Date: 3 November 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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: AstraZeneca AG

Marketing Authorisation No.: 67410

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 29 July 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document which provides information relating to a submission at a particular point in time and will not be 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_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BSA	Body surface area
CALM	Café-au-lait macules
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GI	Gastro-intestinal
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 nonproprietary 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
NCI	National cancer institute
NF1	Neurofibromatosis type 1
NO(A)EL	No observed (adverse) effect level
ORR	Overall response rate
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PN	Plexiform neurofibroma
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)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance selumetinib as selumetinib hydrogen sulfate in the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan Drug Status was granted on 8 March 2019.

Authorisation of a human medicinal product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Koselugo is indicated for the treatment of children and adolescents aged 3 years and above with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN).

2.2.2 Approved Indication

Koselugo is indicated for the treatment of children and adolescent patients aged 3 years and above with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) (see sections *Dosage/Administration* and *Warnings and Precautions*).

2.2.3 Requested Dosage

Summary of the requested standard dosage:

The recommended dosage of Koselugo is 25 mg/m^2 body surface area (BSA) twice daily (within a 12h interval) on an empty stomach, taken without food or beverages other than water. Do not consume food for 2 hours before each dose or for 1 hour after each dose.

Dosage scheme for selumetinib 25 mg/m^2 twice daily

Body surface area*	**Recommended dosage**
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 0.55m^2 has not been established.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	1 October 2020
Formal control completed	30 October 2020
List of Questions (LoQ)	18 February 2021
Answers to LoQ	19 May 2021
Preliminary Decision	12 August 2021
Answers to Preliminary Decision	21 September 2021
2. Preliminary Decision	17 December 2021
Answers to 2. Preliminary Decision	15 February 2022
Labelling corrections	3 May 2022
Answers to Labelling corrections	2 June 2022
Final Decision	29 July 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data of this application. For the remaining parts, Swissmedic relies for its decision on the assessment of the foreign reference authority, the FDA. The current SwissPAR refers to the publicly available Assessment Report Koselugo, application number 213756 (approval date 4 October 2020) issued by the FDA.

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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. Plexiform neurofibromas (PNs) are found in one third of patients with NF1. Diffuse PNs tend to occur in early childhood, while deep nodular PNs usually develop in adolescence.[Fehler! Textmarke nicht definiert.1]
Cutaneous neurofibromas are benign and do not require removal unless they are symptomatic. Surgical resection is the gold standard for treating patients with PN but it is often impractical due to the involvement of nerves and therefore the risk of nerve injury or major bleeding.
In Switzerland, no systemic therapies are licensed for the treatment of PN.

4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority, the FDA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Koselugo, application number 213756 (approval date 4 October 2020) issued by the FDA.

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

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5 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects of this application and relies on the assessment of the foreign reference authority, the FDA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Koselugo, application number 213756 (approval date 4 October 2020) issued by the FDA.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment report and corresponding product information from the FDA were used as a basis for the clinical pharmacology evaluation. A paediatric granule formulation is being developed based on dedicated clinical studies D1532C00089 and D1346C00004 (SPRINKLE).

6.2 Dose Finding and Dose Recommendation

The current capsule formulation is not appropriate for all patients. In particular, younger children (< 6 years) and/or patients with disease-related symptoms are at potential risk for choking. Swallowing training could minimise the risk of choking. However, swallowing training was not standardised in the selumetinib studies. All adverse event (AE) reports relating to the potential risk of choking on the capsule will be closely monitored and assessed through routine pharmacovigilance. In addition, a paediatric age-appropriate granule formulation is being developed (SPRINKLE).

6.3 Efficacy and Safety

This application was submitted according to Article 13, and the evaluation is partly based on the assessment of the foreign reference authority, the FDA. The available assessment report and corresponding product information from the FDA was used as a basis for the clinical evaluation.

For evaluation of efficacy and safety, the applicant submitted results of one pivotal study, SPRINT. The results of SPRINT Phase II Stratum 1 are relevant for the requested indication.

