

Clinical Policy: Lonafarnib (Zokinvy)

Reference Number: ERX.SPA.407

Effective Date: 11.20.20

Last Review Date: 02.22

Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

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 m² 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions[™] 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 \geq 1 year;
4. Body surface area (BSA) \geq 0.39 m²;
5. Dose does not exceed one of the following (a or b):
 - a. New starts or treated for less than 4 months: 230 mg/m² 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/m² per day, rounded to the nearest 25 mg dose (*see table in Section V*).

Approval duration:

New starts: 4 months

Maintenance: 12 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 300 mg/m² 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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents;
- 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.

V. Dosage and Administration

Indication	Dosing Regimen					Maximum Dose	
Progeria and progeroid laminopathy	Initial BSA-based dosage for the starting dosage of 115 mg/m ² twice daily for 4 months:					300 mg/m ² / day	
	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		
	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		

Indication	Dosing Regimen						Maximum Dose
	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.; November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213969s000lbl.pdf. Accessed September 27, 2021.
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. Harhour 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/knci-09-01-1460045.pdf>. Accessed September 27, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	06.27.20	08.20
Drug is now FDA approved - criteria updated per FDA labeling: revised diagnostic criteria to reflect labeling; revised specialist requirement from pediatrician, orthopedist, and cardiologist to geneticist, metabolic disorder specialist, or progeria specialist; added minimum BSA requirement; updated initial lower dosing; revised initial approval duration from 6 months to 4 months; removed specific examples of positive response to therapy; references reviewed and updated.	01.05.21	02.21
1Q 2022 annual review: no significant changes; added to Section III that other progeroid syndromes or processing-proficient progeroid laminopathies will not be coverable per PI; references reviewed and updated.	09.27.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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