menggunakan obat lain. Ini termasuk obat herbal, suplemen, dan obat-obatan yang diperoleh tanpa resep dokter.

Koselugo dapat mempengaruhi cara kerja beberapa obat lain. Selain itu, beberapa obat lain juga dapat mempengaruhi cara kerja Koselugo. Beritahu dokter Anda jika menggunakan obat-obatan berikut ini:

- klaritromisin atau eritromisin (digunakan untuk mengobati infeksi bakteri)
- karbamazepin atau fenitoin (digunakan untuk mengobati kejang dan epilepsi)
- digoxin (digunakan untuk mengobati gagal jantung)
- fexofenadine (digunakan untuk mengobati gejala alergi)
- flukonazol atau itrakonazol (digunakan untuk mengobati infeksi jamur)
- ketokonazol (digunakan untuk mengobati sindrom Cushing)
- furosemid (digunakan untuk mengobati retensi cairan dengan meningkatkan jumlah urin yang Anda keluarkan)
- metotreksat (digunakan untuk mengobati beberapa jenis kanker, psoriasis, atau artritis reumatoid)
- omeprazole (digunakan untuk mengobati refluks asam atau tukak lambung)
- rifampisin (digunakan untuk mengobati tuberkulosis (TBC) dan beberapa infeksi bakteri lainnya)
- *St. John's wort* (*Hypericum perforatum*), obat herbal (digunakan untuk mengobati depresi ringan dan kondisi lainnya)
- tiklopidin (digunakan untuk mencegah penggumpalan darah)

Beritahu dokter atau apoteker Anda jika sedang atau baru saja menggunakan obat di atas atau obat lain, bahkan yang tidak diresepkan.

Koselugo dengan makanan dan minuman

Jangan minum jus jeruk bali (*grapefruit*) saat Anda menggunakan Koselugo karena dapat mempengaruhi cara kerja obat.

Kehamilan - informasi untuk wanita

Koselugo tidak dianjurkan selama kehamilan. Dapat menyebabkan gangguan pada bayi yang belum lahir.

Jika Anda merasa hamil atau berencana untuk memiliki bayi, mintalah saran dari dokter Anda sebelum menggunakan obat ini. Dokter Anda mungkin meminta untuk melakukan tes kehamilan sebelum memulai perawatan.

Anda tidak boleh hamil saat menggunakan obat ini. Jika Anda bisa hamil, Anda harus menggunakan kontrasepsi yang efektif. Lihat 'Kontrasepsi - informasi untuk wanita dan pria' di bawah ini.

Jika Anda hamil selama perawatan, segera beritahu dokter Anda.

Kehamilan - informasi untuk pria

Jika pasangan Anda hamil saat Anda menggunakan obat ini, segera beritahu dokter Anda.

Kontrasepsi - informasi untuk wanita dan pria

Jika Anda aktif secara seksual, Anda harus menggunakan kontrasepsi yang efektif saat Anda menggunakan obat ini dan setidaknya selama 1 minggu setelah dosis terakhir. Tidak diketahui apakah Koselugo dapat mengganggu kerja kontrasepsi hormonal. Beritahu dokter Anda jika sedang menggunakan kontrasepsi hormonal, karena dokter mungkin akan merekomendasikan penambahan metode kontrasepsi non-hormonal.

Menyusui

Jangan menyusui jika Anda menggunakan Koselugo. Tidak diketahui apakah Koselugo mengalir masuk ke dalam ASI.

Menyetir dan mengoperasikan mesin

Koselugo dapat menyebabkan efek samping yang mempengaruhi kemampuan Anda untuk menyetir atau mengoperasikan mesin. Jangan menyetir atau mengoperasikan mesin jika Anda merasa lelah atau memiliki masalah dengan penglihatan (seperti penglihatan kabur).

3. Cara menggunakan Koselugo

Selalu gunakan obat ini persis seperti yang dikatakan oleh dokter atau apoteker Anda. Konsultasikan dengan dokter atau apoteker Anda jika tidak yakin.

Dosis penggunaan

Dokter Anda akan menentukan dosis yang tepat berdasarkan tinggi dan berat badan Anda. Dokter akan memberi tahu Anda berapa banyak kapsul Koselugo yang harus dikonsumsi.

Dokter Anda mungkin meresepkan dosis yang lebih rendah jika Anda memiliki masalah dengan hati (gangguan hati).

Dokter Anda dapat mengurangi dosis jika Anda mengalami efek samping tertentu saat menggunakan Koselugo (lihat bagian 4 'Efek samping yang mungkin dialami') atau dokter dapat memutus perawatan atau menghentikannya secara permanen.

Cara penggunaan

- Minum Koselugo dua kali sehari, dengan jarak sekitar 12 jam, **dengan atau tanpa makanan**.
- Telan kapsul utuh dengan air.
- Jangan mengunyah, melarutkan, atau membuka kapsul.
- Jika Anda pernah, atau merasa kesulitan menelan kapsul utuh, konsultasikan dengan dokter Anda sebelum memulai perawatan.

Jika Anda sakit

Jika Anda sakit (muntah) kapan saja setelah menggunakan Koselugo, jangan minum dosis tambahan. Minum dosis berikutnya pada waktu normal.

Jika Anda menggunakan Koselugo lebih dari yang seharusnya

Jika Anda telah menggunakan Koselugo lebih dari yang seharusnya, segera hubungi dokter atau apoteker Anda.

Jika Anda lupa menggunakan Koselugo

Apa yang perlu dilakukan jika Anda lupa meminum dosis Koselugo tergantung pada berapa lama waktu yang dibutuhkan sampai dosis berikutnya.

