Drug Monograph

Drug Name: **Koselugo™ (selumetinib) Capsule**
Drug Class: **Antineoplastic Agent, MEK Inhibitor**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Koselugo is available in 10 mg and 25 mg capsules of selumetinib.
Distributed by:	AstraZeneca PLC, Wilmington, DE 19803
Summary of Findings:	The efficacy of Koselugo was evaluated in SPRINT Phase II Stratum 1, an open-label, multicenter, single arm trial. A total of 50 pediatric patients with neurofibromatosis type 1 (NF1) with inoperable plexiform neurofibromas (PN) received Koselugo. Patient median age was 10.2 years, and all patients were required to have significant morbidity related to the target PN, including disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction. The primary efficacy outcome was measured as overall response rate (ORR), defined as the total patients that achieved a complete response (complete disappearance of the target lesion) or a partial response (≥20% reduction in PN volume within 3-6 months). Out of 50 patients, 33 (66%) achieved a partial response while 0 patients achieved a complete response, giving an overall response rate of 66% (95% CI: 51,79). The median time to onset of response was 7.2 months and 82% of patients that achieved ORR had a duration of response that lasted ≥12 months.
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Neurofibromatosis (NF) is a genetic disorder characterized by tumor growth in the nervous system, called neurofibromas. There are three distinct types of neurofibromatosis; type 1, type 2, and schwannomatosis. An estimated 100,000 Americans are currently diagnosed with NF. The majority of the tumors that develop are benign, but some may occasionally become cancerous. The exact reason these tumors grow is still not completely understood, but it appears to be related to genetic mutations leading to a loss of production or reduction of function of proteins involved in suppression of cell growth in the nervous system.

NF1 is the most common form of neurofibromatosis, occurring in 1 in 3,000 – 4,000 Americans. The most common signs and symptoms of NF1 are:

- Several light brown spots, called Café-au-lait spots, on the skin larger than 5 millimeters in diameter in children or 15 millimeters across in adolescents and adults.
- Multiple neurofibromas, or one plexiform neurofibroma (a neurofibroma involving several nerves).
- Multiple growths on the iris of the eye, called Lisch nodules or iris hamartomas.
- Abnormal development of the spine, such as scoliosis.
- Other less common signs and symptoms include abnormal head shape and size, hydrocephalus, headache, epilepsy, cardiovascular complications, and learning disabilities.

Symptoms of NF1 are evident at birth or shortly afterwards. NF1 is a progressive disorder where most symptoms worsen over time. Most individuals only develop mild to moderate symptoms but life expectancy is anticipated to be reduced by 8-15 years.

Dosage Form [3]

Koselugo is available as 10 mg and 25 mg capsules of selumetinib.

Manufacturer [3]

Manufactured by AstraZeneca PLC, Wilmington, DE 19803

Indication(s) [3]

Koselugo is indicated for the treatment of pediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN.

Clinical Efficacy [3,4,5,6] (mechanism of action/pharmacology, comparative efficacy)

Selumetinib is a selective inhibitor of mitogen-activated protein kinase 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway and regulate ERK by phosphorylation. MEK and ERK play critical roles in the RAS-regulated RAF-MEK-ERK pathway. This pathway is often activated in different types of cancers.

In genetically modified mouse models with NF1, oral dosing of selumetinib inhibited ERK phosphorylation and reduced the number, volume, and proliferation of neurofibromas.

Pharmacokinetics:

Absorption	Time to peak: 1-1.5 hours.
Metabolism	• Selumetinib is metabolized primarily by CYP3A4, with other CYP enzymes playing a lesser role in its metabolism. • N-desmethyl selumetinib, the active metabolite, is generated by CYP2C19 and CYP1A2. N-desmethyl selumetinib represents less than 10% of plasma levels but is approximately 3-5 times more potent than the parent compound.
Excretion	Feces: 59% (19% unchanged) Urine: 33% (<1% as parent)
Half-life	6.2 hours

Clinical Trials Experience:
"Selumetinib in Children with Inoperable Plexiform Neurofibromas." SPRINT trial.

STUDY 1 DESIGN	Non-randomised, open-label, multicenter, single arm phase 2 trial.
INCLUSION CRITERIA	• Children 2-18 years of age • Clinical diagnosis of NF1 • Inoperable, measurable plexiform neurofibromas • Significant morbidity related to the target PN • Able to swallow intact capsules
EXCLUSION CRITERIA	• Pregnant or breast-feeding females • Patients who anticipate the need for surgical intervention within the first 3 cycles (3 months) • An investigational agent within the past 30 days • Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, immunotherapy, or biologic therapy • Evidence of cancer requiring treatment with chemotherapy or radiation therapy • Clinically significant, uncontrolled, unrelated systemic illness • Inability to swallow capsules, since capsules cannot be crushed or broken • Inability to undergo MRI and/or contraindications for MRI examinations following the MRI protocol, including prosthesis, orthopedic, or dental braces that would interfere with volumetric analysis of target PN on MRI • Prior treatment with selumetinib • Presence of ≥ grade 1 cataract, as cataract was observed in

