Zokinvy Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	07-01-2021

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Zokinvy® (lonafarnib) Capsule	Patients 12 months of age and older with a body surface area (BSA) of 0.39 m^2 and above: • To reduce the risk of mortality in Hutchinson-Gilford progeria syndrome (HGPS) • For the treatment of processing-deficient progeroid laminopathies with either: heterozygous *LMNA* mutation with progerin-like protein accumulation OR homozygous or compound heterozygous *ZMPSTE24* mutations Limitations of Use: 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.		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Progeroid Syndromes	Progeroid syndromes are rare genetic diseases characterized by reduced lifespan and premature appearance of certain signs and symptoms of physiological aging. Major clinical features are hair loss, short stature, skin wrinkling, osteoporosis, and, usually, cardiovascular disease. The first genetically characterized group of progeroid syndromes were recessive diseases associated with mutations in genes encoding DNA repair and maintenance proteins (e.g., Werner syndrome, Bloom syndrome, Cockayne syndrome). A second group of progeroid syndromes, called progeroid laminopathies, were later identified, which are caused by mutations in *LMNA* gene that encodes A-type lamins, or mutations in *ZMPSTE24* gene that encodes the enzyme ZMPSTE24 essential for A-type lamin processing. A-type lamins compose (together with B-type lamins) the nuclear lamina, a critical meshwork of filaments at the interface between the inner nuclear membrane and chromatin. ZMPSTE24 enzyme is necessary for recognizing the farnesylated C-terminal region of prelamin A, catalyzing the proteolytic cleavage reaction to mature lamin A.(2) Progeroid laminopathies are very rare, generally have an earlier age of onset than most other progeroid syndromes, and display more severe symptoms of accelerated aging. The most prevalent of these rare diseases, Hutchinson-Gilford progeria syndrome (HGPS), is caused by a mutation in *LMNA*, the gene coding for A-type lamins. A single base mutation (typically Gly608Gly, in "classic" HGPS) introduces an alternative splice site that produces an abnormal lamin A protein called "progerin". Progerin lacks the proteolytic cleavage site normally used to remove the farnesylated carboxy terminus from lamin A during posttranslational processing.(2,3,4,5,6,8,10,11) The progerin (permanently farnesylated mutant lamin

	A) accumulates inside the nucleus, unable to be released for degradation due to persistent farnesylation.(3,4,6,7,9) Disease in HGPS is produced by a dominant negative mechanism; it is the effect of progerin, *not* the diminution of lamin A, which causes the disease phenotype.(3) Emerging evidence indicates that *LMNA*-linked progerias can be further grouped into two classes: 1) the processing-deficient, early onset "typical" progerias (e.g., HGPS), and 2) the processing-proficient "atypical" progeria syndromes (APS) that are later in onset.(5) Individuals with APS show many of the clinical features of HGPS, but their cells do not accumulate prelamin A or progerin.(9) Disease manifestations include severe failure to thrive, scleroderma-like skin, lipoatrophy, alopecia, joint contractures, skeletal dysplasia, and atherosclerosis, but intellectual development is normal.(2,4,6,8,9,10,11) Death at an average age of 13 years occurs from myocardial infarction or stroke.(4,5,6,8,10,11) Diagnosis of genotype HGPS is established with characteristic clinical features, along with identification of a heterozygous pathogenic variant in *LMNA* that results in production of progerin.(8) Mandibuloacral dysplasia (MAD) and restrictive dermopathy (RD) are caused by extreme accumulation of lamin A precursors (aka prelamin) due to a mutation in *ZMPSTE24* which leads to complete absence of the ZMPSTE24 enzyme.(2,5,6) Because of the absence of ZMPSTE24-enzyme's processing activity, the full-length prelamin A molecules in farnesylated form accumulate in the cell.(5,7) MAD can be associated with either homozygous or compound heterozygous mutations in *LMNA* (MAD-A), or a combination of a nonsense and missense mutation in *ZMPSTE24* (MAD-B).(6,7,8,9,10,11) MAD patients are characterized by postnatal growth retardation, craniofacial anomalies like mandibular hypoplasia (or osteolysis) and protruding mid-face as well as skeletal anomalies including progressive osteolysis of the terminal phalanges and clavicles. RD is caused by *LMNA*-linked heterozygous mutations that result in truncated proteins similar to progerin that accumulate inside the nucleus.(6,11) RD can also be linked to homozygous or compound heterozygous *ZMPSTE24* mutations.(6,7,10,11) Restrictive dermopathy (RD) is a rare and extremely severe congenital genodermatosis, characterized by a tight rigid skin with erosions at flexure sites, multiple joint contractures, low bone density and pulmonary insufficiency generally leading to death in the perinatal period.(7) Genetic testing in the United States can be achieved through the PRF (Progeria Research Foundation) Diagnostic Testing Program, provided at no cost to families. The genetic test is done by coordinating a blood sample submission by mail through home physicians, from anywhere in the world, to PRF. The PRF Diagnostic Testing Program offers genetic testing for any child suspected of having progeria, provided at no cost to families.(12) Management is supportive and involves ensuring optimal nutrition, monitoring of disease progression, and treatment of complications as they present. Without lonafarnib treatment, death typically occurs as a result of complications of cardiac or cerebrovascular disease. More than 80% of deaths are due to heart failure and/or myocardial infarction, most often between ages six and 20 years, with an average life span of approximately 14.5 years. Average life span is extended to approximately 17-19.5 years with lonafarnib therapy, with similar cause of death.(8)
Efficacy	Zokinvy (lonafarnib) is a farnesyltransferase inhibitor, preventing progerin farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane.(1,4) Farnesylation inhibitors are not curative, as many features of disease persist despite treatment. However, evidence suggests that survival may be improved.(3,10,11) Clinical trials have shown improved cardiovascular status of children with HGPS, a potentially important finding because failure of this organ system is the ultimate cause of mortality. A nonrandomized, clinical trial of lonafarnib in 25 children with HGPS provided some evidence of efficacy in reducing the carotid artery echodensity and improving the bone structure in these patients.(4) A subsequent, nonrandomized study evaluated the effect of oral lonafarnib on all-cause mortality in a cohort of 27 patients (median age 8.4 years) with HGPS compared with 27 matched, untreated patients. The median treatment duration was 2.2 years. During

