ZOKINVY (LONAFARNIB) (PRIOR AUTHORIZATION REQUIRED)

X.169

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POLICY

Target Agent

Zokinvy (lonafarnib)

Objective: The intent of the lonafarnib prior authorization is to encourage appropriate use according to clinical trial data and FDA approved labeling.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    a. The patient's age is within FDA labeling for the requested indication for the requested agent; **OR**
    b. The prescriber has provided information in support of using the requested agent for the patient's age; **AND**
2. ONE of the following:
    a. BOTH of the following:
        i. The patient has a diagnosis of Hutchinson-Gilford progeria syndrome (HGPS); **AND**
        ii. Genetic testing has confirmed a pathogenic variant in the *LMNA* gene that results in production of progerin (medical record required); **OR**
    b. The patient has a processing-deficient progeroid laminopathy AND **ONE** of the following:
        i. Genetic testing has confirmed heterozygous *LMNA* mutation with progerin-like protein accumulation (medical record required); **OR**
        ii. Genetic testing has confirmed homozygous or compound heterozygous *ZMPSTE24* mutations (medical record required); **AND**
3. The patient has a body surface area (BSA) of greater than or equal to 0.39 $m^{2;}$ **AND**
4. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis; **AND**

limit; **OR**

b. ALL of the following:

i. The requested quantity (dose) is greater than the program quantity limit; **AND**

ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication; **AND**

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

Renewal Evaluation

Target Agent will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process; **AND**
2. The patient has had clinical benefit with the requested agent; **AND**
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis; **AND**
4. The patient does NOT have any FDA labeled contraindications to the requested agent; **AND**
5. ONE of the following:

a. The requested quantity (dose) does NOT exceed the program quantity limit; **OR**

b. ALL of the following:

i. The requested quantity (dose) is greater than the program quantity limit ; **AND**

ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication; **AND**

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

Dates

Original Effective
05-05-2021
Last Review
11-06-2024
Next Review
11-10-2025

and premature appearance of certain signs and symptoms of physiological aging. Major clinical features are hair loss, short stature, skin wrinkling, osteoporosis, and, usually, cardiovascular disease. The first genetically characterized group of progeroid syndromes were recessive diseases associated with mutations in genes encoding DNA repair and maintenance proteins (e.g., Werner syndrome, Bloom syndrome, Cockayne syndrome). A second group of progeroid syndromes, called progeroid laminopathies, were later identified, which are caused by mutations in *LMNA* gene that encodes A-type lamins, or mutations in *ZMPSTE24* gene that encodes the enzyme ZMPSTE24 essential for A-type lamin processing. A-type lamins compose (together with B-type lamins) the nuclear lamina, a critical meshwork of filaments at the interface between the inner nuclear membrane and chromatin. ZMPSTE24 enzyme is necessary for recognizing the farnesylated C-terminal region of prelamin A, catalyzing the proteolytic cleavage reaction to mature lamin A.[2]

Progeroid laminopathies are very rare, generally have an earlier age of onset than most other progeroid syndromes, and display more severe symptoms of accelerated aging. The most prevalent of these rare diseases, Hutchinson-Gilford progeria syndrome (HGPS), is caused by a mutation in *LMNA*, the gene coding for A-type lamins. A single base mutation (typically Gly608Gly, in "classic" HGPS) introduces an alternative splice site that produces an abnormal lamin A protein called "progerin". Progerin lacks the proteolytic cleavage site normally used to remove the farnesylated carboxy terminus from lamin A during posttranslational processing.[2,3,4,5,6,8,10,11] The progerin (permanently farnesylated mutant lamin A) accumulates inside the nucleus, unable to be released for degradation due to persistent farnesylation.[3,4,6,7,9] Disease in HGPS is produced by a dominant negative mechanism; it is the effect of progerin, *not* the diminution of lamin A, which causes the disease phenotype.[3] Emerging evidence indicates that *LMNA*-linked progerias can be further grouped into two classes: 1) the processing-deficient, early onset "typical" progerias (e.g., HGPS), and 2) the processing-proficient "atypical" progeria syndromes (APS) that are later in onset.[5] Individuals with APS show many of the clinical features of HGPS, but their cells do not accumulate prelamin A or progerin.[9]

Disease manifestations include severe failure to thrive, scleroderma-like skin, lipoatrophy, alopecia, joint contractures, skeletal dysplasia, and atherosclerosis, but intellectual development is normal.[2,4,6,8,9,10,11] Death at an average age of 13 years occurs from myocardial infarction or stroke.[4,5,6,8,10,11] Diagnosis of genotype HGPS is established with characteristic clinical features, along with identification of a heterozygous pathogenic variant in *LMNA* that results in production of progerin.[8]

Mandibuloacral dysplasia (MAD) and restrictive dermopathy (RD) are caused by extreme accumulation of lamin A precursors (aka prelamin) due to a mutation in *ZMPSTE24* which leads to complete absence of the ZMPSTE24 enzyme.[2,5,6] Because of the absence of ZMPSTE24-enzyme's processing activity, the full-length prelamin A molecules in farnesylated form accumulate in the cell.[5,7] MAD can be associated with either homozygous or compound heterozygous mutations in *LMNA* (MAD-A), or a combination of a nonsense and missense mutation in *ZMPSTE24* (MAD-

terminal phalanges and clavicles. RD is caused by *LMNA*-linked heterozygous mutations that result in truncated proteins similar to progerin that accumulate inside the nucleus.[6,11] RD can also be linked to homozygous or compound heterozygous *ZMPSTE24* mutations.[6,7,10,11] Restrictive dermopathy (RD) is a rare and extremely severe congenital genodermatosis, characterized by a tight rigid skin with erosions at flexure sites, multiple joint contractures, low bone density and pulmonary insufficiency generally leading to death in the perinatal period.[7]

Genetic testing in the United States can be achieved through the PRF (Progeria Research Foundation) Diagnostic Testing Program, provided at no cost to families. The genetic test is done by coordinating a blood sample submission by mail through home physicians, from anywhere in the world, to PRF. The PRF Diagnostic Testing Program offers genetic testing for any child suspected of having progeria, provided at no cost to families.[12]

Management is supportive and involves ensuring optimal nutrition, monitoring of disease progression, and treatment of complications as they present.[8]

Zokinvy (lonafarnib) is a farnesyltransferase inhibitor, preventing progerin farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane.[1,4] Farnesylation inhibitors are not curative, as many features of disease persist despite treatment. However, evidence suggests that survival may be improved.[3,10,11] Clinical trials have shown improved cardiovascular status of children with HGPS, a potentially important finding because failure of this organ system is the ultimate cause of mortality. A nonrandomized, clinical trial of lonafarnib in 25 children with HGPS provided some evidence of efficacy in reducing the carotid artery echodensity and improving the bone structure in these patients.[4] A subsequent, nonrandomized study evaluated the effect of oral lonafarnib on all-cause mortality in a cohort of 27 patients (median age 8.4 years) with HGPS compared with 27 matched, untreated patients. The median treatment duration was 2.2 years. During this period, the observed mortality rate was 3.7 percent among patients receiving lonafarnib versus 33.3 percent in the untreated group.[1]

Safety[1]

Zokinvy is contraindicated in patients taking:

- Strong or moderate CYP3A inhibitors or inducers
- Midazolam
- Lovastatin, simvastatin, or atorvastatin

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REVISIONS

12-06-2023

Policy reviewed at Medical Policy Committee meeting on 11/8/2023 – no changes to policy