Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Koselugo 10 mg Hard Capsules
Koselugo 25 mg Hard Capsules

(selumetinib hydrogen sulfate)

(PLGB 17901/0356-0357)

AstraZeneca UK Limited

LAY SUMMARY

Koselugo 10 mg Hard Capsules
Koselugo 25 mg Hard Capsules
(selumetinib hydrogen sulfate)

This is a summary of the Public Assessment Report (PAR) for Koselugo 10 mg and 25 mg Hard Capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

This product will be referred to as Koselugo in this lay summary for ease of reading.

For practical information about using Koselugo, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Koselugo and what is it used for?
These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 17 June 2021, (EMEA/H/C/005244) in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that these medicines are suitable for treating the specified indications.

Koselugo is used to treat children aged 3 years and above with plexiform neurofibromas that cannot be completely removed by surgery. These tumours are caused by a genetic condition called neurofibromatosis type 1 (NF1).

How does Koselugo work?
Koselugo contains the active substance selumetinib, which is a type of medicine called a mitogen-activated protein kinase (MEK) inhibitor. It works by blocking certain proteins involved in the growth of tumour cells. Koselugo is expected to shrink tumours that grow along nerves, called plexiform neurofibromas..

How is Koselugo used?
The pharmaceutical form of these medicines is hard capsules and the route of administration is oral (taken by mouth).

How much to take
The patient's doctor will work out the correct dose for their patient based on the patient's height and weight. The doctor will tell their patient how many capsules of Koselugo to take. The patient's doctor may prescribe a lower dose if the patient has problems with their liver (hepatic impairment).

The doctor may reduce their patient's dose if the patient has certain side effects while they are taking Koselugo or the doctor may interrupt treatment or stop it permanently.

How to take
• Take Koselugo twice a day, about 12 hours apart.
• Take the capsules on an empty stomach. This means that:
  - the patient must wait at least 2 hours before taking Koselugo after eating and
  - after taking Koselugo the patient must wait at least 1 hour before they eat.
• Swallow the capsules whole with water.
• Do not chew, dissolve, or open the capsules.
• If the patient has, or thinks they might have difficulty swallowing capsules whole, they should talk to their doctor before starting treatment.

The patient should not drink grapefruit juice while they are taking Koselugo because, it can affect the way the medicine works.

If the patient is sick
If the patient is sick (vomit) at any time after taking Koselugo, they should not take an extra dose. The patient should take the next dose at the normal time.

For further information on how Koselugo is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Koselugo have been shown in studies?
An ongoing trial (SPRINT Phase II trial) showed that Koselugo was effective at reducing the size of inoperable plexiform neurofibromas in paediatric patients aged 3 years and above with neurofibromatosis type 1. Beyond the duration of the follow-up (about 2 years), the Company will submit safety and efficacy data from the trial as one of the requirements of the 'conditional' approval.

What are the possible side effects of Koselugo?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Koselugo approved?
It was concluded that Koselugo has been shown to be effective at reducing the size of plexiform neurofibromas that cannot be completely removed by surgery in paediatric patients aged 3 years and above with neurofibromatosis type 1.

MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

Koselugo has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

Koselugo has been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Koselugo?
A Risk Management Plan (RMP) has been developed to ensure that Koselugo is used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Koselugo
Marketing Authorisations were granted in Great Britain on 09 August 2021.

The full PAR for Koselugo follows this summary.

This summary was last updated in October 2021.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Koselugo 10 mg and 25 mg Hard Capsules (PLGB 17901/0356-0357) could be approved.

