lonafarnib (Zokinvy®)

Policy # 00584
Original Effective Date: 07/12/2021
Current Effective Date: 07/12/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider lonafarnib (Zokinvy®)‡ for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and processing deficient Progeroid Laminopathies with certain gene mutations to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for lonafarnib (Zokinvy) will be considered when the following criteria are met:
Initial Authorization:

- Patient is 12 months of age or older; AND
- Patient has a body surface area of at least 0.39 m^2; AND
- Dosing is equal to or less than 150 mg/m^2 twice daily; AND
- Patient has (or has had) at least one of the following:
    - Failure to thrive in the first year of life; OR
    - Characteristic facial appearance with micrognathia, prominent eyes, and circumoral cyanosis; OR
    - Alopecia and prominent scalp veins; OR
    - Sclerotic skin changes with outpouching and dimpling/mottling, especially on the abdomen; OR
    - Decreased joint range of motion and joint contractures; AND
- Patient has one of the following diagnoses confirmed below:
    - Patient has a diagnosis of Hutchinson-Gilford Progeria Syndrome; AND
        - Patient has the presence of a mutational analysis showing a G608G mutation in the *LMNA* gene; OR

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- Patient has a diagnosis of a processing deficient Progeroid Laminopathy; AND
  - Patient has a heterozygous *LMNA* mutation with progerin-like protein accumulation; OR
  - Patient has a homozygous or compound heterozygous *ZMPSTE24* mutation.

Continuation Request:

- Patient has an initial authorization for the requested drug; AND
- Dosing is equal to or less than 150 mg/m^2 twice daily; AND
- Patient is tolerating the requested medication.
  *(Note: This specific patient criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the continued use of lonafarnib (Zokinvy) when the patient is not tolerating lonafarnib (Zokinvy) to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of lonafarnib (Zokinvy) when the patient selection criteria are not met (with the exception of those considered to be **not medically necessary****) to be **investigational.***

Background/Overview

Zokinvy is a farnesyltransferase inhibitor indicated in patients 12 months of age and older with a body surface area of 0.39 m^2 and above to: 1) reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome and 2) treat processing-deficient Progeroid Laminopathies with either a heterozygous *LMNA* mutation with progerin-like protein accumulation OR homozygous or compound heterozygous *ZMPSTE24* mutations. Zokinvy is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies. Zokinvy is available in 50 mg and 75 mg capsules. The starting dose is 115 mg/m^2 twice daily with morning and evening meals. After 4 months, the dose should be increased to 150 mg/m^2 twice daily. All total daily doses should be

rounded to the nearest 25 mg increment. Zokinvy capsules should be swallowed whole. If patients are unable to swallow the capsule whole, the contents can be mixed with Ora Blend SF®‡, Ora-Plus®‡, orange juice, or apple sauce. Consult the package insert for more details on administration.

HGPS is an ultra-rare genetic disorder (prevalence is 1 in 20 million in the Unites States) which results from a heterozygous mutation in *LMNA*, the gene that encodes for the production of lamin A, which is a nuclear membrane protein. Normally, prelamin A needs to be farnesylated prior to incorporation into the nuclear membrane. After incorporation, the prelamin A's farnesyl group is cleaved, which produces mature lamin A. The mutated version of lamin A produced due to HGPS is called progerin. Progerin's farnesyl group is unable to be cleaved so progerin remains anchored to the nuclear envelope. This can lead to nuclear blebbing and dysregulated gene transcription, which is thought to ultimately lead to the clinical characteristics of HGPS. Zokinvy prevents the farnesylation and accumulation of progerin in the nuclear membrane. HGPS is characterized by the presence of premature aging, disproportionately large head for face, narrow nasal ridge, narrow nasal tip, thin vermillion of the upper and lower lips, small mouth, small and receding lower jaw, scleroderma, alopecia, and delayed tooth disruption. HGPS is fatal. Mortality from this condition is often due to myocardial infarction or stroke at a mean age of 14 years because of widespread atherosclerosis. Diagnosis of HGPS is typically made with clinical characteristics and genetic testing.

