▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 10 mg of selumetinib (as hydrogen sulfate).

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

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 adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and older .

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/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours).

Dosing in adult and paediatric patients 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 capsules 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 capsules 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.

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 capsules 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, and 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/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 capsules 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 studies no dose adjustment is recommended in patients with mild, moderate, severe renal impairment or those with end stage renal disease (ESRD) (see section 5.2).

Hepatic impairment

Based on clinical studies, no dose adjustment is recommended in patients with mild hepatic impairment. The starting dose should be reduced in patients with moderate hepatic impairment to 20 mg/m^2 BSA, twice daily (see Table 4). Koselugo is 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 Asian patients, however these patients should be closely monitored for adverse events (see section 5.2).

Paediatric population

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

Elderly population

The safety and efficacy of Koselugo in adults with NF1-PN older than 65 years of age has not been established. No data are currently available in NF1-PN patients 65 years of age and older.

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. Koselugo is also available as granules. Patients from 1 year to less than 7 years of age and older patients with swallowing difficulties may be prescribed appropriate doses of Koselugo granules (see SmPC for Koselugo Granules).

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

In the SPRINT clinical study, 26% of paediatric patients experienced asymptomatic decreases in ejection fraction, with a median onset time of 232 days. LVEF reduction have been reported in both paediatric and adult patients. 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).

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 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 studies (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) in the SPRINT clinical study.

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 capsules should not be administered to patients who are unable or unwilling to swallow the capsule whole (see section 4.2). Koselugo is also available as granules. Patients from 1 year to less than 7 years of age, and older patients with swallowing difficulties may be prescribed appropriate doses of Koselugo granules (see SmPC for Koselugo Granules).

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 ≥ 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 embryo-foetal 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 of selumetinib monotherapy has been evaluated in a pooled safety population of 126 paediatric patients (20-30 mg/m^2 twice daily, capsules) from 4 studies with NF1 and inoperable PN [(NF1-PN Paediatric Pool, which includes safety data from SPRINT Phase I (N=24), SPRINT Phase II, Stratum 1 (N=50), China Phase I study; paediatric cohort (N=16), Japan Phase I study (N=12), and Phase I Food effect study (Study 15, N=24)].

In addition, the safety of selumetinib for the granule formulation was evaluated in 36 paediatric patients (dose equivalent to 25 mg/m^2 twice daily, granules) with NF1 and symptomatic inoperable PN from the Phase I/II SPRINKLE study.
The safety of selumetinib monotherapy in adult patients has been evaluated in 137 adult patients with NF1 and inoperable PN (25 mg/m^2 twice daily, capsules) from Phase III KOMET study.

The median total duration of selumetinib treatment in NF1-PN Paediatric Pool was 27 months (range: < 1– 97 months), 57% of patients were exposed to selumetinib treatment for > 24 months and 40% for > 36 months. The median total duration of selumetinib treatment in NF1-PN adult patients was about 12 months (range: < 1 – 32 months). Of these patients 50.4% of patients were exposed to selumetinib treatment for < 12 months and remaining 49.6% patients were exposed to selumetinib for > 12 months.

In the NF1-PN Paediatric pool, the most common adverse reactions of any grade (incidence ≥ 40%) were vomiting (62%), acneiform rashes (60%), diarrhoea (56%), blood creatine phosphokinase increased (54%), nausea (52%), paronychia (50%), and dry skin and pyrexia (44% each). Adverse events leading to dose interruptions and reductions were reported in 61.9% and 27.8% of patients, respectively. A total of 47.6% patients had ADRs leading to dose modification of selumetinib (either dose interruptions or reductions). The ADRs leading to dose modification (incidence ≥ 5%) of selumetinib were vomiting (19.8%), paronychia (15.9%), nausea (11.1%), diarrhea (8.7%), pyrexia (6.3%), and rashes (acneiform and non-acneiform; 5.6% each). Any ADRs leading to treatment discontinuation were reported in 4.8% patients.

In the SPRINKLE study, at the time of first data cut-off (DCO1), the median total duration of selumetinib treatment was 11 months (range: < 3 – < 26 months). Thirty-six paediatric patients were treated with selumetinib granules equivalent to 25 mg/m^2 twice daily. The most common adverse reactions of any grade (incidence ≥ 40%) were pyrexia and dry skin (47% patients each); and paronychia (44%). Adverse events leading to dose interruptions were reported in 30.6% of patients, while no patients had AEs leading to dose reductions. A total 22.2% patients had ADRs leading to dose modification (either dose interruptions or reductions). The ADRs leading to dose modification (incidence ≥ 5%) were vomiting and pyrexia (11.1% patients each), and diarrhea (5.6%). No patient had ADRs that led to treatment discontinuation.