The SPRINT study is an open-label, single-arm, multi-centre study of selumetinib in children with NF1 and inoperable PN.
For SPRINT Phase II, stratum 1 patients were enrolled who already had PN-related morbidity at the time of enrolment. For details concerning the included patient population, see section 8 of this report.

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).

A total of 50 paediatric patients received selumetinib. Efficacy results from SPRINT Phase II Stratum 1 demonstrated a confirmed ORR using the REiNS criteria of 66% (95% CI: 51, 79) based on a National Cancer Institute (NCI) central review and 44% (95% CI: 30, 59) based on an independent central review (ICR). Among the 33 responding patients included in the NCI assessment, the median duration of response (DOR) was not reached and 82% had a DOR of at least 12 months. The progression-free survival (PFS) data were not mature at the time of data cut-off.

Safety was evaluated primarily in the data set from the NCI SPRINT trial (n=74) and supported by data in adult patients (adult monotherapy pool n=347). The median duration of treatment in the NCI SPRINT trial (paediatric pool) was approximately 2 years. However, the data set of n=74 is small for valid evaluation of safety in particular.

The most common AEs in the paediatric pool included vomiting, rash, abdominal pain, diarrhoea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, acneiform dermatitis, stomatitis, headache,

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oropharyngeal pain, paronychia, pruritus, cough, dermatitis, constipation, nasal congestion and hair disorders.
Serious adverse events (SAEs) occurred in 23% of patients including 11% who experienced selumetinib-related SAEs. Grade 3-4 AEs occurred in 68% of patients including 43% who experienced Grade 3-4 AEs considered at least possibly related to selumetinib. There were no grade 5 AEs in the SPRINT trial at data cut-off.

Important risks of selumetinib are similar to those of other mitogen-activated protein kinase (MEK) inhibitors, including ocular, cardiac, musculoskeletal, gastrointestinal (GI) and dermatological toxicities. Relevant serious ocular AEs were retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED).

6.4 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

No systemic therapies are licensed in Switzerland for patients with NF1. These patients have a high level of unmet medical need, in particular taking into account the substantial morbidity.
The ORR rates in SPRINT Phase II Stratum I are clinically meaningful and can be accepted for a temporary authorisation. However, progression free survival (PFS) data are immature and it is therefore not possible to assess whether ORR will translate into prolonged PFS.

Important risks of selumetinib including ocular, cardiac, musculoskeletal, gastrointestinal (GI) and dermatological toxicities are adequately described in the Information for healthcare professionals. However, further long-term safety data are necessary.

In addition, the current formulation could be problematic for patients < 6 years and/or patients with disease-related symptoms due to impaired swallowing. A paediatric age-appropriate granule formulation is being developed based on dedicated clinical studies D1532C00089 and D1346C00004 (SPRINKLE).

In the context of the temporary authorisation in accordance with Art. 9a TPA, conditions to be fulfilled for an ordinary authorisation were defined. Taking into account the concerns regarding the capsule formulation and the limited efficacy and safety data in paediatric patients, the applicant must submit the following clinical data as a requirement. The temporary authorisation is subject to the timely submission of the results of the SPRINKLE study (granule formulation), updated clinical study reports of SPRINT Phase 1, SPRINT Phase II Stratum 1, SPRINT Phase II Stratum 2 and interim data of the PASS study D13R00004 (long-term safety).

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Koselugo, capsules 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 reference document, which is valid and relevant 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. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 is temporarily authorised, see *Properties/Effects* section.

Koselugo®

Composition

Active substances

Selumetinib (as Selumetinib hydrogen sulfate)

Excipients

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).

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), Glycerolmonooleat.

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 is indicated for the treatment of children and adolescent patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) (see sections *Dosage/Administration* and *Warnings and Precautions*).

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 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 Recommended Dosage Based on Body Surface Area

Body Surface Area*	Recommended Dosage
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 0.55m^2 has not been investigated.

