swissmedic

Date: 18 August 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Koselugo

International non-proprietary name: selumetinib as selumetinib hydrogen sulfate

Pharmaceutical form:	hard capsule
Dosage strength(s):	10 mg and 25 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Alexion Pharma GmbH
Marketing authorisation no.:	67410
Decision and decision date:	extension of therapeutic indication approved on 18 June 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 8 March 2019.

2.2 Indication and dosage

Koselugo as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) (see sections "*Dosage/Administration",* "*Warnings and precautions" and "Properties/Effects"*).

2.2.1 Requested indication

Koselugo is indicated for the treatment of adult and paediatric patients aged 3 years and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN).

2.2.2 Approved indication

Koselugo as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) (see sections "*Dosage/Administration",* "*Warnings and precautions" and "Properties/Effects"*).

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	26 May 2025
Formal control completed	11 June 2025
List of Questions (LoQ)	11 September 2025
Response to LoQ	10 November 2025
Preliminary decision	19 January 2026
Response to preliminary decision	19 March 2026
Labelling corrections and/or other aspects	14 April 2026
Response to labelling corrections and/or other aspects	17 May 2026
Final decision	18 June 2026
Decision	approval

3 Medical context

Neurofibromatosis type 1 (NF1) is a rare, autosomal dominant disorder caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Early signs of NF1 are café-au-lait macules (CALMs) and overall cutaneous hyperpigmentation, appearing within the first two years of life.[i] Plexiform neurofibromas (PNs) are found in one third of patients with NF1. Diffuse PNs tend to occur in early childhood, while deep nodular PNs develop in adolescence. Cutaneous neurofibromas are benign and do not require removal unless they are symptomatic. Surgical resection is the gold standard of treatment in patients with PN, but is often impractical due to the involvement of nerves.

In Switzerland, selumetinib is approved for paediatric patients (>3 years) with NF1 and symptomatic, unresectable PN.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

5 Clinical aspects

5.1 Clinical pharmacology

PK data from the pivotal phase 3 study KOMET (D134BC00001), together with data from three additional studies in patients with NF1 and inoperable PN, were incorporated into a pre-existing population pharmacokinetic (popPK) model that was developed from data from 15 studies, including healthy volunteers, adult patients with solid tumours, and paediatric/adolescent patients with NF1. The popPK model structure and covariates were retained unchanged. Model performance was evaluated using data from the newly added studies, employing standard diagnostic methods, including goodness-of-fit (GOF) analyses, visual predictive checks (VPCs), and conditional weighted residuals (CWRES), and was deemed satisfactory. This approach was deemed acceptable because the original model already included patients with NF1-associated PN. Asian patients represented less than 10% of the overall dataset and therefore could not be assessed as a separate covariate.

Exposure–response analyses were performed in 66 adult patients from the KOMET study using model-predicted exposure metrics. No clinically meaningful relationship was identified between selumetinib exposure and efficacy or safety outcomes at the proposed dose of 25 mg/m^2 BID.
No association was observed between exposure and efficacy endpoints, including objective response rate (ORR), pain improvement (PAINS-pNF), or quality-of-life outcomes (PlexiQoL). Logistic regression analysis demonstrated a flat relationship between exposure and probability of response. Although response rates were higher in Asian than in non-Asian patients (50% versus 8.7%), this difference could not be explained by differences in exposure.
Similarly, no clear relationship was observed between exposure to selumetinib or N-desmethyl-selumetinib and safety endpoints, including adverse events, dose modifications, treatment discontinuations, or time to onset of adverse events.
Overall, the exposure-response analyses did not identify any exposure-dependent efficacy or safety trends and support the proposed dosing regimen without dose adjustment in adult patients.

5.2 Efficacy

For the evaluation of efficacy and safety, the applicant submitted the results of one pivotal study, the double-blind, parallel-group, phase 3 study KOMET. In this study, the safety, efficacy, and pharmacokinetics (PK) of selumetinib were compared to placebo in adult participants with NF1 who have symptomatic, inoperable PN.

The current application presented results from the planned primary analysis (data cut-off [DCO] date of 5 August 2024, after the last treated participant had the opportunity to complete the assessment at the end of cycle 16). In addition, results of the final analysis after the last patient had the opportunity to complete 24 cycles were submitted. The primary outcome was (confirmed) objective response rate (ORR) by the end of cycle 16. For details of the study design please refer to the attached Information for healthcare professionals.

51.7% of the total population were male, 55.9% were White, 31.0% were Asian, and the median age at enrolment was 29 years (range: 18 to 60 years). Demographics were balanced overall, with the exception of a higher proportion of female patients in the selumetinib arm (53.5% vs. 43.2%).

Disease characteristics at baseline were well balanced between the treatment groups apart from the following exceptions:

- Median target PN tumour volume (selumetinib: 110.18 mL; placebo: 221.85 mL)
- Percentage of participants with target PN-related disfigurement (selumetinib: 32.4%; placebo: 23.0%)
- Percentage of participants with non-target PN tumours (selumetinib: 25.4%; placebo: 40.5%)

The most frequently observed NF1 diagnostic criteria (> 50% participants in either group) were any cafe-au-lait macules (selumetinib: 78.9%; placebo: 73.0%), bilateral cafe-au-lait spots (selumetinib: 59.2%; placebo: 62.2%), freckling in the axillary or inguinal region (selumetinib: 69%; placebo: 66.2%), and bilateral freckles in the axilla or groin (selumetinib: 63.4%; placebo: 58.1%).

The most frequent reasons for PN inoperability were similar between the treatment groups, including PN encasement of vital structures (selumetinib: 26.8%; placebo: 33.8%), PN close proximity to vital structures (selumetinib: 50.7%; placebo: 54.1%), PN invasiveness (selumetinib: 45.1%; placebo: 45.9%) and high vascularity of the PN (selumetinib: 26.8%; placebo: 33.8%).
There was a statistically significant difference between the selumetinib arm and the placebo arm for the primary endpoint of ORR by the end of cycle 16 (p = 0.0112). The ORR was higher in the selumetinib arm (19.7%; 95% CI:11.2, 30.9) compared with the placebo group (5.4%; 95% CI = 1.5, 13.3). All responders had a partial response (PR), no complete response (CR) was achieved. Median duration of response (DoR) from onset of response had not been reached in the selumetinib arm. At the time of final analysis (DCO 17 March 2025), there were three new responders; all three new confirmed responses were PR.

The observed ORR in adult patients was lower compared to paediatric patients treated with selumetinib in the SPRINT study (ORR 68%, all confirmed PR). Please refer to the attached Information for healthcare professionals for further results in the paediatric population.