	this period, the observed mortality rate was 3.7 percent among patients receiving lonafarnib versus 33.3 percent in the untreated group.(1)
Safety	Zokinvy is contraindicated in patients taking:(1) • Strong or moderate CYP3A inhibitors or inducers • Midazolam • Lovastatin, simvastatin, or atorvastatin

REFERENCES

Number	Reference
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2	Marcelot A, Worman HJ, Zinn-Justin S. Protein Structural and Mechanistic Basis of Progeroid Laminopathies. FEBS J. 2020 Aug;1-16.
3	Gordon LB, Massaro J, D'Agostino RB, et al. Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome. Circulation. 2014 Jul;130(1):27-34.
4	Gordon LB, Kleinman ME, Miller DT, et al. Clinical Trial of a Farnesyltransferase Inhibitor in Children with Hutchinson-Gilford Progeria Syndrome. Proc Natl Acad Sci USA. 2012 Oct;109(41):16666-16671.
5	Kane MS, Lindsay ME, Judge DP, et al. LMNA-Associated Cardiocutaneous Progeria: A Novel Autosomal Dominant Premature Aging Syndrome with Late Onset. Am J Med Genet A. 2013 Jul;161(7):1599-1611.
6	Starke S, Meinke P, Camozzi D, et al. Progeroid Laminopathy with Restrictive Dermopathy-Like Features Caused by an Isodisomic LMNA Mutation p.R435C. Aging (Albany NY). 2013 Jun;5(6):445-459.
7	Navarro CL, Esteves-Vieira V, Courrier S, et al. New ZMPSTE24 (FACE1) Mutations in Patients Affected with Restrictive Dermopathy or Related Progeroid Syndromes and Mutation Update. Eur J Hum Genet. 2014 Aug;22(8):1002-1011.
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9	Carrero D, Soria-Valles C, Lopez-Otin C. Hallmarks of Progeroid Syndromes: Lessons from Mice and Reprogrammed Cells. Dis Model Mech. 2016;9:719-735.
10	Piekarowicz K, Machowska M, Dzianisava V, Rzepecki R. Hutchinson-Gilford Progeria Syndrome – Current Status and Prospects for Gene Therapy Treatment. Cells. 2019;8(88):1-22.
11	Kudlow BA, Kennedy BK, Monnat RJ Jr. Werner and Hutchinson-Gilford Progeria Syndromes: Mechanistic Basis of Human Progeroid Diseases. Nat Rev Mol Cell Biol. 2007 May;8:394-404.
12	The Progeria Handbook: A Guide for Families and Healthcare Providers of Children Living with Progeria - 2nd Edition. The Progeria Research Foundation. 2019. Available at: https://www.progeriaresearch.org/wp-content/uploads/2022/03/English-Progeria-Handbook-Edition-2.pdf.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Zokinvy	lonafarnib cap	50 MG ; 75 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Zokinvy	Lonafarnib Cap	50 MG	120	Capsules	30	DAYS			
Zokinvy	Lonafarnib Cap	75 MG	120	Capsules	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zokinvy	lonafarnib cap	50 MG ; 75 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zokinvy	Lonafarnib Cap	50 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Zokinvy	Lonafarnib Cap	75 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Zokinvy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of Hutchinson-Gilford progeria syndrome (HGPS) **AND** 2. Genetic testing has confirmed a pathogenic variant in the *LMNA* gene that results in production of progerin (medical record required) **OR** B. The patient has a processing-deficient progeroid laminopathy AND ONE of the following: 1. Genetic testing has confirmed heterozygous *LMNA* mutation with progerin-like protein accumulation (medical record required) **OR** 2. Genetic testing has confirmed homozygous or compound heterozygous *ZMPSTE24* mutations (medical record required) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The patient has a body surface area (BSA) of greater than or equal to 0.39 m^2 **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months