Zokinvy (lonafarnib)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Zokinvy (lonafarnib) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Zokinvy (lonafarnib) is indicated in patients 12 months of age and older with a body surface of 0.39 m^2 and above:

- To reduce the risk of mortality in Hutchinson-Gilford progeria syndrome
- For treatment of processing-deficient progeroid laminopathies with either:
    - Heterozygous *LMNA* mutation with progerin-like protein accumulation
    - Homozygous or compound heterozygous *ZMPSTE24* mutations

Limitations of Use

Zokinvy is not approved for use in patients with 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

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

A. Initiation of therapy:

1. Diagnosis of one of the following as confirmed by genetic testing:
    i. Hutchinson-Gilford progeria syndrome (HGPS)
    ii. Processing-deficient progeroid laminopathy with either
        a) Heterozygous *LMNA* mutation with progerin-like protein accumulation
        b) Homozygous or compound heterozygous *ZMPSTE24* mutation
2. Medical records (e.g., chart notes, laboratory values) documenting a body surface area (BSA) of ≥ 0.39m^2.

B. Continuation of therapy:
    1. Documentation supporting that the member is on an appropriate dosage for the member's body surface area

Exclusion
Coverage will not be provided for members with other progeroid syndromes or processing-proficient progeroid laminopathies

Criteria for Initial Approval
A. Zokinvy (lonafarnib) may be considered **medically necessary** for the treatment of patients with Hutchinson-Gilford progeria syndrome (HGPS) or processing-deficient progeroid laminopathy when all the following criteria are met:
    1. The member has a diagnosis of one of the following as confirmed by genetic testing:
        a. Hutchinson-Gilford progeria syndrome (HGPS)
        b. Processing-deficient progeroid laminopathy with either
            i. Heterozygous *LMNA* mutation with progerin-like protein accumulation OR
            ii. Homozygous or compound heterozygous *ZMPSTE24* mutations
    2. The member is 12 months of age or older
    3. The medication is prescribed by, or in consultation with, a specialist in progeria treatment
    4. Member has a body surface area (BSA) of at least 0.39 m^2
    5. Dosage is appropriate for patient's body surface area (BSA)

    Approval will be for **12 months**

Continuation of Therapy
Zokinvy (lonafarnib) may be considered **medically necessary** for the continued treatment of patients with Hutchinson-Gilford progeria syndrome (HGPS) or processing-deficient progeroid laminopathy when the member meets all initial approval criteria and is tolerating therapy with the requested medication.

Approval will be for **12 months**

Zokinvy (lonafarnib) is considered **not medically necessary** for members who do not meet the criteria set forth above.

Members currently receiving the requested medication as samples or via the manufacturer's patient assistance program will be required to meet the criteria for initial approval. This ensures that members are treated equally regardless of their provider's ability to access medication samples.

Quantity Limits Apply
Quantity limit varies based on member's BSA. Refer to Table 1 and Table 2 in Dosage and Administration section for BSA-based dosage. Maximum quantity allowed based on BSA is 120 capsules per 30 days.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

The starting dosage of Zokinvy for patients with a BSA of 0.39 m^2 and above is 115 mg/m^2 twice daily with morning and evening meals to reduce the risk of gastrointestinal adverse reactions (Table 1). After 4 months of treatment, increase the dosage to 150 mg/m^2 twice daily with morning and evening meals (Table 2). Round all total daily dosages to the nearest 25 mg increment.

Table 1: Recommended Dosage and Administration for 115 mg/m^2 Body Surface Area-Based Dosing

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	

Table 2: Recommended Dosage and Administration for 150 mg/m^2 Body Surface Area-Based Dosing

