PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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ZOKINVY (lonafarnib)

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.**

ZOKINVY (lonafarnib)

Criteria:

- **Criteria for initial therapy:** Zokinvy (lonafarnib) 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 a Pediatrician, Cardiologist, Endocrinologist, or Geneticist

  2. Individual is 12 months of age or older with a body surface area of 0.39 m^2 or more

  3. A confirmed diagnosis of **ONE** of the following:
     a. Hutchinson-Gilford Progeria Syndrome with a confirmed mutational analysis showing G608G mutation in the lamin A gene
     b. Processing-deficient Progeroid Laminopathies with either:
        i. Heterozygous *LMNA* mutation with progerin-like protein accumulation
        ii. Homozygous or compound heterozygous *ZMPSTE24* mutations

  4. Individual does not have other progeroid syndromes or processing-proficient Progeroid Laminopathies

  5. There are **NO** FDA-label contraindications, such as:
     a. Concurrent use with strong or moderate CYP3A4 inhibitors or inducers (See Definitions section)
     b. Concurrent use with midazolam
     c. Concurrent use with lovastatin, simvastatin, and atorvastatin

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Zokinvy (lonafarnib) 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 a Pediatrician, Cardiologist, Endocrinologist, or Geneticist

  2. Individual's condition has not worsened while on therapy
     a. Worsening is defined as:
        i. Documented evidence of lack of efficacy, disease stability and/or improvement
        ii. Documented evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
     a. Contraindications as listed in the criteria for initial therapy
     b. Significant adverse effect such as:

i. Myelosuppression such as reductions in absolute neutrophils, white blood cells, lymphocytes, hemoglobin, or hematocrit
ii. Increased liver enzymes (aspartate aminotransferase or alanine aminotransferase)
iii. Nephrotoxicity
iv. Visual changes

5. 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:

Zokinvy (lonafarnib) is a farnesyltransferase inhibitor indicated in patients 12 months of age and older (with a body surface area of 0.39 m^2 and above), to reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS), for treatment of processing-deficient Progeroid Laminopathies with either a heterozygous lamin A/C *(LMNA)* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous zinc metallopeptidase STE24 *(ZMPSTE24)* mutations. Zokinvy (lonafarnib) is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Based upon the mechanism of action of lonafarnib, it would not be expected to be effective in these populations.

The *LMNA* gene on chromosome 1 gene encodes for prelamin A that is ultimately converted to lamin A (LA). LA is an important structural component of the nuclear lamina, a dynamic molecular interface located inside the inner nuclear membrane that stabilizes the nuclear membrane. Pathogenic variants of *LMNA* cause a group of degenerative disorders known as laminopathies. The mutation seen in HGPS causes a mutant or abnormal lamin A protein called progerin that has an internal amino acid deletion that removes the recognition site that normally leads to proteolytic cleavage. The deletion results in permanent farnesylation of the progerin protein causing it to remain anchored to the nuclear envelop. The permanently farnesylated progerin disrupts the normal organization of the nuclear lamina. Lonafarnib inhibits farnesyltransferase to prevent farnesylation and stops the subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane.

The *ZMPSTE24* gene encodes for a metallopeptidase that is also involved in the processing of lamin A. Defects in the *ZMPSTE24* gene lead to similar laminopathies defects seen in lamin A, because the latter is a substrate for the former. Mutations that eliminate the *ZMPSTE24* cleavage site in prelamin A causes a progeroid disorder.

HGPS, or Classic Progeria, is a rare, fatal, segmental premature aging syndrome. Processing-deficient Progeroid Laminopathies, which are rarer than progeria, are often grouped together with progeria based on common disease pathology and similar clinical manifestations. The diagnosis of HGPS is established based upon the

presence of the clinical features and the identification by genetic testing of the known causative pathogenic variant in the *LMNA* gene (c.1824C>T[p.Gly608Gly] or G608G).

Progeria is characterized by extreme short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, tightness or bulging of the skin, decreased joint mobility, hip dislocation, osteolysis, stroke, and facial features that resemble aged persons. This multisystem disorder causes failure to thrive, accelerated atherosclerosis, and cardiovascular disease, leading to early death. HGPS is 100% fatal with death occurring at an average of 14.6 years from accelerated atherosclerosis that leads to stroke and myocardial infarction.

Definitions:

There are 5 major categories that help define *LMNA*-related disorders. The first 2 define HGPS, while the latter 3 are not considered HGPS:

- Progerin-producing classic genotype HGPS
- Progerin-producing non-classic genotype HGPS
- Non-progerin-producing Progeroid Laminopathies:
    - (1) Due to heterozygous *LMNA* pathogenic variant that does not result in progerin production;
    - (2) Due to pathogenic variants in other genes (e.g., zinc metallopeptidase STE24 [*ZMPSTE24]*)
- Non-Progeroid Laminopathies
- Non-laminopathy progeroid syndromes

The diagnosis of **classic genotype HGPS is established** in a proband with suggestive clinical findings and a heterozygous c.1824C>T pathogenic variant in *LMNA* identified on molecular genetic testing.

The diagnosis of **non-classic genotype HGPS is established** in a proband with suggestive clinical findings similar to classic genotype HGPS and an autosomal dominant progerin-producing pathogenic variant in either the exon 11 splice junction or intron 11 of *LMNA* identified on molecular genetic testing.

Strong CYP3A inhibitors:

- Atazanavir
- Clarithromycin
- Darunavir
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Telithromycin
- Tipranavir
- Others

ZOKINVY (lonafarnib)

Moderate CYP3A4 inhibitors:

- Amiodarone
- Amprenavir
- Conivaptan
- Delavirdine
- Diltiazem
- Erythromycin
- Fluconazole
- Fosamprenavir
- Miconazole
- Verapamil
- Others

Resources:

Zokinvy (lonafarnib) product information, revised by Eiger Bio Pharmaceuticals, Inc. 11-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 08, 2022.

Introne WJ, Merideth MA. Hutchinson-Gilford progeria syndrome. In: UpToDate, Hand JL, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated September 22, 2021. Accessed May 09, 2022.