Duration of treatment

Treatment with Koselugo should continue until disease progression or unacceptable toxicity. There is limited data in patients older than 18, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician. However, start of treatment with Koselugo in adults is not appropriate.Mode of administration

Koselugo should be taken on an empty stomach with no food or drink other than water. Do not consume food 2 hours prior to dosing and 1 hour after dosing (see sections *Interactions* and *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 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.Delayed administration

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

Vomiting

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

Dose adjustment following undesirable effects/interactions

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

Table 2 Recommended Dose Reductions for 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 KOSELUGO after two dose reductions.

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 (LVEF) of 10% or greater from baseline and less than lower level of normal	Withhold until resolution. Resume at reduced dose.

Severity of Adverse Reaction	**Recommended Dosage Modifications for KOSELUGO**
• Symptomatic decreased LVEF • Grade 3 or 4 decreased LVEF	Permanently discontinue.
Ocular Toxicity [see Warnings and Precautions]	
• Retinal Pigment Epithelial Detachment (RPED)	Withhold until resolution. Resume at reduced dose.
• Retinal vein occlusion (RVO)	Permanently discontinue.
Gastrointestinal Toxicity [see Warnings and Precautions*]*	
• Grade 3 Diarrhea	Withhold until improved to Grade 0 or 1. Resume at same dose. Permanently discontinue if no improvement within 3 days.
• Grade 4 Diarrhea	Permanently discontinue.
• Grade 3 or 4 Colitis	Permanently discontinue.
Skin Toxicity [see Warnings and Precautions]	
• Grade 3 or 4	Withhold until improvement. Resume at reduced dose.
Increased Creatine Phosphokinase (CPK) [see Warnings and Precautions*]*	
• Grade 4 Increased CPK • Any Increased CPK and myalgia	Withhold until improved to Grade 0 or 1. Resume at reduced dose. Permanently discontinue if no improvement within 3 weeks.
• Rhabdomyolysis	Permanently discontinue.
Other Adverse Reactions [see Undesirable effects]	
• Intolerable Grade 2 • Grade 3	Withhold KOSELUGO until improve to Grade 0 or 1. Resume at reduced dose.
• Grade 4	Withhold KOSELUGO until improved to Grade 0 or 1. Resume at reduced dose. Consider discontinuation.

* Per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

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 *Pharmacokinetics*).

Table 4 Recommended Dosage of KOSELUGO for 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, severe renal impairment or those with End Stage Renal Disease (ESRD) (see section *Pharmacokinetics*).

Children and adolescents

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

Contraindications

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

Warnings and precautions

LVEF Reduction

Asymptomatic decreases in ejection fraction have been reported in 22% of paediatric patients in the pivotal clinical study (see section *Undesirable effetcs*). Median time to initial onset of events was 226 days.

Paediatric patients with a history of impaired left ventricular function or a baseline LVEF below 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 selumetinib 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 based on severity of adverse reaction. In patients who interrupt KOSELUGO for decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks. Upon resolution of decreased 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 paediatric patients receiving selumetinib. Isolated cases of retinal pigment epithelial detachment (RPED), central serous retinopathy (CSR) and retinal vein occlusion (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 *Undesirable effetcs*). Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving KOSELUGO in SPRINT. Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients.
In line with clinical practice an ophthalmological evaluation prior to treatment initiation and at any time a patient reports new visual disturbances is recommended. In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmic assessment should be conducted every 3 weeks until resolution. If RPED or CSR is diagnosed and visual acuity is affected selumetinib therapy should be interrupted and the dose reduced when treatment is resumed (see Table 2). If RVO is diagnosed, treatment with selumetinib should be permanently discontinued (see section *Dosage/Administration*).

Gastrointestinal Toxicity

Advise patients to start an antidiarrhoeal agent immediately after the first episode of loose stool and to increase fluid intake. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of the adverse reaction (see sections *Dosage/Administration* and *Undesirable effects*).

