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Reviewed: 04/09/25

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Subject: Lonafarnib (Zokinvy™)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PLs) are premature aging diseases. In HGPS, the premature aging is due to a point mutation in the lamin A/C gene (LMNA) that leads to the production and permanent farnesylation of a mutant lamin A protein called progerin. However, PLs are due to various mutations either in the LMNA gene and/or the ZMPSTE24 gene. The mutant protein produced in these conditions is distinct from progerin; however, it is also permanently farnesylated, like progerin.

The clinical manifestations of HGPS include a general failure to thrive and progressive growth retardation noticed in the first years of life. The condition is also characterized by dental abnormalities, dermatologic manifestations including a loss of adipose tissue and skin that appears abnormally aged (dry, wrinkled, and taut), and progressive musculoskeletal manifestations including osteoporosis, joint contractures, and skeletal dysplasia. Finally, the finding that is primarily responsible for the mortality of these patients is premature, widespread arteriosclerosis, which can lead to heart failure, myocardial infarction, stroke, or a transient ischemic attack. Patients with HGPS and PLs have a significantly reduced life span, with a range of approximately 8 to 21 years of age and the average age of death being 13 to 14 years. Treatment of HGPS and PLs is supportive and addresses the secondary complications associated with the disease.

Lonafarnib (Zokinvy™) was approved by the U.S. Food and Drug Administration (FDA) in November 2020 for use in patients 12 months of age and older with a body surface area of 0.39 m² and above to reduce the risk of mortality in HGPS and for the treatment of processing-deficient PLs with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. Per the FDA label, lonafarnib is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Based upon its mechanism of action, lonafarnib would not be expected to be effective in these populations.

Lonafarnib is a farnesyltransferase inhibitor that prevents farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane. It is the first disease-modifying treatment approved by the FDA for HGPS and PLs.

The efficacy of lonafarnib is based on results from 2 retrospective, observational cohort survival studies comparing patients with HGPS to those from a natural history cohort. Study 1 included 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation with progerin-like protein accumulation); 27 patients were included in the survival assessment. Patients received lonafarnib 115 mg/m² twice daily and increased to 150 mg/m² after 4 months if tolerated. Patients received lonafarnib for 24 to 40 months. The median age was 7.5 years and the BSA range was 0.38 to 0.75 m². Twenty-six of these patients entered Phase 2 of Study 1 and received lonafarnib and additional therapies for about 5 years. Study 2 included 35 treatment naive patients with HGPS. The median age was 6 years and BSA range was 0.42 to 0.9 m². The mean survival time of Hutchinson-Gilford Progeria Syndrome (HGPS) patients treated with lonafarnib was 2.8 years vs 2.6 years for untreated patients (HR for risk of death, 0.3; 95% CI, 0.1 to 0.89) through the first 3 years of follow-up, and 8 years vs 5.5 years, respectively, through the last follow-up of 11 years (HR, 0.4; 95% CI, 0.21 to 0.77).

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of lonafarnib (Zokinvy) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with either of the following – documentation from the medical record must be provided:
 - a. Hutchinson-Gilford Progeria Syndrome (HGPS)
 - b. Progeroid Laminopathies (PLs) with either:
 - i. Heterozygous LMNA mutation with progerin-like protein accumulation
 - ii. Homozygous or compound heterozygous ZMPSTE24 mutations
2. Member's diagnosis is confirmed by genetic testing – laboratory documentation must be provided
3. Member's body surface area is equal to or greater than 0.39 m²
4. Member is at least 12 months of age
5. Dose does not exceed BSA-based dosing per FDA label (see tables 1 and 2) – documentation of member's height and weight must be provided

Approval duration: 1 year

Continuation of lonafarnib (Zokinvy) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for lonafarnib has been previously approved by Florida Blue or another health plan in the past two years for the treatment of HGPS or PLs (if another health plan, documentation of a health plan-paid claim for lonafarnib during the 90 days immediately before the authorization request must be provided) OR the member currently meets all indication-specific initiation criteria
2. Dose does not exceed BSA-based dosing per FDA label (see tables 1 and 2) – documentation of member's height and weight must be provided

