Clinical Policy: Lonafarnib (Zokinvy)

Reference Number: PA.CP.PHAR.499
Effective Date: 01/2022
Last Review Date: 01/2025

Description
Lonafarnib (Zokinvy®) is farnesyltransferase inhibitor.

FDA Approved Indication(s)
Zokinvy is 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:
  - Heterozygous LMNA mutation with progerin-like protein accumulation
  - Homozygous or compound heterozygous ZMPSTE24 mutations

Limitation(s) of use: Zokinvy is not indicated for other progeroid syndromes or processing-proficient progeroid laminopathies. Based upon its mechanism of action, Zokinvy would not be expected to be effective in these populations.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Zokinvy is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Progeria and Progeroid Laminopathy (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. HGPS with documentation of genetic mutation in the *LMNA* gene;
   b. Processing-deficient progeroid laminopathy with documentation of one of the following (i or ii):
      i. Heterozygous *LMNA* mutation with progerin-like protein accumulation;
      ii. Homozygous or compound heterozygous *ZMPSTE24* mutations;
2. Prescribed by or in consultation with a geneticist, metabolic disorder specialist, or progeria specialist;
3. Age ≥ 1 year;
4. Body surface area (BSA) ≥ 0.39 m^2;
5. Member does not have a history of cardiac arrhythmias;
6. Documentation of current electrocardiogram (ECG) QTc interval < 500 msec;
7. Dose does not exceed one of the following (a or b):
   a. New starts or treated for less than 4 months: 230 mg/m^2 per day, rounded to the nearest 25 mg dose (*see table in Section V*) for a total of 4 months;
   b. Maintenance after 4 months: 300 mg/m^2 per day, rounded to the nearest 25 mg dose (see table in Section V).

Approval duration: 12 months

B. Other diagnoses/indications
1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Progeria and Progeroid Laminopathy (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 300 mg/m^2 per day, rounded to the nearest 25 mg dose (*see table in Section V*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53;
B. Other progeroid syndromes;
C. Processing-proficient progeroid laminopathies.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BSA: body surface area
FDA: Food and Drug Administration
HGPS: Hutchinson-Gilford progeria syndrome

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): concomitant use of Zokinvy with:
  - Strong or moderate CYP3A inhibitors
  - Strong or moderate CYP3A inducers
  - Midazolam
  - Lovastatin, simvastatin, or atorvastatin

- Boxed warning(s): none reported

Appendix D: General information

- The diagnosis of HGPS is established in a proband with characteristic clinical features, along with identification of a heterozygous pathogenic variant in LMNA that results in production of the abnormal lamin A protein, progerin. HGPS is characterized by the following clinical features that typically develop in childhood and resemble some features of accelerated aging:
  - Growth deficiency: Profound failure to thrive usually occurs during the first year. Poor weight gain and loss of subcutaneous fat results in weight less than the third percentile for age, and weight that is distinctly low for height. Stature also decreases to below the third percentile for age.
  - Characteristic facial features: a head that appears disproportionately large for face, narrow nasal ridge with a narrow nasal tip, thin vermilion of the upper and lower lips, small mouth, retrognathia, and micrognathia.
  - Cardiovascular/cerebrovascular: Individuals with HGPS develop severe atherosclerosis, usually without obvious abnormalities in lipid profiles. Systolic dysfunction is usually present in the setting of advanced disease, with or without identified coronary vascular insufficiency. Clinical symptoms of angina, dyspnea on exertion, or overt heart failure appear as late findings in the course of disease.
  - Endocrine: Affected individuals do not become sexually mature. Females reach Tanner Stage 1 (78%) or 2 (22%) during pubertal years, and approximately 60% of females experience menarche
  - Musculoskeletal: Individuals with HGPS are particularly susceptible to hip dislocation because of the progressive coxa valga malformation, which can be accompanied by avascular necrosis of the hip (osteonecrosis).
- Individuals with classic genotype HGPS are heterozygous for pathogenic variant c.1824C>T (~90% of individuals with HGPS). Individuals with nonclassic genotype HGPS have the characteristic clinical features of HGPS and are heterozygous for another LMNA pathogenic variant in exon 11 or intron 11 that results in production of progerin (~10% of individuals with HGPS).
- Genetic testing can be obtained through The Progeria Research Foundation Diagnostic Testing Program, provided at no cost to families. Current link can be found here: https://www.progeriaresearch.org/the-prf-diagnostic-testing-program/.

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Progeria and progeroid laminopathy</td><td>Initial BSA-based dosage for the starting dosage of 115 mg/m^2 twice daily for 4 months:
<table>
<tr><th>BSA (m^2)</th><th>Total Daily Dosage Rounded to</th><th>Morning Dosing Number of Capsule(s)</th><th>Evening Dosing Number of Capsule(s)</th></tr>
</table></td><td>300 mg/m^2/day</td></tr>
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Indication	Dosing Regimen	Maximum Dose

	Nearest 25 mg	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	

Maintenance BSA-based dosage of 150 mg/m^2 twice daily:

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

VI. Product Availability

Capsules: 50 mg, 75 mg

VII. References

1. Zokinvy Prescribing Information. Palo Alto, CA: Eiger BioPharmaceuticals, Inc.; March 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213969s002s003lbl.pdf. Accessed November 7, 2025.
2. Gordon LB, Shappel H, Massaro J et al. Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford Progeria Syndrome. JAMA 2018; 319(16):1687-1695. doi:10.1001/jama.2018.3264.
3. Harhouri K, Frankel D, Bartoli C, et al. An overview of treatment strategies for Hutchinson-Gilford Progeria syndrome. Nucleus 2018; 9(1):246-257. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5973194/pdf/kncl-09-01-1460045.pdf. Accessed November 7, 2025.

Reviews, Revisions, and Approvals	Date
Policy created	01/2022

Reviews, Revisions, and Approvals	Date
1Q 2023 annual review: no significant changes; updated Appendix D to include Progeria Research Foundation Diagnostic Testing Program link; references reviewed and updated.	01/2023
1Q 2024 annual review: no significant changes; references reviewed and updated.	01/2024
1Q 2025 annual review: no significant changes; references reviewed and updated.	01/2025
1Q 2026 annual review: added safety criteria regarding hx of arrhythmias and QTc threshold per labeling updates; extended initial approval duration from 4 months for new starts to 12 months; references reviewed and updated.	01/2026