Skin and Subcutaneous Tissue Disorders

Skin rash (including maculopapular rash and acneiform rash), paronychia and hair changes have been reported very commonly in the pivotal clinical study (see section “Undesirable effects”). Pustular rash, hair colour changes and dry skin 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). Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction (see section *Dosage/Administration*).

Vitamin E Supplementation

Advise patients not to take any supplemental vitamin E.
KOSELUGO 10 mg capsules contain 32 mg vitamin E as the excipient, 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 medications (e.g., warfarin or aspirin).. Monitor for bleeding in these patients. Increase international normalized 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 anti-platelet agents as appropriate (see section *Interactions*).

Elevated Creatine Phosphokinase (CPK)

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

Risk of Choking

Selumetinib is available as a capsule which must be swallowed whole. Some patients, in particular children < 6 years of age, may be at risk of choking on a capsule formulation due to developmental, anatomical or psychological reasons. Therefore, selumetinib should not be administered to patients who are unable or unwilling to swallow the capsule whole (see section *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 selumetinib plasma concentrations
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 medicinal products that are 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 Coadministration 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
1.10 – 1.29 m²	25	25	25	10
1.30 – 1.49 m²	30	25	25	20
1.50 – 1.69 m²	35	30	25	25
1.70 – 1.89 m²	35	35	30	25
≥ 1.90 m²	40	40	30	30

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% 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 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 any restrictions.

Other interactions

Vitamin E

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

Pregnancy, lactation

Women of childbearing age/contraception in women

It is recommended that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Koselugo. 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. 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 receiving Koselugo becomes pregnant, she should be apprised of the potential hazard to the foetus.

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 breastfeeding.

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 and, 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 in paediatric patients with NF1 who have inoperable PN has been evaluated in a combined safety population of 74 paediatric patients. This paediatric ‘pool’ of patients comprised 50 patients in SPRINT phase II stratum I and 24 patients in SPRINT phase I. There were no clinically relevant differences in the safety profile between SPRINT phase I and SPRINT phase II stratum I. This safety profile was also substantiated by a pool of safety data from 7 AstraZeneca sponsored studies in adult patients with multiple tumour types (N = 347).

The median total duration of selumetinib treatment in paediatric patients with NF1 PN was 28 months (range: <1 – 71 months), 23% of patients were exposed to selumetinib treatment for >48 months.
In the paediatric pool, (N = 74), The most common adverse reactions of any grade (incidence ≥10%) were vomiting (82%), rash (all)* (80%), diarrhea (77%), abdominal pain (78%), diarrhea (77%), blood CPK increased (76%), nausea (73%), asthenic events (59%), dry skin (58%), pyrexia (57%), acneiform rash* (54%), hypoalbuminaemia (50%), aspartate aminotransferase increased (50%), paronychia (45%), haemoglobin decreased (45%), pruritus (42%), hair changes (39%), stomatitis (38%), alanine aminotransferase increased (36%), constipation (34%), dermatitis (34%), epistaxis (30%), blood creatinine increased (28%), sinus tachycardia (26%), hematuria (24%), ejection fraction decreased (23%), proteinuria (23%), skin infection (22%), increased blood pressure (16%) and peripheral oedema (12%).
The most reported adverse reactions of Grade ≥3 were diarrhoea (15%), paronychia (9%), blood CPK increased (9%), pyrexia (8%), vomiting (8%), rash (all) (5%), rash (acneiform((3%), haemoglobin decreased (3%), alanine aminotransferase increased (3%), dermatitis (3%), skin infection (3%), abdominal pain (1%), nausea (1%), stomatitis (1%), aspartate aminotransferase increased (1%), blood creatinine increased (1%), hematuria (1%) and ejection fraction decreased (1%).
Dose interruptions and reductions due to adverse events were reported in 78% and 32% of patients, respectively. The most commonly reported ADRs leading to dose modification of selumetinib were vomiting (26%), paronychia (16%), diarrhoea (15%) and nausea (11%). Permanent discontinuation due to adverse events was reported in 12% of the patients.