In additional exploratory subgroup analyses by race, a potential association between ORR by the end of cycle 16 and race was observed. The ORR was comparable for selumetinib (7.9%; 3/38 patients) and placebo (4.7%, 2/43 patients) in White patients. In contrast, ORR by end of cycle 16 was higher for selumetinib (45.5%; 10/22 patients) compared to placebo (0%, 0/23 patients) in Asian patients.

Another NCI-sponsored, single-arm, phase 2 study (Gross et al. 2025) with selumetinib in mainly White US patients with NF1 who had at least one PN that was inoperable, symptomatic or growing with the potential to cause morbidity, reported an ORR of 63.6%. The majority of patients included in this study were White (25/33 patients).

They key secondary quality of life endpoints PAINS-pNF and PlexiQoL were not statistically significant.

5.3 Safety

Safety was analysed in the KOMET study during the randomised period compared to placebo and during the on-selumetinib period (starting from first dose of selumetinib).

In total, 71 (100%) participants in the selumetinib group and 68 (91.9%) participants in the placebo group reported one or more adverse events (AEs). A total of 23 (32.4%) participants in the selumetinib group and 13 (17.6%) participants in the placebo group experienced one or more grade ≥ 3 AE. No participants died during that period and 10 (14.1%) participants in the selumetinib group vs. 9 (12.2%) participants in the placebo group experienced one or more serious adverse events (SAEs). The most common AEs (≥10%) in the selumetinib arm were dermatitis acneiform, diarrhoea, blood increased creatine phosphokinase, nausea, vomiting, fatigue, alopecia, dry skin, and increased AST, increased ALT, COVID-19, peripheral oedema, rash, paronychia, and headache.

The safety profile during the on-selumetinib period was comparable overall to that observed during the randomised period.

However, long-term follow-up data are limited and are relevant for evaluating the impact of selumetinib on malignancy risk. Individuals with NF1 have a higher overall cumulative risk of cancer, and the risk of developing MPNST is higher in adolescents and young adults than in children. [1], [2], [3]

5.4 Final clinical benefit risk assessment

There was a statistically significant improvement in the primary endpoint of ORR by the end of cycle 16 with selumetinib in the KOMET study. However, no statistically significant and no clinically relevant differences were observed with selumetinib for both quality of life-related key secondary endpoints, and there are concerns for subgroup analyses according to race. However, taking into account the supportive results reported by Gross et al. with an ORR of 63.6% in a population consisting predominantly of White adult patients, together with the medical need in this population and the manageable toxicity profile of selumetinib, the final benefit-risk assessment was evaluated as positive in adult patients with NF1 who have symptomatic, inoperable PN.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

[1] Evans DGR et al. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002; 39: 311–14.
[2] Uusitalo E et al. Distinctive cancer associations in patients with neurofibromatosis type 1. J Clin Oncol 2016; 34: 1978–86.
[3] Chen AP et al.; KOMET study investigators. Efficacy and safety of selumetinib in adults with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas (KOMET): a multicentre, international, randomised, placebo-controlled, parallel, double-blind, phase 3 study. Lancet. 2025 Jun 21;405(10496):2217-2230.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Koselugo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

[i] Wilson et al. Neurofibromatosis Type 1: New Developments in Genetics and Treatment. J Am Acad Dermatol. 2020 Aug 6;S0190-9622(20)32307-0.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Koselugo®

Composition

Active substances

Selumetinib (as selumetinib hydrogen sulfate)

Excipients

Koselugo 10 mg hard capsule

- Capsule content: tocofersolan.
- Capsule shell: hypromellose (E 464), carrageenan (E 407), potassium chloride (E 508), titanium dioxide (E 171), carnauba wax (E 903) and purified water.
- Printing ink: shellac (E 904), iron oxide black (E 172), propylene glycol (E 1520).

Koselugo 25 mg hard capsule

- Capsule content: tocofersolan.
- Capsule shell: hypromellose (E 464), carrageenan (E 407), potassium chloride (E 508), titanium dioxide (E 171), indigotine (E 132), iron oxide yellow (E 172), purified water, carnauba wax (E 903), maize starch.
- Printing ink: iron oxide red (E 172), iron oxide yellow (E 172), indigotine (E 132), carnauba wax (E 903), shellac (E 904), glycerol monooleate.

Pharmaceutical form and active substance quantity per unit

Hard capsules containing 10 mg or 25 mg selumetinib (hydrogen sulfate).

Koselugo 10 mg hard capsule

White to off-white, opaque, size 4 hard capsule, banded and marked with “SEL 10” in black ink.

Koselugo 25 mg hard capsule

Blue, opaque, size 4 hard capsule, banded and marked with “SEL 25” in black ink.

Indications/Uses

Koselugo as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) (see sections “*Dosage/Administration”,* “*Warnings and Precautions” and “Properties/Effects”*).

Dosage/Administration

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

Usual dosage

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). Koselugo is not recommended in patients with a BSA <0.55 m^2.

Table 1 Dosage regimen for Koselugo 25 mg/m^2 twice daily

Body Surface Area (BSA)*	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

* The recommended dosage for patients with a BSA less than 0.55 m^2 has not been investigated.

Duration of treatment

Treatment with Koselugo should continue until disease progression or unacceptable toxicity.

Mode of administration

Koselugo should be taken with or independently of meals (see *Pharmacokinetics*).
Koselugo capsules should be swallowed whole with water, and should not be chewed, dissolved, or opened.

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

Missed dose

If a dose of Koselugo is missed, it should only be taken if there are more than 6 hours until the next scheduled dose.

Vomiting

If vomiting occurs after Koselugo administration treatment should be continued with the next scheduled dose. An additional dose should not be taken.

Dose adjustment following undesirable effects/interactions

Interruption of treatment and/or dose reduction or permanent discontinuation of Koselugo may be required based on individual tolerability (see sections *Warnings and Precautions* and *Undesirable effects*).

Recommended dose reductions 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).

Table 2 Recommended dose reductions for Koselugo for adverse reactions

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

* Permanently discontinue Koselugo in patients unable to tolerate it after the second dose reduction.

