



Drug Coverage Policy

Effective Date5/1/2025

Coverage Policy Number.....IP0107

Policy Title Zokinvy

Zokinvy

- Zokinvy™ (lonafarnib capsules – Eiger Biopharmaceuticals)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Zokinvy, a protein farnesyltransferase inhibitor, is indicated in patients ≥ 12 months of age with a body surface area $\geq 0.39 \text{ m}^2$ for the following conditions: ¹

- **Hutchinson-Gilford Progeria Syndrome (HGPS)**, to reduce risk of mortality.
- **Progeroid laminopathies** that are processing-deficient, with either:
 - Heterozygous LMNA mutation with progerin-like protein accumulation; or
 - Homozygous or compound heterozygous ZMPSTE24 mutations.

Disease Overview

Hutchinson-Gilford Progeria Syndrome (HGPS)

HGPS is an ultra-rare, fatal, autosomal dominant genetic disorder with an estimated incidence of 1:4,000,000 live births and prevalence of 1:20,000,000 living individuals.² As of September 30, 2024, there were 16 patients identified with HGPS in the US.³ HGPS results from a heterozygous mutation in LMNA, the gene encoding lamin A, a nuclear membrane protein.⁴ "Classic" HGPS is caused by a single point variant in LMNA involving c.1824C>T (G608G variant) and accounts for 90% of HGPS cases.^{4,5} Other LMNA variants have also been identified in either the exon 11 splice junction or intron 11; these variants increase activation of the cryptic splice site, thus producing progerin. These are referred to as "non-classic" HGPS and comprise the remaining 10% of HGPS cases (refer to Appendix). The mutated prelamin A is referred to as progerin. Accumulation of progerin causes stiffening of the nuclear membrane and disorganized nuclear pores and chromatin, leading to hallmark symptoms including rapidly progressive atherosclerosis. Severe, rapidly progressing atherosclerosis results in an average mortality at 14.6 years of age due to myocardial infarction or stroke.⁴ It is estimated that 50% of affected children have had a radiographically detectable stroke by 8 years of age.

Progeroid Laminopathies

To date, over 400 variants in the LMNA gene have been identified, giving rise to different laminopathies which encompass a range of phenotypes including muscular dystrophy, peripheral neuropathy, lipodystrophy, and premature aging diseases.⁴ Some of these may have phenotypic overlap with HGPS ("progeroid" laminopathies).^{5,6} In addition, pathogenic variants in ZMPSTE24 can result in excess prelamin A proteins and a related phenotype. As of September 30, 2024, there were 11 patients identified with progeroid laminopathies in the US.³ Of note, mortality data are not available regarding the effect of Zokinvy in patients with progeroid laminopathies; the pivotal study only included patients with HGPS in its analysis.

Guidelines

Formal guidelines for progeria are not in place. The Progeria Research Foundation provides a Progeria Handbook (updated March 2019) with information about the disease for patients and families, as well as for healthcare providers.⁶ Clinical data with Zokinvy are acknowledged in the handbook as having positive results with regard to cardiovascular, bone, and survival outcomes. Diagnosis is made on the basis of clinical examination and genetic testing. It is noted that other progeroid laminopathies are closely related genetic diseases; less is known about these conditions. These conditions may be more or less severe than HGPS. Applying knowledge from classic progeria (i.e., HGPS) to other progeroid syndromes may be helpful, but good judgment must be applied since patients with other progeroid syndromes will have different needs.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for prescription benefit coverage of Zokinvy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zokinvy as well as the monitoring required for adverse events and long-term efficacy, approval requires Zokinvy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, and/or other information.

