BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Koselugo (selumetinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Pediatrician, or Geneticist

  2. Individual is 2 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. Neurofibromatosis type 1 (NF1) who has symptomatic, inoperable plexiform neurofibromas (PN) (See Definitions section for explanations for symptomatic and inoperable)

     b. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Negative pregnancy test in a woman of child bearing potential
     b. Ejection fraction is above institutional lower limit of normal
     c. Ophthalmic assessment

  5. Individual does not have severe hepatic impairment (Child-Pugh Class C)

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Koselugo (selumetinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Pediatrician, or Geneticist

  2. Individual's condition responded while on therapy
     a. Response is defined as **TWO** of the following:
        i. Disappearance of the target PN (i.e., the PN that caused relevant clinical symptoms or complications)
        ii. At least a 20% reduction in PN volume confirmed at a subsequent tumor assessment
        iii. No evidence of disease progression

  3. Individual has been adherent with the medication

  4. Individual has not developed any significant adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:

i. Symptomatic decrease or severe or life threatening decrease in LVEF
ii. New or worsening visual changes
iii. Retinal vein occlusion (RVO)
iv. Life threatening diarrhea or severe diarrhea that does not improve in 3 days of dose modification
v. Colitis
vi. Life threatening increase in CPK or any increase in CPK with myalgia that does not improve in 3 weeks of dose modification
vii. Rhabdomyolysis

5. Individual does not have severe hepatic impairment (Child-Pugh Class C)

6. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Koselugo (selumetinib) is a selective mitogen-activated extracellular kinase (MEK) inhibitor indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

Selumetinib is an inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Both MEK and ERK are critical components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. Selumetinib inhibits ERK phosphorylation, and reduces neurofibroma numbers, volume, and proliferation.

Neurofibromatosis type 1 (NF1) is a condition characterized by changes in skin pigmentation and the growth of tumors along nerves in the skin, brain, and other areas of the body. The most common form is neurofibromatosis type 1 (NF1, 96%), followed by neurofibromatosis type 2 (NF2, 3%), and schwannomatosis (SWN or sometimes referred to as NF type 3).

NF1, is also known as von Recklinghausen disease or peripheral neurofibromatosis, is an autosomal dominant tumor syndrome characterized by the development of multiple neurofibromas of the peripheral nerves. Malignancies associated with NF1 include malignant peripheral nerve sheath tumors, gliomas, leukemia,

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pheochromocytomas, gastrointestinal (GI) stromal tumors, and others. NF1 is caused by a mutation in the neurofibromin tumor suppressor gene located on chromosome 17.

NF1, NF2, and SWN are tumor suppressor syndromes caused by germline mutations in a tumor suppressor gene (TSG). TSG encode proteins that are responsible for regulating cell division. Tumor suppressor syndromes are due to mutations in a TSG, which results in dysregulation of pathways responsible for cell division and proliferation.

The hallmarks of NF1 are multiple café-au-lait macules and associate cutaneous neurofibromas. Cutaneous and subcutaneous neurofibromas can cause significant deformity and discomfort. The major peripheral nerve tumor impacting patients with NF1 is the plexiform neurofibroma (pNF). The tumors composed of a variety of cell types including neuronal axons, Schwann cells, fibroblasts, mast cells, macrophages, perineural cells, and extracellular matrix; they can be confined to diffuse. They occur in the trunk, head and neck and the extremities. The pNFs can be a source of neuropathic pain and neurologic dysfunction.

Key differences between NF1 and NF2 include: a) Café-au-lait macules can be seen but are much less frequent in NF2, and Lisch nodes are not seen; b) The schwannomas associated with NF2 do not undergo malignant transformation into a malignant peripheral nerve sheath tumor (MPNST); c) The spinal root tumors that are seen with both NF2 and NF1 are schwannomas in NF2 and neurofibromas in NF1; d) NF2 is not associated with the cognitive impairment that is often seen with NF1; and e) NF2 is associated with a very high prevalence of bilateral acoustic schwannomas and meningiomas.

Definitions:

Symptomatic define as disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction

Inoperable defined as a plexiform neurofibromas (PN) that could not be completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN

Diagnostic Criteria of NF1:

Presence of ≥ 2 of the following:
At least 6 café-au-lait macules (> 5 mm in diameter in prepubertal individuals and > 15 mm in postpubertal individuals
Freckling in axillary or inguinal regions
Optic glioma
At least 2 Lisch nodules (iris hamartomas)
At least 2 neurofibromas of any type or 1 plexiform neurofibroma
A distinctive osseous lesion (sphenoid dysplasia or tibial pseudarthrosis)
A first degree relative with NF 1 (parent, sibling, or offspring)

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Activities of daily living (ADL):

Instrumental ADL:

Prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.

Self-care ADL:

Bathe, dress and undress, feed self, use the toilet, take medications, not bedridden

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

The Child-Pugh classification system:

The Child-Pugh classification is a scoring system used to determine the prognosis of individuals with cirrhosis. Scoring is based upon several factors: albumin, ascites, total bilirubin, prothrombin time, and encephalopathy, as follows:

	Score: 1 point	Score: 2 points	Score: 3 points
Serum Albumin (g/dL)	> 3.5	3.0 - 3.5	< 3.0
Serum Bilirubin (mg/dL)	< 2.0	2.0 - 3.0	> 3.0
Prothrombin time (seconds)	1 - 4	4 - 6	> 6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:

- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score > 9: Decompensated disease

Resources:

Koselugo (selumetinib) product information, revised by AstraZenica Pharmaceuticals, LP 12-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 12, 2022.

Korf BR, Lobbous M, Metrock LK. Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis. In: UpToDate, Patterson MC, Firth HV, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 26, 2022. Accessed May12, 2022.

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Evans DG. Neurofibromatosis type 2. In: UpToDate, Loeffler JS, Wen PY, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated November 05, 2021. Accessed May 12, 2022.

Yohay K, Bergner A. Schwannomatosis. In: UpToDate, Firth HV, Shefner JM, Wen PY, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated May 18, 2021. Accessed May 12, 2022.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.