Table 3 Recommended dosage modifications for Koselugo for adverse reactions

Severity of adverse reaction	Recommended dosage modifications for Koselugo
Cardiomyopathy [see Warnings and Precautions*]*	
• Asymptomatic decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline and LVEF less than the lower level of normal	Withhold treatment until normalisation. Resume treatment at reduced dose.
• Symptomatic decrease in LVEF • Grade 3 or 4 decrease in LVEF	Permanently discontinue treatment.
Ocular Toxicity [see Warnings and Precautions]	
• Retinal pigment epithelial detachment (RPED)	Withhold treatment until normalisation. Resume treatment at reduced dose.
• Retinal vein occlusion (RVO)	Permanently discontinue treatment.
Gastrointestinal Toxicity [see Warnings and Precautions*]*	
• Grade 3 Diarrhoea	Withhold treatment until toxicity has improved to Grade 0 or 1. Resume treatment at same dose. Permanently discontinue treatment if no improvement after 3 days.
• Grade 4 Diarrhoea	Permanently discontinue treatment.
• Grade 3 or 4 Colitis	Permanently discontinue treatment.
Skin Toxicity [see Warnings and Precautions]	
• Grade 3 or 4	Withhold treatment until improvement. Resume treatment at reduced dose.
Increased Creatine Phosphokinase (CPK) [see Warnings and Precautions*]*	
• Grade 4 Increased CPK • Any grade of increased CPK and myalgia	Withhold treatment until toxicity has improved to Grade 0 or 1. Resume treatment at reduced dose. Permanently discontinue treatment if no improvement after 3 weeks.
• Rhabdomyolysis	Permanently discontinue treatment.
Other Adverse Reactions [see Undesirable effects]	
• Grade 2 intolerance • Grade 3	Withhold treatment until toxicity has improved to Grade 0 or 1. Resume treatment at reduced dose.
• Grade 4	Withhold treatment until toxicity has improved to Grade 0 or 1. Resume treatment at reduced dose. Consider permanent discontinuation.

* According to the National Cancer Institute CTCAE (Common Terminology Criteria for Adverse Events) version 5.0

Special dosage instructions

Patients with impaired hepatic function

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 (Child-Pugh B) to 20 mg/m^2 BSA, twice daily. Koselugo is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) (see section *Kinetics in specific patient groups - Hepatic impairment*).

Table 4 Recommended dosage of Koselugo in moderate hepatic impairment

Body Surface Area	Moderate Hepatic Impairment (Child-Pugh B) (mg/dose)	
	Morning	Evening
0.55 – 0.69 m^2	10	10
0.70 – 0.89 m^2	20	10
0.90 – 1.09 m^2	20	20
1.10 – 1.29 m^2	25	25
1.30 – 1.49 m^2	30	25
1.50 – 1.69 m^2	35	30
1.70 – 1.89 m^2	35	35
≥ 1.90 m^2	40	40

Patients with impaired renal function

Based on clinical studies no dose adjustment is recommended in patients with mild, moderate or severe renal impairment or those with end-stage renal disease (ESRD) (see section *Kinetics in specific patient groups - Renal impairment*).

Children and adolescents

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

Elderly population

The safety and efficacy of Koselugo in adults with NF1-PN older than 65 years have not been investigated.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

LVEF Reduction

Left ventricular ejection fraction (LVEF) reduction has been reported in both paediatric and adult patients (see section ”*Undesirable effects”*). A small number of serious cases of LVEF reduction associated with selumetinib have been reported in paediatric patients who participated in an expanded access programme (see section “*Undesirable effects”*). Patients with a history of impaired left ventricular function or a baseline LVEF below the institutional lower level of normal (LLN) have not been studied. LVEF should be evaluated before initiation of treatment to establish baseline values. Prior to starting Koselugo treatment, patients should have an ejection fraction above the institutional LLN.

Assess ejection fraction by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue Koselugo depending on the severity of the adverse reaction. In patients who interrupt Koselugo because of a decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks. Upon normalisation of the LVEF to greater than or equal to the institutional LLN, obtain an echocardiogram or a cardiac MRI every 2 to 3 months or as directed by the cardiologist.

Ocular toxicity

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

In line with clinical practice, an ophthalmological evaluation prior to treatment initiation, and at any time a patient reports new visual disturbances, is recommended. In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmological assessment should be conducted every 3 weeks until resolution. If RPED or CSR is diagnosed and visual acuity is affected, Koselugo therapy should be interrupted, and the dose reduced when treatment is resumed (see Table 2). If RVO is diagnosed, treatment with Koselugo should be permanently discontinued (see section “*Dosage/Administration”*).

Liver Enzyme Abnormalities

Abnormalities of liver enzymes, especially aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, can occur with Koselugo (see section “*Undesirable effect*s”). The liver enzyme values should be monitored before the initiation of Koselugo treatment and at least once a month during the first 6 months of treatment, and thereafter according to clinical needs. Liver enzyme abnormalities should be managed by dose suspension or reduction or treatment discontinuation (see Table 2 in section “*Dosage/Administration*”).

Gastrointestinal Toxicity

Advise patients to start an antidiarrhoeal agent immediately after the first episode of loose stools and to increase fluid intake. Withhold, reduce dose, or permanently discontinue Koselugo treatment depending on the severity of the adverse reaction (see sections "*Dosage/Administration", "Warnings and Precautions"*).

Skin and Subcutaneous Tissue Disorders

Skin rash (including maculopapular skin rash and acneiform skin rash), paronychia and hair changes have been reported very commonly in the pivotal clinical studies in both the paediatric and the adult NF1 PN population (see section *"Undesirable effects"*). Dry skin, hair colour changes, paronychia and maculopapular skin rash were seen more frequently in younger children (aged 3-11 years) and acneiform skin rash was seen more frequently in post-pubertal children (aged 12-16 years).
Monitor patients for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo treatment depending on the severity of the adverse reaction (see section "*Dosage/Administration"*).

Vitamin E Supplementation

Advise patients not to take any supplemental vitamin E.
Koselugo 10 mg hard capsules contain 32 mg vitamin E as an excipient in the form of D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Koselugo 25 mg hard 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 medications (e. g., warfarin or aspirin). Monitor for bleeding in these patients. Increase international normalised ratio (INR) monitoring, as appropriate, in patients taking a vitamin-K antagonist. Perform anticoagulant assessments, including INR or prothrombin time, more frequently and adjust the dose of vitamin K antagonists or antiplatelet agents as appropriate (see section *Interactions*).

Elevated Creatine Phosphokinase (CPK)

Increased CPK and rhabdomyolysis can occur. Obtain serum CPK prior to initiating treatment with Koselugo, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo treatment depending on the severity of the adverse reaction (see section "*Dosage/Administration"*).