Koselugo 10 mg and 25 mg Hard Capsules, as monotherapy, are indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

The name of the active substance, selumetinib, is a potent, selective, oral, inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) that is not competitive with respect to adenosine triphosphate. MEK1/2 are critical components of the RAS regulated, RAF-MEK-ERK pathway which is frequently activated in human cancer. Selumetinib blocks MEK activity and inhibits growth of RAF-MEK-ERK pathway activated cell lines. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 17 June 2021, (EMEA/H/C/005244), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 50 of the Human Medicines Regulations 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

Koselugo 10 mg and 25 mg Hard Capsules have been authorised as Conditional Marketing Authorisations (CMAs). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Koselugo 10 mg and 25 mg Hard Capsules. The CMAs for Koselugo 10 mg and 25 mg Hard Capsules, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

These applications were evaluated for fulfilment of orphan designation criteria and were considered by the Commission on Human Medicines (CHM) on 27 May 2021. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

In line with the legal requirements for children's medicines, the applications included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) P/0279/2019.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations were granted on 09 August 2021.

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of Marketing Authorisations is recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of Marketing Authorisations is recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of Marketing Authorisations is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

Koselugo 10 mg and 25 mg Hard Capsules have been authorised with Conditional Marketing Authorisations (CMAs). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

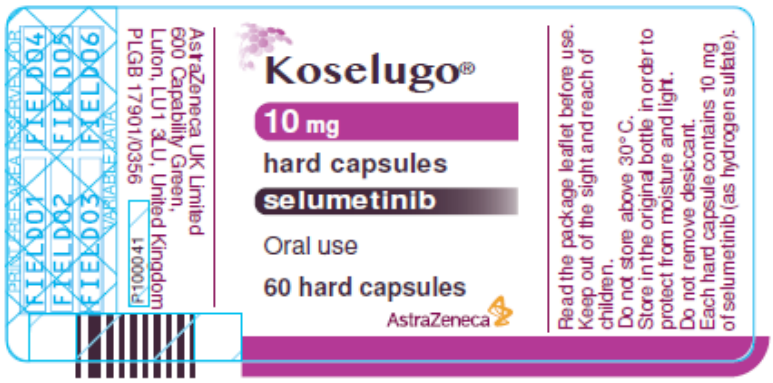
Description	**Due date**
In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above, the applicant will submit the results from a longer follow-up of patients from study SPRINT Phase II Stratum 1 with a data cut-off of 31 March 2021.	The clinical study report will be submitted by 31/03/2022
In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above, the applicant will submit the results from a longer follow-up of patients from study SPRINT Phase I with a data cut-off of 27 February 2021.	The clinical study report will be submitted by 31/03/2022
Non-interventional post-authorisation safety study (PASS): in order to confirm the long-term safety of selumetinib in the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above, the applicant will conduct and submit the results of a non-interventional PASS in patients with NF1 who have been prescribed at least one dose of selumetinib and who are aged 3 to ≤18 years at the start of selumetinib treatment. A cohort of patients aged ≥8 years old (and prior to attainment of Tanner Stage V [sexual maturity rating]) will be followed prospectively. The protocol is to be submitted within 3 months of authorisation and the final report is estimated as Q4 2027.	Due date is 31/12/2027.

The Summaries of Product Characteristics (SmPCs), PIL and labelling are satisfactory.

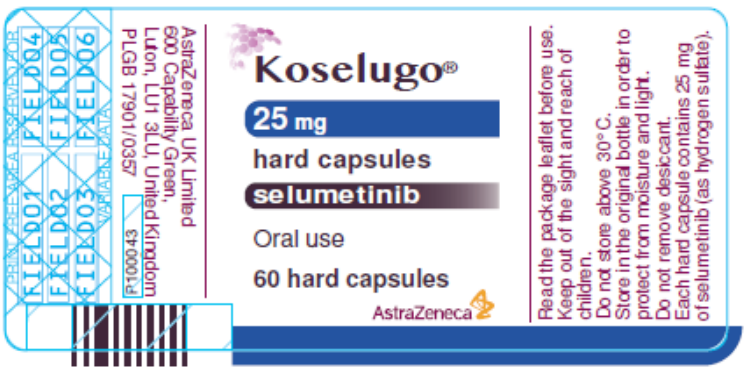
In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of GB licensing are provided below.