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

CLINICAL RATIONALE

Hutchinson-Gilford progeria syndrome (HGPS) and progeroid laminopathies (PLs) are rare, fatal, premature aging diseases that generally lead to death at approximately 13 years of age due to myocardial infarction or stroke. In HGPS, the premature aging is due to a point mutation in the lamin A/C gene *(LMNA)* that leads to the production and permanent farnesylation of a mutant lamin A protein called progerin. Progeroid Laminopathies (PLs) are different in that they are caused by various mutations either in the *LMNA* gene and/or the *ZMPSTE24* gene. The mutant protein produced in PLs is distinct from progerin; however; it is also permanently farnesylated, like progerin. The buildup of these mutant proteins leads to the pathogenesis of these diseases. Disease manifestations include failure to thrive, scleroderma-like skin, global lipodystrophy, alopecia, joint contractures, skeletal dysplasia, and arteriosclerosis. Premature, widespread arteriosclerosis is the main cause of mortality in these patients, leading to heart failure, myocardial infarction, stroke, or transient ischemic attack. Zokinvy is an oral farnesyltransferase inhibitor that prevents farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane, which are the proteins implicated in the pathogenesis of Hutchinson-Gilford progeria syndrome (HGPS) as well as some processing-deficient progeroid laminopathies (PLs). Zokinvy is the first

and only approved FDA-approved treatment for HGPS and PLs. Until now, treatment has been supportive and focused on complications of the disease.

The efficacy of Zokinvy is based on results from the Observational Cohort Survival Study, which retrospectively compared survival data from two open label, single-arm, clinical trials in patients with HGPS to those from a natural history cohort. In Study 1, 28 patients received Zokinvy twice daily for 24 to 30 months. 26 patients had classic HGPS, 1 had non-classic HGPS, and 1 had processing-deficient progeroid laminopathy (PL) with and LMNA heterozygous mutation. Following completion of the Study 1, 26 patients of the 28 patients enrolled in Study 2 (Phase 1), where they continued to receive Zokinvy in conjunction with additional therapies for 5 years. These additional therapies included pravastatin and zoledronic acid. In the second phase of Study 2, 35 treatment-naïve patients received Zokinvy twice daily for up to 3 years.

The Observational Cohort Survival Study was based on the mortality data from 62 treated patients (27 in Study 1 and 35 treatment-naïve patients in Study 2) and compared it to the data from matched, untreated patients from a separate natural history cohort. This included only HGPS patients. Treated patients were matched 1:1 to untreated patients (who were alive at the age when the treated patient began Zokinvy) by mutation status, sex, and continent of residence using a fixed 50^{th} percentile matching algorithm. Follow-up time for a matched pair of treated and untreated patients began at the age of the treated patient at Zokinvy initiation. The median life span of HGPS patients treated with Zokinvy increased by an average of 3 months through the 3 year follow-up time and by an average of 2.5 years through the last follow-up time (up to 11 years) compared to untreated patients. These results may be understated due to the median duration of Zokinvy exposure varying from patient to patient, with the shortest follow-up time ranging from only a few years and up to 11 years for a small number of patients.

The safety of Zokinvy was evaluated in a total of 63 patients that received Zokinvy for a median duration of 2.2 years, with 1.9 years being at the recommended dosage of 150mg/m^2. Data was collected from patients in Study 1 and treatment-naïve patients from Study 2. Most patients had classic HGPS (60) compared to non-classic HGPS (2) and 1 patient had Progeroid Laminopathy with *LMNA* heterozygous gene mutation. The most common adverse reactions (≥25%) in the clinical trials were vomiting, diarrhea, infection, nausea, decreased appetite, fatigue, upper respiratory tract infection, abdominal pain, musculoskeletal pain, electrolyte abnormalities, decreased weight, headache, myelosuppression, increased aspartate aminotransferase, decreased blood bicarbonate, cough, hypertension, and increased alanine aminotransferase. Zokinvy is contraindicated with concurrent use of strong or moderate CYP3A inhibitors or inducers, midazolam, lovastatin, simvastatin, and atorvastatin.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- N/A

REFERENCES

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- FDA Approves First Treatment for Hutchinson-Gilford Progeria Syndrome and Some Progeroid Laminopathies. FDA.gov website. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-hutchinson-gilford-progeria-syndrome-and-some-progeroid-laminopathies. Published November 20, 2020. Accessed December 22, 2020.

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- Progeria Research Foundation (PRF). The Progeria Handbook: A Guide for Families & Health Care Providers of Children with Progeria. Second Edition. PRF. https://www.progeriaresearch.org/wp-content/uploads/2019/03/PRF_Handbook_2019_eFile.pdf. Accessed November 27, 2020.

POLICY HISTORY

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