The observed safety profile of selumetinib granules in the SPRINKLE study was comparable with pooled safety data in paediatric patients treated with selumetinib capsules (NF1-PN Paediatric Pool).

In the NF1-PN adult patients, the most common adverse reactions of any grade (incidence ≥ 20%) were acneiform rashes (55%), blood creatine phosphokinase increased (37%), diarrhoea (30%), non-acneiform rashes (27%) and vomiting (20%). A total of 25.5% patients had adverse reactions leading to dose modification of selumetinib (either dose interruptions or reductions). The adverse drug reaction (ADR) leading to dose modification (incidence ≥ 5%) of selumetinib was blood creatine phosphokinase increased (5.8%). The adverse reactions leading to treatment discontinuation were reported in 1.5% patients.

The safety profile was also substantiated by a pool of safety data from 7 clinical studies in adult patients with multiple tumour types (N=347) who received 75 to 100 mg of selumetinib twice daily.

Tabulated list of adverse reactions

Table 5 presents the adverse reactions identified in the paediatric and adult population with NF1 who have inoperable PN and also in adult patients with multiple tumour types (see footnote to Table 5). The frequency is determined from the paediatric pool (N = 126) and adult patients (N = 137) as defined above. 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 selumetinib NF1-PN studies and in other identified clinical trials in adult patients with multiple tumour types

MedDRA SOC and MedDRA term	**Paediatric Pool [a] (N = 126)**		**KOMET Study [b] (N = 137)**	
	Overall Frequency (All CTCAE Grades) [c]	**Frequency of CTCAE Grade 3 and above [d]**	**Overall Frequency (All CTCAE Grades) [c]**	**Frequency of CTCAE Grade 3 and above [e]**
Eye disorders				
Vision blurred ^	Common (9%)	-	Common (4%)	-

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 126)		KOMET Study [b] (N = 137)	
	Overall Frequency (All CTCAE Grades) [c]	Frequency of CTCAE Grade 3 and above [d]	Overall Frequency (All CTCAE Grades) [c]	Frequency of CTCAE Grade 3 and above [e]
Retinal pigment epithelial detachment (RPED)/ Central serous retinopathy (CSR) * ††	-	-	Uncommon (0.6%)	-
Retinal vein occlusion (RVO) * ††	-	-	Uncommon (0.3%)	-
Respiratory, thoracic and mediastinal disorders				
Dyspnoea *	Common (6%)	-	Common (3%)	Common (1%)
Gastrointestinal disorders				
Vomiting ^	Very common (62%)	Common (7%)	Very common (20%)	-
Diarrhoea ^	Very common (56%)	Very common (10%)	Very common (30%)	-
Nausea ^	Very common (52%)	Common (2%)	Very common (17%)	-
Stomatitis ^*	Very common (40%)	Common (1%)	Very common (14%)	Common (1%)
Constipation	-	-	Very common (10%)	-
Dry mouth	Common (4%)	-	Common (6%)	-
Skin and subcutaneous tissue disorders				
Rashes (acneiform) ^*	Very common (60%)	Common (2%)	Very common (55%)	Common (2%)
Paronychia ^	Very common (50%)	Very common (10%)	Very common (17%)	Common (3%)
Dry skin	Very common (44%)	Common (1%)	Very common (13%)	-
Rashes (non-acneiform) ^*	Very common (39%)	Common (2%)	Very common (27%)	Common (1%)
Hair changes ^*	Very common (29%)	-	Very common (18%)	-
General disorders				
Pyrexia	Very common (44%)	Common (5%)	Common (5%)	Common (1%)
Asthenic events *	Very common (37%)	-	Very common (15%)	-
Peripheral oedema *	Very common (18%)	-	Very common (16%)	-
Facial oedema *	Common (8%)	-	Common (4%)	-
Investigations [f]				
Blood CPK increased ^	Very common (54%)	Common (6%)	Very common (37%)	Common (7%)
AST increased	Very common (37%)	Common (2%)	Very common (12%)	Common (1%)