Koselugo 10 mg hard capsules



Koselugo 25 mg hard capsules



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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

Annex 1
Summary of fulfilment of the criteria for orphan drug designation

Products: Koselugo 10 mg and 25 mg Hard Capsules
Active substance: Selumetinib hydrogen sulfate
Orphan Designation Numbers: PLGB 17901/0356-0357/OD1

Background:
These applications were evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered fulfilled.

Evaluation:
Orphan condition
The orphan condition is Neurofibromatosis type 1 (NF1). This is acceptable and in line with the guidance on what constitutes a valid condition.

Neurofibromatosis type 1 (NF1) is an autosomal dominant clinically heterogeneous neurocutaneous genetic disorder characterised by café-au-lait spots, iris Lisch nodules, axillary and inguinal freckling, and multiple neurofibromas. This is a progressive multi-system disorder and there is no approved therapy for the treatment of NF1.

Orphan indication
The orphan indication is:

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

Life threatening/debilitating condition
The condition is life-threatening or seriously debilitating. NF1 is a complex disorder with a lifelong risk of debilitating and potentially life-threatening complications. The most common characteristic are neurofibromas which, although benign tumours, can be disfiguring and associated with pain, depending on the anatomical location. Plexiform neurofibromas (PNs) may be life threatening as some PNs cannot be surgically removed without risk for substantial morbidity due to encasement of, or close proximity to vital structures, or the invasiveness or high vascularity of the PNs. The cumulative risk of malignancy in individuals with NF1 is increased, relative to the general population, with a 50-fold increased risk for high-grade tumours. Life expectancy is reduced by 8 to 15 years relative to the general population, with malignancy constituting the major reason for death prior to the age of 30.

Optic pathway gliomas (OPGs) occur in 15–20% of children with NF1 and usually are identified within the first decade of life. Most have an indolent course and do not require therapy; however, a subset of children with NF1 have low grade glioma (LGG) in the optic chiasmal/hypothalamic region, posterior optic tract, optic nerve, and other locations that progress and become symptomatic, requiring initiation of therapy.

The risk of malignancy is increased by 2 to 5-fold in individuals with NF1, relative to the general population, with a 50-fold increased risk for high-grade tumours. Individuals with NF1 have high risk of developing malignant brain tumours (~40-fold increased risk of high-grade glioma), endocrine cancers (>74-fold increased risk for adrenal cancer) and connective

tissue malignancies (>1,000-fold increased risk for malignant peripheral nerve sheath tumour). Life expectancy is reduced by 8 to 15 years relative to the general population, with malignancy constituting the major reason for death prior to the age of 30.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects less than 5 in 10,000 in GB. The point prevalence is estimated to be between 2 in 10,000 and 3 in 10,000. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of treatment
There is no authorised or unauthorised effective and global (available for all patients) standard of care for either adults or paediatrics. The current management strategy uses a multi-disciplinary approach to the treatment of NF1-related conditions with early detection and symptom management being key. No satisfactory treatments are authorised in the EU for this condition. Treatment mainly involves managing the symptoms of the disease. Surgery is commonly used to remove the tumours.

At each age, there are different problems that may develop, necessitating a focused and age-appropriate evaluation for children and adults. The mainstay of the management of NF1 is anticipatory guidance. Genetic counselling as well as the evaluation of first-degree family members is considered important. At every visit, monitoring for macrocephaly, growth failure, precocious puberty, hypertension, developmental delays, learning disabilities and scoliosis is recommended.

There are two national disease management guidelines for NF1 available in Europe: from the UK (Neuro Foundation (UK) Guidelines 2016) and France (French National Protocol for NF1 2016). Although these guidelines do suggest certain strategies for the treatment of some NF1-related malignancies based on somewhat limited evidence, they mainly describe how to diagnose NF1 and manage patients.

Surveillance neuroimaging in asymptomatic patients as a screening test for optic pathway gliomas (OPGs) is not recommended. However, prompt brain MRI is warranted by the development of visual loss, or other concerning symptoms such as precocious puberty. Annual ophthalmologic examinations by an ophthalmologist expert in NF1 are recommended until the age of 12 years to screen for optic pathway gliomas.