Risk of Choking

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

Interactions

Pharmacokinetic interactions

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

Pharmacodynamic interactions

Not applicable

Effect of Koselugo on other medicinal products

Not applicable

Effect of other medicinal products on Koselugo

Active substances that may increase the selumetinib plasma concentration
Co-administration with a strong CYP3A4 inhibitor (200 mg itraconazole twice daily for 4 days) increased selumetinib C_{max} by 19% and AUC by 49% in healthy adult volunteers.
Co-administration with a strong CYP2C19/moderate CYP3A4 inhibitor (200 mg fluconazole once daily for 4 days) increased selumetinib C_{max} by 26% and AUC by 53% in healthy adult volunteers, respectively.
Avoid co-administering Koselugo with strong or moderate inhibitors of CYP3A4 (e. g., clarithromycin, grapefruit juice, oral ketoconazole) and CYP2C19 (e. g., ticlopidine). If co-administration is unavoidable, patients should be carefully monitored for adverse events (see section *Dosage/Administration* and *Interactions*).

Table 5 Recommended dosage of Koselugo for co-administration with strong or moderate CYP3A4 inhibitors or fluconazole

Body Surface Area	**If the current dosage is 25 mg/m² twice daily, reduce to 20 mg/m² twice daily (mg/dose)**		**If the current dosage is 20 mg/m² twice daily, reduce to 15 mg/m² twice daily (mg/dose)**	
	Morning	**Evening**	**Morning**	**Evening**
0.55 – 0.69 m²	10	10	10 mg once a day	
0.70 – 0.89 m²	20	10	10	10
0.90 – 1.09 m²	20	20	20	10

Body Surface Area	If the current dosage is 25 mg/m^2 twice daily, reduce to 20 mg/m^2 twice daily (mg/dose)		If the current dosage is 20 mg/m^2 twice daily, reduce to 15 mg/m^2 twice daily (mg/dose)	
	Morning	Evening	Morning	Evening
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

Active substances that may decrease the selumetinib plasma concentration

Co-administration with a strong CYP3A4 inducer (600 mg rifampicin daily for 8 days) decreased selumetinib C_{max} by 26% and AUC by 51%.

Avoid concomitant use of strong CYP3A4 inducers (e.g. phenytoin, rifampicin, carbamazepine, St. John's Wort) or moderate CYP3A4 inducers with Koselugo.

Effect of gastric acid reducing agents on Koselugo

Koselugo hard capsules do not exhibit pH dependent dissolution. Koselugo can be used concomitantly with gastric pH modifying agents (ie, H2-receptor antagonists and proton pump inhibitors) without any restrictions.

Other interactions

Vitamin E

Koselugo hard capsules contain vitamin E as the excipient TPGS. Therefore, patients should avoid taking supplemental vitamin E, and anticoagulant assessments should be performed more frequently in patients taking concomitant anticoagulant or antiplatelet medications (see section *Warnings and Precautions*).

Pregnancy, lactation

Women of childbearing age/contraception in women

It is recommended that a pregnancy test should be performed in women of childbearing potential prior to initiating treatment. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with selumetinib. Both male and female patients should be advised to use effective contraception during and for at least 1 week after completion of treatment with Koselugo. Koselugo is not recommended in women of child-bearing potential not using contraception. If a female patient or a female partner of a male patient on Koselugo treatment becomes pregnant, she should be apprised of the potential hazard to the fetus.

Pregnancy

There are no data on the use of selumetinib in pregnant women. In animal studies, embryotoxicity, fetotoxicity and teratogenic effects occurred in mice (see section *Preclinical data*). Koselugo is not recommended during pregnancy.

Lactation

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. A risk for the newborn/infant cannot be excluded. Koselugo should not be used during breast-feeding.

Fertility

There are no data on the effect of Koselugo on human fertility. Data from preclinical studies do not suggest that selumetinib would be associated with an increased risk of decreased fertility (see section *Preclinical data*).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Fatigue, asthenia and visual disturbances have been reported during treatment with Koselugo. Koselugo therefore has a minor influence on the ability to drive and use machines in patients who experience these symptoms.

Undesirable effects

The safety of selumetinib monotherapy has been evaluated in a combined population of 74 paediatric patients (20-30 mg/m^2 twice daily, capsules) with NF1 and inoperable PN (NF1-PN Paediatric Pool). This paediatric 'pool' of patients comprised 50 patients in the SPRINT phase II study, stratum 1, and 24 patients in the SPRINT phase I study. In addition, safety data from 137 adult patients with NF1 and inoperable PN from the Phase III KOMET (D134BC00011) study were included.
The median total duration of selumetinib treatment in the NF1-PN Paediatric Pool was approximately 55 months (range: <1 – <97 months). 61% of patients were exposed to selumetinib treatment for >48 months and 16% of patients for >72 months.
The median total duration of selumetinib treatment in adult NF1-PN patients was approximately 12 months (range: < 1 – < 32 months). 50.4% of patients were exposed to selumetinib treatment for < 12 months and 49.6% for > 12 months.

In the Paediatric Pool (N = 74), the most common adverse reactions of any grade (incidence ≥ 10%) were vomiting (87%), diarrhoea (81%), abdominal pain (77%), blood CPK increased (77%), nausea (77%), acneiform rash (65%), dry skin (62%), pyrexia (60%), asthenic events (60%), paronychia (57%), stomatitis (55%), haemoglobin decreased (54%), non-acneiform rashes (51%), blood albumin decreased (51%), aspartate aminotransferase increased (51%), pruritus (47%), hair changes (39%),

alanine aminotransferase increased (39%), constipation (39%), dermatitis (37%), epistaxis (34%), blood creatinine increased (32%), haematuria (31%), peripheral oedema (30%), ejection fraction decreased (28%), proteinuria (28%), sinus tachycardia (27%), skin infection (23%), increased blood pressure (18%), blurred vision (15%) and facial oedema (11%).
The most commonly reported adverse reactions of Grade ≥3 were diarrhoea (18%), paronychia (14%), vomiting (12%), blood CPK increased (10%), pyrexia (8%), rash (acneiform) (4%), skin infection (4%), haemoglobin decreased (3%), alanine aminotransferase increased (3%), dermatitis (3%), skin rash (non-acneiform) (3%), nausea (3%), abdominal pain (1%), stomatitis (1%), aspartate aminotransferase increased (1%), blood creatinine increased (1%), haematuria (1%), dry skin (1%) and ejection fraction decreased (1%).
Treatment interruptions and dose reductions due to adverse events were reported in 82% and 39% of patients, respectively. The most commonly reported ADRs leading to dose modification 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.