Tabulated list of adverse reactions

Table 6 presents the adverse reactions identified in the paediatric population with NF1 who have inoperable PN and in adult patients (see footnote to Table 6). The frequency is determined from the paediatric pool (N = 74). 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 <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data), including isolated reports.

Table 6. Adverse drug reactions reported in the paediatric pool (n=74) and in other clinical studies (N = 347)

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE grades) [CTCAE grade 3 and Above] NF1 paediatric pool‡ (N = 74)
Blood and lymphatic system disorders	Haemoglobin decreased*	Very common (45%) [3%]
Cardiac disorders	Ejection fraction decreased^	Very common (23%) [1%]
	Sinus tachycardia	Very common (26%) [-**]
Eye disorders	Vision blurred^	Common [-**]
	Retinal pigment epithelial detachment (RPED)/ Central serous retinopathy (CSR)* ††	Uncommon†† [-**]
	Retinal vein occlusion (RVO)* ††	Uncommon†† [-**]
Gastrointestinal disorders	Vomiting^	Very common (82%) [8%]
	Diarrhoea^	Very common (77%) [15%]
	Nausea^	Very common (73%) [1%]
	Stomatitis^	Very common (38%) [1%]
	Dry mouth	Common [-**]
	Abdominal Pain*	Very common (78%) [1%]
	Constipation	Very common (34%) [-**]
General disorders	Asthenic events*	Very common (59%) [-**]
	Pyrexia	Very common (57%) [8%]
	Peripheral oedema*	Very common (12%) [-**]
	Facial oedema*	Common [-**]

MedDRA SOC	**MedDRA Term**	**Overall Frequency (All CTCAE grades) [CTCAE grade 3 and Above]** **NF1 paediatric pool‡ (N = 74)**
Hepatobiliary disorders	AST increased	Very common (50%) [1%]
	ALT increased	Very common (36%) [3%]
Infections	Skin infection*	Very common (22%) [3%]
Investigations	Blood CPK increased^	Very common (76%) [9%]
Metabolism and nutrition disorders	Hypoalbuminaemia	Very common (50%) [-**]
Renal and urinary disorders	Blood creatinine increased	Very common (28%) [1%]
	Hematuria	Very common (24%) [1%]
	Proteinuria	Very common (23%) [-**]
Respiratory, thoracic & mediastinal disorders	Dyspnoea*	Common [3%]
	Epistaxis	Very common (30%) [-**]
Skin and subcutaneous tissue disorders	Rash^ *	Very common (80%) [5%]
	Dry skin	Very common (58%) [-**]
	Rash acneiform^ *	Very common (54%) [3%]
	Paronychia^	Very common (45%) [9%]
	Hair changes^ *	Very common (39%) [-**]
	Pruritus	Very common (42%) [-**]
	Dermatitis*	Very common (34%) [3%]
Vascular disorders	Increased blood pressure*	Very common (16%) [-**]

Per National Cancer Institute CTCAE version 4.03
CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
^ See Description of selected adverse reactions
† All reactions were CTCAE grade 3, except for one CTCAE grade 4 event of blood CPK increased and one CTCAE grade 4 event of blood creatinine increased. There were no deaths.
†† Identified ADRs from other clinical trial experience. These ADRs have not been reported in paediatric population with NF1 who have inoperable PN.
‡ Paediatric pool (N=74) percentage rounded to the nearest decimal.
** no undesirable effects CTCAE grade 3 and above have been reported.*ADRs based on grouping of individual preferred terms (PT):

Abdominal pain: Abdominal pain, abdominal pain upper, abdominal discomfort, gastrointestinal pain
Asthenic events: asthenia, fatigue,