Other progeroid laminopathies do exist (non-HGPS progeroid laminopathies). The prevalence of these disorders is 1 in 36 million worldwide. They can present similarly and are even more rare than HGPS. Non-HGPS progeroid laminopathies can be caused by similar or different gene mutations (e.g., *LMNA ZMPSTE24*), however they both result in a permanently farnesylated mutant protein.

Zokinvy is the first and only drug approved by the FDA for these conditions. Formal guidelines for progeria have not been established.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Zokinvy is a farnesyltransferase inhibitor indicated in patients 12 months of age and older with a body surface area of 0.39 m^2 and above to: 1) reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome and 2) treat processing-deficient Progeroid Laminopathies with either

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heterozygous *LMNA* mutation with progerin-like protein accumulation OR homozygous or compound heterozygous *ZMPSTE24* mutations. Zokinvy is not indicated for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Zokinvy is based on results from the Observational Cohort Survival Study, which retrospectively compared survival data from two Phase 2 studies in patients with HGPS to those from a natural history cohort. Study 1 was a Phase 2 open-label, single-arm trial that evaluated the efficacy of Zokinvy in 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient Progeroid Laminopathy with *LMNA* heterozygous mutation with progerin-like protein accumulation). Patients received Zokinvy for 24 to 30 months. Patients initiated treatment with Zokinvy 115 mg/m^2 twice daily. After 4 months of treatment, patients who tolerated treatment had an increase in dose to 150 mg/m^2 twice daily. Among the 28 patients treated, 27 patients with HGPS (16 females, 11 males) were included in the survival assessment. The median age at treatment initiation for the 27 patients was 7.5 years (range: 3 to 16 years). The body weight range was 6.6 to 17.6 kg and the BSA range was 0.38 to 0.75 m^2 (Zokinvy is not indicated in patients with a BSA less than 0.39 m^2 because the appropriate dosage strength is not available for this population). Following completion of Study 1, 26 patients enrolled in a second Phase 2 open label, single-arm trial (Study 2) which consisted of two study phases. In the first phase of Study 2, patients received Zokinvy with additional therapies for about 5 years. In the second phase of Study 2, patients received Zokinvy 150 mg/m^2 twice daily for a period of up to 3 years. There were 35 treatment naïve patients with HGPS enrolled into the second phase of Study 2. Among the 35 treated patients (22 males, 13 females), 34 (97.1%) patients had classic HGPS and 1 (2.9%) patient had non-classic HGPS. The median age was 6 years (range: 2 to 17 years). The body weight range was 6.7 to 22 kg and the BSA range was 0.42 to 0.90 m^2. Throughout Study 1 and Study 2, Zokinvy was administered orally via capsules or the capsule contents were mixed with Ora Blend SF or OraPlus and administered orally

as a suspension. The retrospective survival analysis was based on the mortality data from 62 treated patients (27 patients in Study 1 and 35 treatment-naïve patients in Study 2) and data from matched, untreated patients in a separate natural history cohort. The mean lifespan of HGPS patients treated with Zokinvy increased by an average of 3 months through the first three years of follow-up and 2.5 years through the last follow-up time (11 years) compared to untreated patients.

References

1. Zokinvy [package insert]. Eiger BioPharmaceuticals, Inc. Palo Alto, California. Updated November 2020.
2. Hutchinson-Gilford Progeria Syndrome. UpToDate. Accessed May 2021.
3. Zokinvy for the Treatment of Progeria and Progeroid Laminopathies. IPD Analytics. Updated December 2020.
4. Zokinvy Drug Evaluation. Express Scripts. January 2021.

Policy History

Original Effective Date: 07/12/2021
Current Effective Date: 07/12/2021
06/03/2021 Medical Policy Committee review
06/09/2021 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 06/2022

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.