If an optic pathway glioma is identified on neuroimaging, repeat ophthalmologic examinations are recommended every 3 months for the first year. A two-line decrement in visual acuity prompts treatment, typically with carboplatin and vincristine. Surgery has limited therapeutic value in tumours intrinsic to the optic pathway and can produce further visual deficit. Therefore, it is primarily limited to those patients with pre-existing loss of vision, bulky disease and proptosis and/ or at relapse after initial treatment Radiation is not employed, because of increased risk for secondary high-grade central nervous system (CNS) gliomas and concerns about vascular damage with subsequent strokes.

Cutaneous neurofibromas may be treated with surgery and, occasionally, with CO_2 laser therapy or electrodessication. In certain instances, plexiform neurofibromas may benefit from surgical debulking, although there is a high risk of iatrogenic injury to associated nerves and surrounding soft tissue, as well as haemorrhage due to the significant degree of tumour vascularity. Currently, there are several chemotherapeutic trials underway aimed at halting

plexiform neurofibroma growth, however no agent has demonstrated clinically significant benefit as yet.

The management of malignant peripheral nerve sheath tumours (MPNSTs) involves the coordinated involvement of surgical oncologists, medical oncologists, and radiation oncologists. Small biopsies are inaccurate for diagnosing MPNST; for this reason, when clinical symptoms or fluorodeoxyglucose positron emission tomography (18-FDG-PET) imaging suggests the possibility of malignancy, open biopsy or wide surgical excision is recommended. The aim of treatment is complete excision of MPNSTs with tumour-free margins. In some cases, isolated lung metastases can also be managed surgically. Neoadjuvant chemotherapy (administration of chemotherapy before surgery) with an anthracycline (such as doxorubicin) and ifosfamide can be used to reduce the size of tumours and facilitate surgical removal. While radiation therapy delays the time to tumour recurrence, it does not improve long-term survival. Chemotherapy for MPNST has sometimes entailed the use of doxorubicin and ifosfamide; however, there is no current effective chemotherapy for these cancers. In addition to local recurrence, these malignancies are prone to metastasis to the lungs and bone. Even with treatment, most patients with NF1-associated MPNST die within 5 years of diagnosis. MPNSTs are often refractory to treatment despite multiple clinical trials with various regimens.

Treatment of gastrointestinal stromal tumours (GISTs) associated with NF1 is complete surgical resection; however, individuals with higher-risk lesions (for example, those of larger size or with a higher mitotic index) might be treated with adjuvant imatinib. Imatinib (Glivec) is a tyrosine kinase inhibitor that is approved in the EU/UK for the treatments of GISTs. Imatinib selectively inhibits the KIT-associated tyrosine kinase 85% of GISTs are driven by oncogenic mutations in either of 2 receptor tyrosine kinases: KIT or PDGFRα; however GIST associated with NF1 do not typically harbour mutations in KIT and PDGFRA, which are more commonly associated with sporadic GISTs, and also tend to occur at an earlier age, are located more distally in the gastrointestinal tract and have lower mitotic indices than sporadic tumours.

Justification as to why other methods are not satisfactory
The treatments currently used in NF1 symptom management are unsatisfactory as they are not specifically targeted at the pathway involved in the development of NF1, have limited efficacy and may be associated with significant toxicities (e.g., in many of the chemotherapy agents used for the treatment of malignancies).

Justification of significant benefit
It is agreed that there are no approved treatments for the condition and indication proposed. However, several agents are used off-label in the management of subjects with NF1.

The data supporting the clinical efficacy of selumetinib in the proposed indication is based on the SPRINT study, an open-label, multi-centre, single-arm study phase II study (stratum 1) of 50 paediatric patients with NF1and inoperable PN that caused significant morbidity. The results showed an objective response rate of 66% (33 patients; 95%CI: 51.2-78.8). There were no complete responses. 27 patients (82% of the responders) had a duration of response ≥12 months.

The above results are supportive of a benefit in the proposed indication for selumetinib.

Conclusion on acceptability of orphan designation
The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 08 August 2021