Zokinvy is considered medically necessary when the following criteria are met:

FDA-Approved Indication

- 1. Hutchinson-Gilford Progeria Syndrome.** Approve for 1 year if the patient meets the following (A, B, C, and D):
 - A)** Patient is ≥ 12 months of age; AND
 - B)** Documentation provided that the patient has a body surface area of $\geq 0.39 \text{ m}^2$; AND
 - C)** Documentation provided that genetic testing demonstrates a confirmed pathogenic variant in the *LMNA* gene consistent with Hutchinson-Gilford Progeria Syndrome; AND
Note: Refer to Appendix for listing of genetic mutations associated with Hutchinson-Gilford Progeria Syndrome.
 - D)** The medication is prescribed by or in consultation with a geneticist or pediatric cardiologist.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Zokinvy for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

- 1. Progeroid Laminopathies.** The efficacy of Zokinvy has not been established for patients with genetic disorders other than Hutchinson-Gilford Progeria Syndrome.² Although FDA labeling includes processing-deficient progeroid laminopathies, there are no clinical data demonstrating a treatment effect of Zokinvy in this population. Zokinvy is not indicated for use in processing-proficient progeroid laminopathies; based on its mechanism of action, Zokinvy would not be expected to be effective in this population.¹
- 2. Other Progeroid Syndromes.** Zokinvy is not indicated for use in other progeroid syndromes.¹ Based on its mechanism of action, Zokinvy would not be expected to be effective in this population.

References

1. Zokinvy[™] capsules [prescribing information]. Palo Alto, CA: March 2024; Eiger Biopharmaceuticals.
2. Gordon LB, Shappell H, Massaro J, et al. Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford Progeria Syndrome. *JAMA*. 2018 Apr 24;319(16):1687-1695.
3. Progeria Research Foundation. PRF by the numbers. Updated December 31, 2023. Available at: https://www.progeriaresearch.org/wp-content/uploads/2024/10/PRF-By-the-Numbers_-Sept-2024.pdf. Accessed on January 28, 2025.
4. Gonzalo S, Kreienkamp R, Askjaer P. Hutchinson-Gilford Progeria Syndrome: a premature aging disease caused by LMNA gene mutations. *Ageing Res Rev*. 2017;33:18-29.
5. Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford Progeria Syndrome. 2003 Dec 12 [Updated 2019 Jan 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews[®] [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at <https://www.ncbi.nlm.nih.gov/books/NBK1121/>. Accessed on January 28, 2025.

6. Progeria Research Foundation. The progeria handbook: a guide for families and health care providers of children with progeria, 2nd edition. Updated March 2019. Available at: <https://www.progeriaresearch.org/patient-care-and-handbook/>. Accessed on January 28, 2025.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	06/01/2024
Annual Revision	Added "<u>Documentation</u>": Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, and/or other information." Hutchinson-Gilford Progeria Syndrome: Updated criteria from "Patient has a body surface area of $\geq 0.39 \text{ m}^2$ " to "Documentation provided that the patient has a body surface area of $\geq 0.39 \text{ m}^2$." For confirmation by genetic testing, rephrased the term "mutation" to "variant."	5/1/2025

The policy effective date is in force until updated or retired.

APPENDIX

Genetic mutations consistent with a diagnosis of Hutchinson-Gilford Progeria Syndrome are outlined below.^{2,3} Of note, all of the following mutations are heterozygous; only one affected gene copy is required for confirmation of the diagnosis.

Appendix Table 1. Genetic Mutations Associated with Hutchinson-Gilford Progeria Syndrome.

Location on LMNA Gene	Mutation
Classic Hutchinson-Gilford Progeria Syndrome	
Exon 11	c.1824C>T; p.G608G
Non-Classic Hutchinson-Gilford Progeria Syndrome	
Exon 11	c.1821G>A; p.V607V
Exon 11	c.1822G>A; p.G608S
Exon 11	c.1868C>G; p.T623S
Intron 11	c.1968+1G>A
Intron 11	c.1968+1G>C
Intron 11	c.1968+2T>A
Intron 11	c.1968+2T>C
Intron 11	c.1968+5G>C

"Cigna Companies" refers to operating subsidiaries of The Cigna Group. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Evernorth Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of The Cigna Group. © 2025 The Cigna Group.