In the adult NF1-PN patients, the most common adverse reactions of any grade (incidence ≥ 20%) were acneiform rashes (54.7%), blood CPK increased (37.2%), diarrhoea (29.9%), non-acneiform rashes (27.0%) and vomiting (19.7%). Adverse reactions leading to dose interruptions and reductions were reported in 31.0% and 16.9% of patients, respectively. A total of 24.8% of patients had adverse reactions leading to dose modification of selumetinib (either dose interruptions or dose reductions). The only adverse reaction leading to dose modification (incidence ≥ 5%) of selumetinib was blood CPK increased (5.8%). The adverse reactions leading to treatment discontinuation were reported in 1.5% patients.
The most commonly reported adverse reactions of grade ≥3 were blood CPK increased (7%), paronychia (3%) and acneiform rashes (2%).

Tabulated list of adverse reactions

Table 6 presents the adverse reactions identified in the selumetinib studies in paediatric and adult patients with NF1-PN. The 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. The 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 the available data), including isolated reports.

Table 6 Adverse drug reactions reported in the selumetinib NF1-PN studies

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 74)		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]
Blood and lymphatic system disorders				
Haemoglobin decreased*	Very common (54%)	Common (3%)	Very common (11%)	Common (2%)
Cardiac disorders				
Ejection fraction decreased^	Very common (28%)	Common (1%)	Common (7%)	Common (1%)
Sinus tachycardia	Very common (27%)		-	
Eye disorders				
Vision blurred^	Very common (15%)	-	Common (4%)	-
Retinal pigment epithelial detachment (RPED)/ Central serous retinopathy (CSR) *††	Uncommon	-	Uncommon	-
Retinal vein occlusion (RVO) *††	Uncommon	-	Uncommon	-
Hepatobiliary disorders				
AST increased	Very common (51%)	Common (1%)	Very common (12%)	Common (1%)
ALT increased	Very common (39%)	Common (3%)	Very common (11%)	Common (1%)
Infections				
Skin infection *	Very common (23%)	Common (4%)	Common (6%)	Common (2%)
Metabolism and nutrition disorders				
Blood albumin decreased *	Very common (51%)	-	Common (2%)	-
Musculoskeletal and connective tissue disorders				
Blood CPK increased^	Very common (77%)	Very common (10%)	Very common (37%)	Common (7%)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	Very common (34%)	-	Common (2%)	-

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 74)		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]
Dyspnoea *	Common (8%)	-	Common (3%)	Common (1%)
Gastrointestinal disorders				
Vomiting^	Very common (87%)	Very common (12%)	Very common (20%)	-
Diarrhoea^	Very common (81%)	Very common (18%)	Very common (30%)	-
Nausea^	Very common (77%)	Common (3%)	Very common (17%)	-
Abdominal Pain*	Very common (77%)	Common (1%)	Very common (10%)	Common (2%)
Stomatitis ^*	Very common (55%)	Common (1%)	Very common (14%)	Common (1%)
Constipation	Very common (39%)	-	Very common (10%)	-
Dry mouth	Common (5%)	-	Common (6%)	-
Skin and subcutaneous tissue disorders				
Rashes (acneiform) ^*	Very common (65%)	Common (4%)	Very common (55%)	Common (2%)
Dry skin	Very common (62%)	Common (1%)	Very common (13%)	-
Paronychia^	Very common (57%)	Very Common (14%)	Very common (17%)	Common (3%)
Rashes (non-acneiform) ^*	Very common (51%)	Common (3%)	Very common (27%)	Common (1%)
Pruritus	Very common (47%)	-	Common (7%)	-
Hair changes^*	Very common (39%	-	Very common (18%)	-
Dermatitis *	Very common (37%)	Common (3%)	Common (4%)	-

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 74)		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]
General disorders				
Pyrexia	Very common (60%)	Common (8%)	Common (5%)	Common (1%)
Asthenic events *	Very common (60%)	-	Very common (15%)	-
Peripheral oedema *	Very common (30%)	-	Very common (16%)	-
Facial oedema *	Very common (11%)	-	Common (4%)	-
Renal and urinary disorders				
Blood creatinine increased	Very common (32%)	Common (1%)	Common (2%)	-
Haematuria	Very common (31%)	Common (1%)	Common (2%)	-
Proteinuria	Very common (28%)	-	-	-
Vascular disorders				
Increased blood pressure *	Very common (18%)	-	Common (4%)	Common (2%)

a NF1-PN Paediatric Pool data (N = 74) are pooled from SPRINT Phase I (D1532C00057, N = 24), SPRINT Phase II, stratum 1 (D1532C00057, N = 50).In ADR Table 6, frequency percentages are rounded up to the next whole number.

b NF1-PN Adult Pool data are pooled from the KOMET study (D134BC00001, N = 137). In ADR Table 6, frequency percentages are rounded up to the next whole number.

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

d All events were CTCAE grade 3, except for two CTCAE grade 4 events 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.

In the SPRINT study, all laboratory abnormalities were reported as AEs. In other studies included in the NF1-PN paediatric pool and in the KOMET study, laboratory abnormalities were only reported as AEs when they met the 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

†† ADRs identified in other clinical studies 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):

Abdominal pain: Abdominal pain, abdominal pain upper, abdominal discomfort, gastrointestinal pain
Asthenic events: Fatigue, Asthenia
Blood albumin decreased: Hypoalbuminaemia, Blood albumin decreased.
CSR/RPED: Detachment of macular retinal pigment epithelium, chorioretinopathy
Dermatitis: Dermatitis, dermatitis atopic, nappy rash, eczema, seborrhoeic dermatitis, skin irritation, dermatitis bullous, contact dermatitis
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: Hypertension, Blood pressure increased
Peripheral oedema: Oedema peripheral, Oedema, Localised oedema, Peripheral swelling
RVO: retinal vascular disorder, retinal vein occlusion, retinal vein thrombosis
Rashes (acneiform): Dermatitis acneiform, Acne, Folliculitis
Rashes (non-acneiform): Rash maculo-papular, Rash papular, Rash, Rash erythematous, Rash macular, Rash pruritic
Skin infection: skin infection; abscess; cellulitis; impetigo; staphylococcal skin infection
Stomatitis: Stomatitis, Mouth ulceration, Aphthous ulcer, Gingival swelling

Description of selected undesirable effects

Left ventricular ejection fraction (LVEF) reduction

In the SPRINT study, LVEF reduction (PT: ejection fraction decreased) was reported in 21 patients (28%); the majority of cases were grade 2, asymptomatic and did not lead to treatment discontinuation; two cases led to treatment interruption and then to a dose reduction. Of the 21 patients, 17 patients recovered, and for 4 patients the outcome was not reported. The median time to first occurrence of LVEF reduction was 441 days (median duration 108 days). The majority of the reported LVEF reductions were reductions from baseline (≥ 10% reduction). The values were, however, within the normal range at all times.

Patients with LVEF below the institutional LLN at the start of the study 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 programme. For clinical management of LVEF reduction, see sections "*Dosage/Administration"* and "*Warnings and Precautions"*.