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 126)		KOMET Study [b] (N = 137)	
	Overall Frequency (All CTCAE Grades) [c]	Frequency of CTCAE Grade 3 and above [d]	Overall Frequency (All CTCAE Grades) [c]	Frequency of CTCAE Grade 3 and above [e]
Haemoglobin decreased *	Very common (35%)	Common (2%)	Very common (11%)	Common (2%)
Blood albumin decreased *	Very common (35%)	-	Common (2%)	-
ALT increased	Very common (29%)	Common (2%)	Very common (11%)	Common (1%)
Ejection fraction decreased ^	Very common (21%)	Common (1%)	Common (7%)	Common (1%)
Blood creatinine increased	Very common (19%)	Common (1%)	Common (2%)	-
Increased blood pressure *	Very common (11%)	-	Common (4%)	Common (2%)

[a] NF1-PN Paediatric Pool data (N = 126) is pooled from SPRINT Phase I (N = 24), SPRINT Phase II, Stratum 1 (N = 50), China Phase I study; paediatric cohort (N=16), Japan Phase I Study (N=12), and Phase I Food effect (N=24) studies. Frequency percentage numbers are rounded to the nearest full number.

[b] NF1-PN adult patients data is from KOMET study (N = 137). Frequency percentage numbers are rounded to the nearest full number.

[c] Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), all studies used CTCAE v5.0, except for SPRINT paediatric study which used CTCAE v4.03.

[d] All events were CTCAE grade 3, except for two CTCAE grade 4 event of blood CPK increased and one CTCAE grade 4 event of blood creatinine increased. There were no deaths.

[e] All events were CTCAE grade 3, except for one CTCAE grade 4 event of pyrexia and four CTCAE grade 4 events of blood CPK increased. There were no deaths.

[f] In the SPRINT study, all lab abnormalities were reported as AEs. In other studies included in the NF1-PN paediatric and adult patients, lab abnormalities were only reported as AEs when they met SAE criteria, resulted in discontinuation, or were clinically relevant as judged by the investigator.

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

^ See Description of selected adverse reactions

†† 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 or adult population with NF1 who have inoperable PN.

* ADRs based on grouping of individual Preferred Terms (PT):

Asthenic events: fatigue, asthenia
Blood albumin decreased: hypoalbuminaemia, blood albumin decreased
CSR/RPED: detachment of macular retinal pigment epithelium, chorioretinopathy
Dyspnoea: dyspnoea exertional, dyspnoea, dyspnoea at rest
Facial oedema: periorbital oedema, face oedema, lip swelling, eyelid oedema, swelling face
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 (acneiform): dermatitis acneiform, acne, folliculitis
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
Stomatitis: stomatitis, mouth ulceration, aphthous ulcer, gingival swelling

Description of selected adverse reactions

Left ventricular ejection fraction (LVEF) reduction

In the NF1-PN Paediatric Pool (N=126), LVEF reduction (PT: ejection fraction decreased) was reported in 26 (21%) patients; among them, in 25 (19.8%) patients, the reported ADRs were CTCAE

grade 2, and in 1 (0.8%) patient, the ADR reported was CTCAE grade 3. In 4 (3.2%) patients, LVEF decrease led to dose reduction and in 2 (1.6%) patients, LVEF decrease led to dose interruption. At the time of analysis, of the 26 patients, 20 patients were recovered. The median time to first occurrence of LVEF reduction was 283 days (median duration 110.5 days).

In the NF1-PN adult patients (N = 137), LVEF reduction (PT: ejection fraction decreased) was reported in 10 (7%) patients; among them, in 1 (0.7%) patient, the reported ADR was CTCAE grade 3. In 2 (1.5%) patients, LVEF decrease led to dose interruption. At the time of analysis, 7 of the 10 patients had recovered. The median time to first occurrence of LVEF reduction was 342 days (approximately 11 months) [median duration 112.5 days (approximately 4 months)].

Patients with LVEF lower than the institutional LLN at baseline were not included in the pivotal studies. 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 the NF1-PN Paediatric Pool (N=126), CTCAE grade 1 and 2 events of blurred vision were reported in 11 (9%) patients. Two patients (1.6%) required dose interruption. At the time of analysis, of the 11 patients, 10 patients were recovered.

In the NF1-PN adult patients (N = 137), CTCAE grade 1 event of blurred vision was reported in 5 (4%) patients. One patient (0.7%) required dose interruption. All events were managed without dose reduction and at the time of analysis, all 5 patients had recovered.