	preclinical studies with selumetinib • Supplementation with vitamin E greater than 100% of the daily recommended dose
TREATMENT REGIMEN	Selumetinib was administered at the recommended phase 2 dose of 25 mg per square meter of body-surface area approximately every 12 hours in 28-day cycles on a continues dosing schedule. Patients received a median of 36 cycles. N=50.
RESULTS	• The major efficacy outcome measure was a partial response defined as a target neurofibroma volume decrease from baseline of at least 20% • A durable partial response was defined as a partial response lasting for at least 12 cycles (approximately 1 year) • Results were compared to age-matched patients in the NCI natural-history study of neurofibromatosis type 1 who did not receive selumetinib • 33 of the 50 patients achieved a partial response for an ORR of 66% (95% CI: 51, 79), and 27 (82%) achieved a durable response. The median time to onset of response was 7.2 months • For comparison, 73 of 93 (78%) of age-matched controls in the NCI study of neurofibromatosis type 1 had a neurofibroma volume increase of at least 20% over the same period of time as this treatment trial (3.2 years). No patients had a tumor shrinkage greater than 20%
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3]

- None

Warnings and Precautions [3,4]

- Cardiomyopathy: Before initiation, an assessment of ejection fraction should be completed. A reassessment should occur every 3 months during the first year, then every 6 months thereafter.
- Ocular toxicity: Ophthalmic assessment should be conducted prior to initiating treatment and at regular intervals during treatment.
- Gastrointestinal toxicity: Patients are advised to start an anti-diarrheal agent and increase fluid intake immediately after the first episode of loose stool.
- Skin toxicity: Monitor for severe skin rash.
- Increased CPK and rhabdomyolysis: Obtain serum CPK prior to initiation and periodically during treatment.
- Increased Vitamin E levels and risk of bleeding: Koselugo capsules contain vitamin E and daily intake that exceeds recommended levels of vitamin E may increase the risk of bleeding.

Adverse Effects [3,5]

Most common, ≥ 20 %	(n = 50) %
Vomiting	82
Rash	80
Abdominal pain	76
Diarrhea	70
Nausea	66
Dry skin	60
Musculoskeletal pain	58
Fatigue	56
Pyrexia	56
Stomatitis	50
Rach acneiform	50
Paronychia	48
Headache	48
Pruritus	46
Dermatitis	36
Constipation	34
Hair changes	32
Epistaxis	28
Hematuria	22
Proteinuria	22
Decreased appetite	22
Decreased ejection fraction	22
Edema	20
Sinus tachycardia	20
Skin infection	20

Drug Interactions [3,4]

- Strong or moderate CYP3A4 inhibitors
- Strong or moderate CYP3A4 inducers
- Fluconazole
- Vitamin E

Dosage and Administration [3]

- The recommended dosage of Koselugo is 25 mg/m^2 orally twice daily (approximately every 12 hours).
- Koselugo should be taken on an empty stomach and food should not be consumed for at least 2 hours before or 1 hour after each dose.
- Swallow Koselugo capsule whole with water.
- Do not take a missed dose of Koselugo unless it is more than 6 hours until the next scheduled dose.
- If vomiting occurs after Koselugo administration, do not take an additional dose, but continue with the next scheduled dose.

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

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.

Recommended Dosage Modifications for Koselugo for Adverse Reactions	
Severity of Adverse Reaction	**Recommended Dosage Modifications for Koselugo**
Cardiomyopathy	
• Asymptomatic decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline and less than lower level of normal	Withhold until resolution. Resume at reduced dose.
• Symptomatic decreased LVEF • Grade 3 or 4 decreased LVEF	Permanently discontinue.
Ocular Toxicity	
• Retinal Pigment Epithelial Detachment (RPED)	Withhold until resolution. Resume at reduced dose.
• Retinal Vein occlusion (RVO)	Permanently discontinue
Gastrointestinal Toxicity	
• 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	
• Grade 3 or 4	Withhold until improvement. Resume at reduced dose.
Increased Creatinine Phosphokinase (CPK)	

• 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	
• Intolerable Grade 2 • Grade 3	Withhold Koselugo until improved 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.

Cost

Generic Name	Brand Name	Distributor	Dose	Cost** /Month
Selumetinib	Koselugo	AstraZeneca	25 mg/m^2 orally twice daily (approximately every 12 hours)	$6,498.00 - $21,810

** Wholesale Acquisition Cost

Conclusion

Koselugo is the first therapeutic treatment approved by the FDA for children 2 years of age or older for NF1, a genetic disorder of the nervous system causing uncontrolled tumor growth on nerves. The efficacy for Koselugo was established in a non-randomised, open-label, multicenter, single arm phase 2 trial in 50 children 2-18 years old. 33 of the 50 patients achieved a partial response of ≥20% shrinking in tumor volume during the trial, with 27 achieving a partial response of longer than 12 months. In comparison, 73 of 93 age-matched controls had neurofibroma volume increase of at least 20% over the same time period, with no patient having a shrinkage of ≥20%. There are several common adverse reactions from Koselugo, including vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus being experienced by at least 40% of patients in the trial.

Recommendation

The MO HealthNet Division recommends adding this drug to the current Rare Disease clinical edit.

References

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