Among the adult NF1-PN patients (N = 137), LVEF reduction (PT: ejection fraction decreased) was reported in 10 patients (6.5%); among them, for one of these patients (0.7%), the adverse reaction reported was CTCAE grade 3. In 2 patients (1.5%), the 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 169 days (approximately 6 months) [median duration 112.5 days (approximately 4 months)].

Ocular toxicity

In the SPRINT study, blurred vision, photophobia, cataracts and ocular hypertension occurred in 15 (20%) of 74 paediatric patients receiving Koselugo. Blurred vision resulted in treatment interruption in 2 patients (2.7%). Ocular toxicity resolved in 13 (87%) of the 15 patients. All adverse reactions were managed without a dose reduction. For the clinical management of new visual disturbances, see sections "*Dosage/Administration"* and "*Warnings and Precautions"*. 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 signally pathway in an externally sponsored paediatric study (see sections "*Dosage/Administration"* and "*Warnings and Precautions"*).

Among the adult NF1-PN patients (N **=** 137), CTCAE grade 1 events of blurred vision were reported in 5 patients (4%). One patient (0.7%) required treatment interruption. All events were managed without dose reduction and at the time of analysis, all 5 patients had recovered.
Blurred vision, cataracts and vitreous floaters occurred in 8 (6%) of 137 adult patients receiving Koselugo in the adult NF1 PN pool. Ocular toxicity resolved in 100% of 8 patients.

Paronychia

In the SPRINT study, paronychia was reported in 42 patients (57%); the median time to first onset of a maximum grade paronychia adverse event was 574 days and the median duration of the event was 50 days. The majority of these events were grade 1 or 2 and were treated with supportive or symptomatic therapy and dose reduction. Grade ≥3 events occurred in 10 patients (14%). In sixteen patients, administration of selumetinib was interrupted because of an adverse event of paronychia; in 7 of these patients, treatment interruption was followed by dose reduction (2 patients required a second dose reduction). In one patient (1.4%), the event led to discontinuation of treatment. At the time of analysis, 39 of the 42 patients had recovered.
Among the adult NF1-PN patients (N = 137), paronychia was reported in 23 patients (17%). The median time to first onset of maximum CTCAE grade paronychia was 206 days (approximately 7 months) and the median duration of the event was 63 days (approximately 2 months). Nineteen patients (13.9%) had a maximum CTCAE grade of 1 or 2. Grade 3 events occurred in 4 patients (3%). One patient (0.7%) required treatment interruption because of paronychia, and 3 patients (2.2%) had an event of paronychia that led to dose reduction. Paronychia did not lead to treatment discontinuation in any of the patients. At the time of analysis, 11 of the 23 patients had recovered.

Blood creatine phosphokinase (CPK) increase

In the SPRINT study, adverse events of blood CPK elevation occurred in 57 patients (77%). The median time to first onset of the maximum grade CPK increase was 112 days and the median duration of the event was 142 days. The majority of the events were grade 1 or 2 and two patients (2.7%) required treatment interruption. Grade ≥3 events occurred in 7 patients (9.5%). Two grade 4 events led to treatment interruption followed by dose reduction. At the time of analysis, 48 of the 57 patients had recovered.
In the adult NF1-PN patients (N **=** 137), adverse events of blood CPK increase occurred in 51 patients (37%). The median time to first onset of the maximum CTCAE grade blood CPK increase was 103 days (approximately 3 months), and the median duration of the events was 122 days (approximately 4 months). Forty-two patients (30.7%) had a maximum CTCAE grade of 1 or 2. Maximum CTCAE grade 3 events occurred in 5 patients (3.6%), and CTCAE grade 4 events occurred in 4 patients (2.9%). Six patients had an event of blood CPK increase that led to dose interruptions,

and a dose reduction was required in 3 patients. At the time of analysis, 21 of the 51 patients had recovered.

Gastrointestinal toxicities

In the SPRINT study, vomiting (64 patients, 87%), diarrhoea (60 patients, 81%), nausea (57 patients, 77%) and stomatitis (41 patients, 55%) were the most commonly reported gastrointestinal (GI) reactions. The majority of these cases were grade 1 or 2 and did not require any treatment interruption or dose reduction.

Grade 3 events were reported for diarrhoea (11 patients, 15%), nausea (2 patients, 2.7%) and vomiting (7 patients, 9.5%). In one patient (1.4%), diarrhoea led to dose reduction and subsequent treatment discontinuation. Dose reduction was required in two patients (2.7%) with stomatitis. One event of nausea and one event of stomatitis led to treatment discontinuation. No dose reduction or treatment discontinuation was required for adverse events of vomiting. No grade ≥4 events were reported. At the time of analysis, 66 of the 71 patients had recovered.

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

Skin toxicities

In the SPRINT study, acneiform rash was observed in 45 patients (61%) (median time to onset 55 days; median duration of the maximum CTCAE grade event 176 days). The majority of these cases were grade 1 or 2, were observed in post-pubertal patients (>12 years) and did not require any treatment interruption or dose reduction. Grade 3 events were reported in 3 patients (4%). Other (non-acneiform) rashes were observed in 39 patients (53%) in the pivotal study and were predominantly grade 1 or 2.

In the adult NF1-PN patients (N **=** 137), rashes (acneiform) were observed in 75 patients (54.7%) [median time to onset 12 days; median duration of 124 days (approximately 4 months) for the maximum CTCAE grade event]. Seventy-two patients (53 %) reported adverse effects with maximum CTCAE grade 1 or 2. CTCAE grade 3 events were reported in 3 patients (2.2%). In 3 patients (2.2%), acneiform rashes led to treatment interruption, and in 2 patients (1.5%) each, acneiform rashes led to dose reduction or treatment discontinuation. Rashes (non-acneiform) were observed in 37 patients (27%) and were predominantly CTCAE grade 1 or 2 (36 patients, 26.3%).

Hair changes

In the SPRINT study, 29 patients (39%) experienced hair changes (reported as hair lightening [PT: hair colour changes] and hair loss [PT: alopecia]). In the paediatric pool, 14 patients (19%) experienced both events during treatment, 22 patients (30%) experienced at least one adverse event of alopecia, and 21 patients (28%) experienced at least one event of hair colour change. All cases were grade 1 and did not require treatment interruption or dose reduction.

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for overdose. If overdose occurs, patients should be treated supportively with appropriate monitoring as necessary. Dialysis is ineffective in the treatment of overdose.