CSR/RPED: Detachment of macular retinal pigment epithelium, chorioretinopathy
Dermatitis: Dermatitis, dermatitis atopic, dermatitis diaper, eczema, seborrheic dermatitis, skin irritation dermatitis bullous, dermatitis contact
Dyspnoea: dyspnoea exertional, dyspnoea, dyspnoea at rest
Facial oedema: face odema, periorbital oedema
Haemoglobin decreased: anaemia, haemoglobin decreased
Hair changes: alopecia, hair colour change
Increased blood pressure: blood pressure increased, hypertension
Peripheral oedema: oedema peripheral, oedema
Rash (acneiform): dermatitis acneiform
Rash: dermatitis acneiform, rash maculo-papular, rash papular, rash, rash erythematous, rash macular
RVO: retinal vascular disorder, retinal vein occlusion, retinal vein thrombosis
Skin infection: skin infection; abscess; cellulitis; impetigo; staphylococcal skin infection

Description of selected undesirable effects

LVEF reduction

In SPRINT, phase II stratum 1, LVEF reduction (PT: ejection fraction decreased) was reported in 11 (22%) patients; all cases were grade 2, asymptomatic and did not lead to dose interruptions, reductions or discontinuation. Of the 11 patients, 6 patients recovered and for 5 patients the outcome was not reported. The median time to first occurrence of LVEF reduction was 226 days (median duration 78 days). The majority of LVEF reduction adverse reactions were reported as reductions from baseline (≥ 10% reduction) but were considered to remain in the normal range. Patients with LVEF lower than the institutional LLN at baseline were not included in the pivotal study. In addition, 2 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 *Dosage/Administration* and *Warnings and Precautions*.

Ocular toxicity

In SPRINT, phase II stratum 1, grade 1 and 2 adverse reactions of blurred vision were reported in 4 (8%) patients. Two patients required dose interruption. All adverse reactions were managed without dose reduction. For 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/m2 twice daily) for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study (see sections *Dosage/Administration* and *Warnings and Precautions*).

Paronychia

In SPRINT, paronychia was reported in 23 (46%) patients, the median time to first onset of maximum grade paronychia adverse event was 306 days and the median duration of events was 96 days. The majority of these events were grade 1 or 2 and were treated with supportive or symptomatic therapy and dose modification. Grade ≥3 events occurred in three (6%) patients. Seven patients had a selumetinib dose interruption for adverse events paronychia, of whom 3 had dose interruption

followed by dose reduction (2 patients required a second dose reduction). In one patient (2%) the event led to discontinuation.

Blood creatine phosphokinase (CPK) increase

Adverse events of blood CPK elevation occurred in 76% of patients in SPRINT. The median time to first onset of the maximum grade CPK increase was 106 days and the median duration of events was 126 days. The majority of events were grade 1 or 2 and resolved with no change in selumetinib dose. Grade ≥3 events occurred in three (6%) patients. A grade 4 event led to treatment interruption followed by dose reduction.

Gastrointestinal toxicities

Vomiting (82%), diarrhoea (70%), nausea (66%), and stomatitis (50%) were the most commonly reported gastrointestinal (GI) reactions. The majority of these cases were grade 1 or 2 and did not require any dose interruptions or dose reductions.

Grade 3 events were reported for diarrhoea (16%), nausea (2%), and vomiting (6%). For one patient diarrhoea led to dose reduction and subsequent discontinuation. No dose reduction or discontinuation was required for adverse events of nausea, vomiting or stomatitis. No grade ≥4 events were reported.

Skin toxicities

In SPRINT, acneiform rash was observed in 25 (50%) patients (median time to onset 13 days; median duration of 60 days for the maximum CTCAE grade event). The majority of these cases were grade 1 or 2, observed in post-pubertal patients (>12 years) and did not require any dose interruptions or reductions. Grade 3 events were reported for 4%.

Other (non-acneiform) rashes were observed in 35 (70%) patients in the pivotal study and were predominantly grade 1 or 2.

Hair changes

In SPRINT, 32% of patients experienced hair changes (reported as hair lightening [PT: hair colour changes] and hair thinning [PT: alopecia]). In the paediatric pool 13/74 (18%) patients experienced both events during treatment, 22 (30%) experienced at least one adverse event of alopecia and 20 (27%) experienced at least one event of hair colour change. All cases were grade 1 and did not require dose interruption or dose reduction.