- Jika sudah lebih dari 6 jam sampai dosis berikutnya, minum dosis yang terlewat. Kemudian minum dosis berikutnya pada waktu normal.
- Jika kurang dari 6 jam sampai dosis berikutnya, hiraukan dosis yang terlewat. Kemudian minum dosis berikutnya pada waktu normal.

Jangan minum dosis ganda (dua dosis sekaligus) untuk mengganti dosis yang terlupa.

Jika Anda berhenti menggunakan Koselugo

Jangan berhenti menggunakan Koselugo kecuali diberitahu oleh dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Efek samping yang mungkin dialami

Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping serius**Masalah mata (penglihatan)**

Koselugo dapat menyebabkan masalah mata. Segera beritahu dokter Anda jika mengalami penglihatan kabur (efek samping yang sangat umum yang dapat mempengaruhi lebih dari 1 dari 10 orang) atau perubahan lain pada penglihatan Anda selama perawatan. Dokter Anda mungkin akan meminta untuk berhenti minum obat ini atau mengirim Anda ke dokter spesialis, jika mengalami gejala-gejala yang meliputi:

- penglihatan kabur
- kehilangan penglihatan
- bintik-bintik gelap pada penglihatan Anda (floaters)
- perubahan lain pada penglihatan Anda (seperti penglihatan yang berkurang)

Segera beritahu dokter Anda jika Anda menyadari adanya efek samping di atas.

Efek samping lainnya

Beritahu dokter atau apoteker Anda jika menyadari adanya efek samping berikut:

Sangat umum (dapat dialami lebih dari 1 dari 10 orang)

- sakit (muntah), merasa mual

- diare
- radang mulut (stomatitis)
- masalah kulit dan kuku - tanda-tandanya bisa berupa kulit kering, ruam, kemerahan di sekitar kuku
- penipisan rambut (alopecia), perubahan warna rambut
- merasa lelah, lemah, atau kekurangan energi
- demam (pyrexia)
- pembengkakan pada tangan atau kaki (edema perifer)
- penurunan sedikit jumlah darah yang dipompa jantung (fraksi ejeksi menurun) - tanda-tandanya dapat berupa sesak napas atau bengkak pada tungkai, pergelangan kaki, atau kaki Anda
- tekanan darah tinggi (hipertensi)
- berkurangnya tingkat albumin, protein penting dalam darah (ditunjukkan dalam tes darah)
- berkurangnya hemoglobin, protein pembawa oksigen dalam sel darah merah (ditunjukkan dalam tes darah)
- peningkatan enzim (ditunjukkan dalam tes darah) yang menunjukkan adanya stres pada hati, cedera ginjal, atau kerusakan otot

Umum (dapat dialami hingga 1 dari 10 orang)

- mulut kering
- pembengkakan pada wajah (edema wajah)
- sesak napas (dispnea)

Pelaporan efek samping

Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan Koselugo

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tertera pada botol dan karton setelah EXP. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Jangan simpan di atas suhu 30 °C.

Simpan di dalam botol aslinya untuk melindungi dari kelembapan dan cahaya. Jaga agar botol tetap tertutup rapat.

Setelah botol dibuka, agar obat digunakan dalam kurun waktu 30 hari

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan Koselugo

Zat aktifnya adalah selumetinib. Setiap kapsul keras Koselugo 10 mg mengandung 12.10 Selumetinib Sulfate setara dengan 10 mg selumetinib. Setiap kapsul keras Koselugo 25 mg mengandung 30.25 mg Selumetinib Sulfate setara dengan 25 mg selumetinib.

Kandungan lain dalam kapsul keras Koselugo 10 mg adalah:

- isi kapsul: vitamin E polietilen glikol suksinat (D α -tokoferil polietilen glikol suksinat).
- cangkang kapsul: hipromelosa (E464), karagenan (E407), kalium klorida (E508), titanium dioksida (E171), lilin karnauba (E903).
- tinta cetak: standar selak cetak (E904), besi oksida hitam (E172), propilen glikol (E1520) amonium hidroksida (E527).

Kandungan lain dalam kapsul keras Koselugo 25 mg adalah:

- isi kapsul: vitamin E polietilen glikol suksinat (D α -tokoferil polietilen glikol suksinat).
- cangkang kapsul: hipromelosa (E464), karagenan (E407), kalium klorida (E508), titanium dioksida (E171), danau aluminium indigo carmine (E132), besi oksida kuning (E172), lilin karnauba (E903), pati jagung.
- tinta cetak: oksida besi merah (E172), oksida besi kuning (E172), danau aluminium indigo carmine (E132), lilin karnauba (E903), standar selak cetak (E904), gliseril mono-oleat.

Tampilan Koselugo dan isi kemasannya

Kapsul keras Koselugo 10 mg adalah kapsul keras berwarna putih hingga putih pudar, buram, dan memiliki pita di tengahnya dan ditandai "SEL 10" dengan tinta hitam.

Kapsul keras Koselugo 25 mg adalah kapsul keras berwarna biru, buram, dan memiliki pita di tengah dan ditandai "SEL 25" dengan tinta hitam.

Koselugo tersedia dalam botol plastik putih, ditutup dengan penutup tahan anak berwarna putih (10 mg) atau biru (25 mg) yang berisi 60 kapsul keras dan pengering silika gel. Jangan keluarkan pengering dari botol dan jangan ditelan.

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Apabila Anda ingin melaporkan dugaan efek samping produk AstraZeneca menanyakan/ meminta informasi medis terkait produk AstraZeneca mohon dikirimkan dengan mengisi form elektronik pada tautan berikut ini: <http://contactazmedical.astrazeneca.com>

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