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/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 the NF1-PN Paediatric Pool (N=126), paronychia was reported in 63 (50%) patients. The median time to first onset of maximum grade paronychia adverse event was 375 days (approximately 12 months) and the median duration of events was 55 days (approximately 2 months). The majority (51 patients, 40.5% the NF1-PN Paediatric Pool) had a maximum CTCAE grade of 1 or 2. Grade ≥ 3 events occurred in 12 (10%) patients. Eighteen patients (14.3%) required dose interruption for adverse event of paronychia, and 9 patients (7.1%) had an AE of paronychia that led to dose reduction. In one patient (0.8%) the event led to treatment discontinuation.

In the NF1-PN adult patients (N = 137), paronychia was reported in 23 (17%) patients. The median time to first onset of maximum grade paronychia was 390 days (approximately 13 months) and the median duration of the maximum grade event was 63 days (approximately 2 months). Nineteen (13.9%) patients had a maximum CTCAE grade of 1 or 2. Grade 3 events occurred in 4 (3%) patients. One patient (0.7%) required dose interruption for adverse event of paronychia, and 3 patients (2.2%) had an event of paronychia that led to dose reduction. Paronychia did not lead to dose discontinuation in any of the patients. At the time of analysis, 11 of the 23 patients had recovered.

Blood creatine phosphokinase (CPK) increase
ADRs of blood CPK elevation occurred in 68 (54%) patients in the NF1-PN Paediatric Pool (N=126). The median time to first onset of the maximum CTCAE grade CPK increase was 112 days (approximately 4 months) and the median duration of the maximum CTCAE grade event was 126 days (approximately 4 months). The majority (61 cases, 48.4% of the NF1-PN Paediatric Pool) had maximum CTCAE grade event that was grade 1 or 2. A maximum CTCAE grade 3 events occurred in 5 (4%) patients, and CTCAE grade 4 event occurred in 2 (1.6%) patients. Five patients had an AE of blood CPK increase that led to treatment interruptions and required dose reduction.

In the NF1-PN adult patients (N = 137), ADRs of blood CPK increase occurred in 51 (37%) patients. The median time to first onset of the maximum CTCAE grade blood CPK increase was 167 days (approximately 6 months), and the median duration of maximum grade event was 122 days (approximately 4 months). Forty-two patients (30.7%) had maximum CTCAE grade of 1 or 2. A maximum CTCAE grade 3 events occurred in 5 (3.6%) patients, and CTCAE grade 4 events occurred in 4 (2.9%) patients. Six patients had an event of blood CPK increase that led to dose interruptions and dose reduction was required in 3 patients. At the time of analysis, 21 of the 51 patients had recovered.

Gastrointestinal toxicities
In the NF1-PN Paediatric Pool (N=126), vomiting (78 patients, 62%), diarrhoea (71 patients, 56%), nausea (66 patients, 52%), and stomatitis (50 patients, 40%) were the most commonly reported gastrointestinal (GI) events. The majority of these cases were CTCAE grade 1 or 2. CTCAE grade ≥ 3 events were reported for diarrhoea (10%), vomiting (7%), nausea (2%) and stomatitis (1%). Dose modification was required in 25 (19.8%) patients with vomiting, 14 (11.1%) with nausea, 11 (8.7%) with diarrhoea, and 6 (4.8%) with stomatitis. One patient each reported an event of diarrhoea, nausea and stomatitis led to treatment discontinuation. Dose reduction had occurred in 1 patient with ADR of diarrhoea and in 2 patients with ADR of stomatitis. No CTCAE grade ≥ 4 events were reported.

In the NF1-PN adult patients (N = 137), diarrhoea (41 patients, 30%), vomiting (27 patients, 20%), nausea (23 patients, 17%), stomatitis (19 patients, 14%), and constipation (13 patients, 10%) were the most reported gastrointestinal (GI) events. Most of these events were CTCAE grade 1 or 2. In 1 patient (0.7%), CTCAE grade 3 event was reported for stomatitis. Dose interruption was required in 2 patients (1.5%) each with nausea and vomiting, and in 1 patient (0.7%) each with diarrhoea and stomatitis. Dose reduction occurred in 1 patient (0.7%) each with an ADR of nausea and stomatitis. One patient reported an event of nausea that led to treatment discontinuation.