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 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 tumour cells.

Pharmacodynamics

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

SPRINT

The efficacy of Koselugo was evaluated in an open-label, multi-centre, single-arm study [SPRINT Phase II Stratum 1 (NCT01362803)] of 50 paediatric patients with 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 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 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 (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 tumor 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 per Response Evaluation in

Neurofibromatosis and Schwannomatosis (REiNS) criteria. Tumor 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).
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 endpoint, ORR was 66% (95% CI, 51.2 – 78.8). Of the 66% of patients who experienced a response, all of these patients had a partial response, no patients experienced a complete response. An independent centralized review of tumor response per 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%).

Temporary authorisation
The medicinal product Koselugo has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

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

Absorption

In healthy adult subjects, the mean absolute oral bioavailability of selumetinib was 62%.
Following oral dosing, selumetinib is rapidly absorbed, producing peak steady state plasma concentrations (T_{max}) between 1-1.5 hours post-dose.
Effect of food
In separate clinical studies, in healthy adult subjects at a dose of 75 mg, co-administration of selumetinib with a high-fat meal resulted in a mean decrease in C_{max} of 50%, compared to fasting

administration. Selumetinib mean AUC was reduced by 16%, and the time to reach maximum concentration (T_{max}) was delayed by approximately 1.5 hours (see section *Dosage/Administration*). In healthy adult subjects at a dose of 50 mg, co-administration of selumetinib with a low-fat meal resulted in 60% lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 38%, and the time to reach maximum concentration (T_{max}) was delayed by approximately 0.9 hours (see section *Dosage/Administration*).

Distribution

The mean apparent volume of distribution at steady state of selumetinib across 20 to 30 mg/m^2 ranged from 78 to 171 L in paediatric patients, indicating moderate distribution into tissue.
In vitro plasma protein binding is 98.4% in humans. Selumetinib mostly binds to serum albumin (96.1%) than α-1 acid glycoprotein (<35%).

Metabolism

In vitro, selumetinib undergoes Phase 1 metabolic reactions including oxidation of the side chain, N-demethylation, and loss of the side chain to form amide and acid metabolites. CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. *In vitro* studies indicate that selumetinib also undergoes direct Phase 2 metabolic reactions to form glucuronide conjugates principally involving the enzymes UGT1A1 and UGT1A3. Glucuronidation is a significant route of elimination for selumetinib Phase 1 metabolites involving several UGT isoforms. It is estimated that 56% of the observed intrinsic clearance of selumetinib could 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 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.

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 parent) was found in urine by 9 days of sample collection.

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

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 but is unlikely to be subjected to clinically relevant drug interactions 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 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 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 *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 paediatric Asian patients, however, these patients should be closely monitored for adverse events.

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 were in the skin, scabs associated with microscopic erosions and ulceration in rats at a free exposure similar to the clinical exposure (free AUC) at the MRHD; inflammatory and ulcerative GI tract findings in mice associated with secondary changes in the liver and lymphoreticular system at free exposures approximately 28 times the clinical free exposure at the MRHD; and growth plate (physeal) dysplasia 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 physeal 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 hemorrhage 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.
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 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 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 foetuses 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-fold human free exposure at the MRHD).

Embryofoetal toxicity

In embryofoetal development studies in mice, selumetinib caused a reduction in the number of live foetuses due to an increase in post-implantation loss, a reduction in mean foetal and litter weights, 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-fold the clinical exposure at MRHD based on free AUC and indicate that selumetinib may have potential to cause defects in the foetus.

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 maternal concentration (C_{max}) 0.4-fold below the mean free clinical concentration at 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 ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging to protect the contents from light and moisture.
Do not remove desiccant.
Keep out of the reach of children.

Authorisation number

67410 (Swissmedic)

Packs

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

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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