

PRIOR AUTHORIZATION POLICY

POLICY: Zokinvy Prior Authorization Policy

- Zokinvy™ (lonafarnib capsules – Eiger Biopharmaceuticals)

REVIEW DATE: 01/17/2024

OVERVIEW

Zokinvy, a protein farnesyltransferase inhibitor, is indicated in patients ≥ 12 months of age with a body surface area ≥ 0.39 m² 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 December 31, 2023, 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 mutation in *LMNA* involving c.1824C>T (G608G mutation) and accounts for 90% of HGPS cases.^{4,5} Other *LMNA* mutations have also been identified in either the exon 11 splice junction or intron 11; these mutations 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 mutations 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 December 31, 2023, there were 12 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

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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.

POLICY STATEMENT

Prior Authorization is recommended 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zokinvy is recommended in those who meet the following criteria:

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)** Patient has a body surface area of ≥ 0.39 m²; AND
 - C)** Genetic testing demonstrates a confirmed pathogenic mutation 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zokinvy is not recommended in the following situations:

- 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.
- 3.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zokinvy™ capsules [prescribing information]. Palo Alto, CA: November 2020; 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/prf-by-the-numbers/>. Accessed on January 10, 2024.
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 6, 2023.
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 10, 2024.

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.