Properties/Effects

ATC code

L01EE04

Mechanism of action

Selumetinib is an orally available inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are critical components of the *RAS*-regulated RAF-MEK-ERK signalling pathway, which is often activated in different types of cancers. Selumetinib blocks MEK activity and can therefore inhibit the growth of RAF-MEK-ERK pathway-activated cell lines.

Pharmacodynamics

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

Further information

Cardiac electrophysiology

At a dose 1.5 times the maximum recommended dose, Koselugo does not prolong the QT/QTc interval to any clinically relevant extent.

Clinical efficacy

The efficacy of selumetinib in paediatric and adult NF1-PN patients was evaluated in the following studies as described below.

SPRINT Phase II stratum 1, NF1-PN Patients (2 to ≤ 18 years of age)

The efficacy of Koselugo was evaluated in an open-label, multi-centre, single-arm study [SPRINT Phase II Stratum 1 (NCT01362803)] in 50 paediatric patients with neurofibromatosis type 1 (NF1) inoperable plexiform neurofibromas (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. Patients with the following ocular toxicities were excluded from the study: 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 were also required to have significant morbidity related to the target PN. Morbidities that were present in ≥ 20% of patients included disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment and bladder/bowel dysfunction. Patients received 25 mg/m^2 body surface area (BSA) twice daily, for 28 days (1 treatment cycle), on a continuous dosing schedule until disease progression or unacceptable toxicity.

The major efficacy outcome measure was overall response rate (ORR), defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as ≥ 20% reduction in PN volume confirmed at a subsequent tumour assessment within 3-6 months). The target PN, defined as the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was evaluated for response rate using centrally read volumetric magnetic resonance imaging (MRI) analysis as 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. An additional efficacy outcome measure was duration of response (DoR).

On study enrolment, the median age of the patients was 10.2 years (range: 3.5 - 17.4 years), 60% were male, 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, ORR, was 66% (95% CI, 51.2 – 78.8). Of the 66% of patients who experienced a response, all had a partial response (PR), no patients experienced a complete response (CR). An independent centralized review of tumour response according to REiNS criteria 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 1.6 years). The median DoR from onset of response was not reached; at the time of data cut-off the median follow-up time was 22.1 months. Furthermore, of the patients who responded, the number of patients who experienced a DoR of greater than 12 months was 27 (82%).

Updated results according to the data cut-off of 31 March 2021
The primary efficacy endpoint, ORR, was 68% (95% CI, 53.3 - 80.5). Of the 68% of patients who experienced a response, all had a partial response (PR), no patient had a complete response (CR). After a median follow-up period of 41.3 months, the median time to onset of the response and the proportion of patients with a DoR of greater than 12 months was unchanged. The median DoR from onset of the response was not reached.

KOMET, NF1-PN Patients (≥ 18 years of age)
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 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. This occurred at an earlier point in time 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 or decided against treatment, in the case of disease (PN) progression, or at the discretion of the investigator.

The KOMET study enrolled male and female adult patients (≥ 18 years of age at enrolment) 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 out of 7 days for at least 2 weeks during the screening period); stable chronic PN pain medication use at the time of enrolment.

The target PN, the clinically most relevant PN, which is measurable by volumetric MRI analysis and, if relevant, one additional non-target PN, were 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 until Cycle 24, and then every 6 cycles. Patients had target and non-target PN MRI volumetric evaluations and clinical course assessments.

Demographics and baseline disease characteristics were generally well balanced between the selumetinib and placebo treatment arms with the following exceptions: median target PN volume (selumetinib: 110.18 mL; placebo: 221.85 mL), percentage of participants with target PN-related disfigurement (selumetinib: 32.4%; placebo: 23.0%) and percentage of participants with non-target PN tumors (selumetinib: 25.4%; placebo: 40.5%). 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 number of PN-related morbidities was 2. The most common PN-related morbidities were pain, motor dysfunction and disfigurements, affecting 23% or more of the patients in both groups. Airway, vision, and bowel/bladder problems were less frequent, affecting 4.2% or less of the patients in both the selumetinib and placebo groups.

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

In the planned primary analysis, the study met its primary endpoint and demonstrated a statistically significant ORR versus placebo. At the end of Cycle 16, the ORR for selumetinib was 19.7% (95% CI: 11.2; 30.9) versus an ORR for placebo of 5.4% (95% CI: 1.5; 13.3). No complete response (CR) was achieved. The median TTR was 3.7 months (95% CI: 3.61; 11.07).
At the time of the final data cut-off (DCO), the median total duration of exposure was 749 days (approximately 25 months) in patients randomised to selumetinib. In the patients with a response in the primary analysis, the median DoR from onset of response was not reached, and 9 patients (64.3%) had a DoR of 12 months or longer.

Exploratory subgroup analyses of the ORR by Cycle 16 in the selumetinib FAS (full analysis set) by ethnic origin showed the following results: at the end of Cycle 16, the ORR for selumetinib in the White subgroup was 7.9% (3 of 38 patients), compared with an ORR of 4.7% for placebo (2 of 43 patients), and in the Asian subgroup, the ORR for selumetinib was 45.5% (10 of 22 patients), compared with an ORR of 0% for placebo (0 of 23 patients). Given the exploratory nature and the small number of patients, the results should be interpreted with caution.

Pharmacokinetics

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.

In the SPRINT Phase II stratum 1, at the recommended dosage of 25 mg/m^2 BSA twice daily in paediatric patients (aged 3 to ≤18 years), the geometric mean (coefficient of variation [CV%]) of the maximum plasma concentration (C_{max}) was 731 ng/mL (62%) and that of the area under the plasma concentration curve (AUC_{0-12}) following the first dose was 2009 ng·h/mL (35%). Selumetinib AUC and C_{max} increase proportionally over a dose range from 20 mg/m^2 to 30 mg/m^2 (0.8 to 1.2 times the recommended dose). A minimal ~1.1-fold accumulation was observed at steady state after twice daily dosing.

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

In all age groups, the minimal accumulation range was 1.2 to 1.5 following administration of selumetinib.

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}) within 1-1.5 hours post-dose.

Effect of food

A population-based PK analysis that included children and adolescent patients with NF1 and inoperable PN, adult patients with advanced solid malignancies and healthy adult subjects from 15 studies showed that the concomitant administration of a low-fat or high-fat meal led to a mean reduction in selumetinib exposure (AUC) compared with administration in the fasting state (23.1% and 20.7%, respectively), which was not considered clinically relevant (see section "Dosage/Administration").

In separate clinical studies in healthy adult subjects, the administration of selumetinib at a dose of 75 mg together with a high-fat meal resulted in a mean decrease in C_{max} of 50%, compared to fasting administration. Selumetinib mean AUC was reduced by 16%, and the time to reach the maximum concentration (t_{max}) was delayed by approximately 1.5 hours.