Skin toxicities
In the NF1-PN Paediatric Pool (N=126), acneiform rashes were observed in 76 (60%) patients [median time to onset 29 days; median duration of 176 days (approximately 6 months) for the maximum CTCAE grade event]. The majority (73 patients, 58% of the NF1-PN Paediatric Pool) of these reported ADRs with maximum CTCAE were grade 1 or 2. In 4 patients (3.2%), acneiform rashes led to dose interruption and 3 patients (2.4%) acneiform rashes led to dose reduction. CTCAE grade 3 events were reported in 3 (2.4%) patients. Other (non-acneiform) rashes were observed in 49 (39%) patients in the NF1-PN Paediatric Pool and were predominantly (46 patients, 36.5% of the NF1-PN Paediatric Pool) CTCAE grade 1 or 2.

In the NF1-PN adult patients (N = 137), acneiform rashes were observed in 75 (55%) patients [median time to onset 19 days; median duration of 124 days (approximately 4 months) for the maximum CTCAE grade event]. Seventy-two (53%) patients reported ADRs with maximum CTCAE grade 1 or 2. CTCAE grade 3 events were reported in 3 (2.2%) patients. In 3 patients (2.2%) acneiform rashes led to dose interruption, and in 2 patients (1.5%) each acneiform rashes led to dose reduction and dose discontinuation. Rashes (non-acneiform) were observed in 37 (27%) patients and were predominantly (36 patients, 26.3%) CTCAE grade 1 or 2.

Hair changes
In the NF1-PN Paediatric Pool (N=126), 37 (29%) patients experienced hair changes adverse event (reported as [PT: hair colour changes] in 21 patients (16.7%) and hair thinning [PT: alopecia] in 30 patients (23.8%)). All cases were CTCAE grade 1 (33 patients, 26.2%) or 2 (4 patients, 3.2%) and dose interruption was reported in 1 (0.8%) patient.

In the NF1-PN adult patients (N = 137), 24 (18%) patients experienced hair changes adverse event [reported as (PT: hair colour changes) in 6 (4.4%) patients and hair thinning (PT: alopecia) in 20 (14.6%) patients]. All cases were CTCAE grade 1 or 2. Dose interruption was reported in 1 (0.7%) patient and dose reduction in 2 (1.5%) patients.

Reporting of suspected adverse reactions

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 via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: https://medicinesauthority.gov.mt/adrportal

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 selumetinib in paediatric and adult NF1-PN patients was evaluated in studies as described below.

SPRINT
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 selumetinib capsules, 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, n (%) (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.

KOMET

The efficacy of Koselugo in adult patients was evaluated in a Phase III, multicentre, international study that had a parallel, randomised 1:1, double-blind, placebo-controlled, 2 arm design. A total of 145 adult patients were randomised to receive either selumetinib 25 mg/m^2 (BSA) or placebo twice daily for 12 cycles (28-day cycles). After the end of Cycle 12, placebo patients crossed over to receive open label selumetinib or earlier if disease progression was confirmed by the Independent Central Review (ICR). Treatment was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity, patient's decision, if PN progressed, or at the discretion of the investigator.

KOMET study enrolled male and female adult (≥ 18 years of age at enrollment) patients with a diagnosis of NF1 who have symptomatic, inoperable PN; at least one target PN measurable by volumetric MRI analysis; chronic target PN pain score documented for a minimum period (for at least

4 days out of 7 days for at least 2 weeks during the screening period); stable chronic PN pain medication use at time of enrollment.

The target PN, the clinically most relevant PN, which is measurable by volumetric MRI analysis and, if relevant, one additional non-target PN, was evaluated for response rate using centrally read volumetric MRI analysis per 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 and non-target PN MRI volumetric evaluations and clinical outcome assessments.

Demographics and baseline disease characteristics were generally well balanced between the selumetinib and placebo treatment arms. Baseline demographics in the selumetinib and placebo groups were as follows: median age at enrolment was 29 years (range: 18 to 60 years), male (51.7%), White (55.9%), and Asian (31%). The median volume of the target PN was 110.18 mL for the selumetinib group and 221.85 mL for the placebo group. The most common PN related morbidities were pain, motor dysfunction and disfigurement, affecting 23% or more of the patients in both groups. Airway, vision, and bowel/bladder morbidities were less frequent, affecting 4.2% or less of the patients in both the selumetinib and placebo groups.

The primary efficacy endpoint was ORR for selumetinib by the end of Cycle 16. ORR was defined as the percentage of patients with confirmed complete response (disappearance of the target PN, confirmed by consecutive scan within 3–6 months after the first response) or confirmed partial response (target PN volume decrease ≥ 20%, compared to baseline, confirmed by a consecutive scan within 3–6 months after the first response) by the end of Cycle 16 as determined by ICR per REiNS criteria.