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- The starting dosage for patients with a BSA of 0.39 m² and above is 115 mg/m² twice daily with morning and evening meals (see Table 1)
- An appropriate dosage strength is not available for patients with a BSA of less than 0.39 m²
- After 4 months of treatment, increase the dosage to 150 mg/m² twice daily with morning and evening meals (see table 2)
- Round all total daily dosages to the nearest 25 mg increment (see tables 1 and 2)

Table 1

Recommended Dosage and Administration for 115 mg/m ² Body Surface Area-Based Dosing					
BSA(m ²)	Total Daily Dosage Rounded to Nearest 25 mg	Morning Dosing Number of Capsule(s)		Evening Dosing Number of Capsule(s)	
		ZOKINVY 50 mg	ZOKINVY 75 mg	ZOKINVY 50 mg	ZOKINVY 75 mg
0.39 - 0.48	100	1		1	
0.49 - 0.59	125		1	1	
0.6 - 0.7	150		1		1
0.71 - 0.81	175	2			1
0.82 - 0.92	200	2		2	
0.93 – 1	225	1	1	2	

Table 2

Recommended Dosage and Administration for 150 mg/m ² Body Surface Area-Based Dosing
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BSA(m ²)	Total Daily Dosage Rounded to Nearest 25 mg	Morning Dosing Number of Capsule(s)		Evening Dosing Number of Capsule(s)	
		ZOKINVY 50 mg	ZOKINVY 75 mg	ZOKINVY 50 mg	ZOKINVY 75 mg
0.39 - 0.45	125		1	1	
0.46 - 0.54	150		1		1
0.55 - 0.62	175	2			1
0.63 - 0.7	200	2		2	
0.71 - 0.79	225	1	1	2	
0.8 - 0.87	250	1	1	1	1
0.88 - 0.95	275		2	1	1
0.96 – 1	300		2		2

Dose Adjustments

- If concomitant use with a weak CYP3A inhibitor is unavoidable
 - Reduce to or continue at the starting dosage of 115 mg/m² twice daily
 - Resume the previous dosage 14 days after discontinuing the concomitant use of the weak CYP3A inhibitor.
- Temporarily discontinue for 10 to 14 days before and 2 days after administration of midazolam

Drug Availability

- Capsules: 50 mg and 75 mg

PRECAUTIONS:

Boxed Warning

- None

Contraindications

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

Precautions/Warnings

- Risk of Reduced Efficacy or Adverse Reactions Due to Drug Interactions: Prior to and during treatment, consider potential for drug interactions and review concomitant medications; monitor for adverse reactions
- Laboratory Abnormalities: Monitor for changes in electrolytes, complete blood counts, and liver enzymes
- Nephrotoxicity: Caused nephrotoxicity in rats. Monitor renal function at regular intervals

- **Retinal Toxicity:** Caused rod-dependent, low-light vision decline in monkeys. Perform ophthalmological evaluation at regular intervals and at the onset of any new visual changes
- **Impaired Fertility:** Caused impaired fertility in female rats, impaired fertility and testicular toxicity in male rats, and toxicity in the male reproductive tract in monkeys. Advise females and males of reproductive potential of the animal fertility findings

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified
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ICD-10 Diagnosis Codes That Support Medical Necessity

E34.8	Other specified endocrine disorders
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REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#).

DEFINITIONS:

Adjuvant Treatment: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biologic therapy. Adjuvant therapy can be used after or in combination with another form of cancer therapy and is commonly used following removal of a cancerous tumor to further help in treatment.

Metastatic cancer: when cancer spreads from the primary site (place where it started) to other places in the body.

Neo-adjuvant treatment: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 4/1/25]. Available from: <http://www.clinicalpharmacology.com/>.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 4/1/25] Available from: <http://clinicaltrials.gov/>.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 4/1/25].
4. MacroGenics, Inc. Margenza (margetuximab-cmkb injection, solution, concentrate. 2025 [cited 4/1/25]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e97a5872-eabf-463b-8f4c-5b5aed9c7bf0>.
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 4/1/25]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm/>.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/09/25.

GUIDELINE UPDATE INFORMATION:

03/15/21	New Medical Coverage Guideline.
07/15/22	Review and revision to guideline; updated references.
05/15/24	Review and revision to guideline; updated references.
05/15/25	Review and revision to guideline; updated references.