In healthy adult subjects, administration of selumetinib at a dose of 50 mg together with a low-fat meal resulted in a 60% lower C_{max} compared to fasting administration. Selumetinib AUC was reduced by 38%, and the time to reach the maximum concentration (t_{max}) was delayed by approximately 0.9 hours.

In adolescent patients with NF1 and inoperable PN treated with several doses of 25 mg/m^2 twice daily, the concomitant administration of selumetinib and a low-fat meal led to a 24% lower C_{max} compared to fasting administration. Selumetinib AUC was reduced by 8% and the t_{max} was delayed by approximately 0.57 hours.

Distribution

The mean apparent volume of distribution of selumetinib 20 to 30 mg/m^2 BSA at the steady state ranged from 78 to 171 L in paediatric patients. Comparable values were observed in adult patients with a dose of 25 mg/m^2 and ranged from 40 to 3710 L. These values indicate moderate distribution in the tissue.

In vitro plasma protein binding is 98.4% in humans. Selumetinib mainly binds to serum albumin (96.1%) and secondarily to α-1 acid glycoprotein (<35%).

Metabolism

In vitro, selumetinib undergoes Phase 1 metabolic reactions including oxidation of the side chain, N-demethylation, and loss of the side chain to form amide and acid metabolites. CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism, with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. *In vitro* studies indicate that selumetinib also undergoes direct Phase 2 metabolic reactions to form glucuronide conjugates principally involving the enzymes UGT1A1 and UGT1A3. Glucuronidation is a significant route of elimination for selumetinib Phase 1 metabolites involving several UGT isoforms. It is estimated that 56% of the observed intrinsic clearance of selumetinib can be attributed to CYP metabolism and about 29% attributed to direct glucuronidation by UGT enzymes *in vitro*.
Following oral dosing of ^{14}C-selumetinib to healthy male subjects, unchanged selumetinib (~40% of the radioactivity) with other metabolites including the glucuronide of the imidazoindazole metabolite (M2; 22%), the 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 the selumetinib concentration 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 pharmacological activity.

Elimination

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

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

In adult patients, selumetinib had an apparent oral clearance of 14.1 L/h and a mean elimination half-life of approximately 9.04 hours following a dose of 25 mg/m^2.

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 CYP3A4, CYP1A2 and CYP2B6.

Interactions with transport proteins

Based on *in vitro* studies, selumetinib is a substrate for BCRP and P-gp transporters; however, clinically relevant drug interactions with other medicinal products are unlikely at the recommended paediatric dose. *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.

Kinetics in specific patient groups

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 the values in subjects with normal hepatic function (see section "*Dosage/Administration"*).

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 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 compared to the normal group. As exposure in ESRD subjects was similar to those with normal renal function, investigations in subjects

with mild, moderate or severe renal impairment were not performed. Renal impairment is expected to have no meaningful influence on the exposure of selumetinib (see section "*Dosage/Administration"*).

Ethnicity

Selumetinib exposure appears to be higher in Japanese, non-Japanese-Asian and Indian healthy adult volunteers compared to Western adult volunteers. However, there is considerable overlap with Western subjects when corrected for body weight or BSA. No specific adjustment to the starting dose is recommended for Asian patients; however, these patients should be closely monitored for adverse reactions.

Preclinical data

Repeat dose toxicity

In repeat-dose toxicity studies (up to 26 weeks) in mice and rats, the main effects seen after selumetinib exposure involved the skin. Scabs associated with microscopic erosions and ulceration occurred in rats at a free exposure similar to the clinical exposure (free AUC) at the MRHD; inflammatory and ulcerative GI tract findings associated with secondary changes in the liver and lymphoreticular system occurred in mice at free exposures approximately 28 times the clinical free exposure at the MRHD; and growth plate (epiphyseal) dysplasia occurred in male rats 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 epiphyseal dysplasia were not evaluated.
Vascular engorgement of the corpus cavernosum of the bulbocavernosus muscle was observed in male mice in a 26-week study at a dose 28 times the free AUC in humans at the MRHD, leading to significant urinary tract obstruction as well as inflammation and luminal haemorrhage of the urethra, and to early death in male mice.

Mutagenicity

Selumetinib showed no mutagenic or clastogenic potential *in vitro* but produced an increase in micronucleated immature erythrocytes (chromosome aberrations) in mouse micronucleus studies, predominantly 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 BSA.

Carcinogenicity

Selumetinib was not carcinogenic in a 6-month study in rasH2 transgenic mice at free exposures 24 times (females) and 16 times (males) the free clinical AUC at the MRHD and in a 2-year carcinogenicity study in rats at free exposures 2.9 times (females) and 3.7 times (males) the clinical free AUC at the MRHD.

Reproductive toxicity

Fertility

In a 6-month mouse study, selumetinib did not affect male mating performance at any dose up to 20 mg/kg twice daily corresponding to approximately 22 times the human clinical exposure based on free AUC at the MRHD. In female mice exposed to selumetinib at 12.5 mg/kg twice daily, mating performance and fertility were not affected, but the number of live fetuses was slightly reduced. Following a three-week treatment withdrawal period, no effects were apparent on any parameter. The no observed adverse effect level (NOAEL) for both maternal toxicity and effects on reproductive performance was 2.5 mg/kg twice daily (approximately, 3.5 times the human free exposure at the MRHD).

Embryofetal toxicity

In embryofetal development studies in mice, selumetinib caused a reduction in the number of live fetuses due to an increase in post-implantation loss, a reduction in mean fetal and litter weights and increased occurrence of open eye and cleft palate at dose levels that did not induce significant maternal toxicity. These effects were seen at an exposure >3.5 times the clinical exposure at the MRHD based on free AUC and indicate that selumetinib may have the potential to cause defects in the fetus.

Pre- and postnatal development

Administration of selumetinib to pregnant mice from gestation Day 6 through to lactation Day 20 resulted in reduced pup body weights, and fewer pups met the pupil constriction criterion on Day 21 post-partum. The incidence of malformations (prematurely open eye(s) and cleft palate) was increased at all dose levels. Malformations occurred at a maternal blood concentration (C_{max}) 0.4 times the mean free clinical concentration 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date marked as EXP on the container.

Special precautions for storage

Do not store above 30°C.

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

Do not remove the desiccant.

Keep out of the reach of children.

Authorisation number

67410 (Swissmedic)

Packs

Koselugo 10 mg and 25 mg hard capsules: plastic bottle with child-resistant closure and silica gel desiccant each containing 60 hard capsules [A].

Marketing authorisation holder

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