At the planned primary analysis, the study met its primary endpoint demonstrating a statistically significant ORR versus placebo. At the time of the final data cut-off (DCO), the median total duration of exposure was 749 days (approximately 25 months) in patients randomized to selumetinib; the median DoR from onset of response was not reached. Efficacy results are presented in Table 7 below.

Table 7. Efficacy results from KOMET

Efficacy Parameters	**Selumetinib (N = 71)**	**Placebo (N = 74)**
Objective Response Rate by the end o Cycle 16 (ORR) [a, b, c]		
ORR % (95% CI)	19.7 (11.2, 30.9)	5.4 (1.5, 13.3)
p value [d]	0.0112	
Best objective response (BOR) by the end of Cycle 16, n (%)[a, b, c, e]		
Confirmed Complete Response	0	0
Confirmed Partial Response	14 (19.7%)	4 (5.4%)
Time to Response (TTR) [a]		
Median (95% CI) months	3.7 (3.61, 11.07)	ND
Duration of Response (DOR) [f, g, h]		
Median (95% CI) months	NR (11.5, NE)	ND
Number and percentage remaining in response		
≥ 6 months, n (%)	14 (100%)	ND
≥ 12 months, n (%)	9 (64.3%)	ND

CI – confidence interval, NE – not estimated, NR - not reached, ND – Not determined for placebo treatment arm.

[a] Results are based on planned primary analysis (DCO: 05 August 2024) which occurred when all the patients had the opportunity to complete Cycle 16.

[b] Each treatment cycle in the study is of 28 calendar days (Cycle 16 corresponds to approximately 15 months).

[c] Patients with confirmed complete response or partial response by independent central review (ICR) per REiNS criteria. Response confirmation was by a consecutive scan within 3 to 6 months after the first response as determined by ICR per REiNS criteria.

[d] 2-sided p-value calculated using Fisher's exact method (alpha of 0.047) by comparison of Selumetinib vs Placebo.

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

[f] Duration of Response from date of first documented response (subsequently confirmed) until date of documented progression by ICR per REiNS criteria.

[g] Calculated using Kaplan-Meier method.

[h] Calculated for patients randomized to selumetinib arm that achieved a confirmed partial response (cPR) by end of Cycle 16 and including data until the final DCO (17 March 2025, which occurred when all the patients had the opportunity to complete Cycle 24).

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) parameters in paediatric patients (3 to ≤ 18 years old) with NF1-PN and in adult patients (≥ 18 years old) with NF1-PN are comparable.

Following administration of selumetinib capsule, 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 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 the KOMET study, at the recommended dose of 25 mg/m^2 twice daily in adult patients (≥ 18 years old), the geometric mean (geometric coefficient of variation [gCV%]) maximum plasma concentration (C_{max}) was 789 (47%) ng/mL and the area under the plasma drug concentration curve (AUC_{0-12}) was 2986 (43%) ng·h/mL at steady-state.

Across all ages, the minimal accumulation range was 1.2 to 1.5 following administration of selumetinib.

In paediatric patients (3 to ≤ 18 years old), 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.

In adult patients (≥ 18 years old), at a dose level of 25 mg/m^2, selumetinib has an apparent oral clearance of 14.1 L/h, mean apparent volume of distribution at steady state of 126.1 L and mean elimination half-life of ~9.0 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}) at 2 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 capsules 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 capsules 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). Similarly, in healthy male subjects, following a low-fat meal (400 to 500 calories, 25% fat) selumetinib granules C_{max} and AUC reduced by 39% and 4%, respectively, and t_{max} was delayed by approximately 1.3 hours.

In adolescent patients with NF1 and inoperable PN treated with multiple doses of 25 mg/m^2 bid, co-administration of selumetinib capsules 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 popPK analysis also 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.

Based on the above results, the effect of food (high-fat, low-fat and without regard to food) for both formulations (capsules and granules) is not expected to result in a clinically relevant impact on the AUC of selumetinib since the magnitude of effect on the oral administration bioavailability (F1) is less than 30%.

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. Comparable values were observed in adult patients across 25 mg/m^2 and ranged from 40 to 3710 L. These values indicate 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.

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).

Other 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 (1 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 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.

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1552/001 10 mg hard capsules
EU/1/21/1552/002 25 mg hard capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 June 2021
Date of latest renewal: 25 April 2025

10. DATE OF REVISION OF THE TEXT

09 January 2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ONC 26 0001