lonafarnib (Zokinvy™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO227

Description

Lonafarnib (Zokinvy) is a farnesyltransferase inhibitor.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lonafarnib (Zokinvy)	50 mg capsules	Hutchinson-Gilford Progeria Syndrome (HGPS); processing-deficient Progeroid Laminopathies (PL)	**Initial:** Maximum 230mg/m^2/day **Renewal:** Maximum 300mg/m^2/day
	75 mg capsules		

Initial Evaluation

I. Lonafarnib (Zokinvy) may be considered medically necessary when the following criteria are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics, or metabolic disorders; **AND**
   C. Documentation of members body surface area (BSA); **AND**
   D. Member has a BSA of 0.39m^2 or greater; **AND**
   E. Provider attestation the member's cardiovascular status will be monitored [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]; **AND**
   F. A diagnosis of one of the following:
      1. **Hutchinson-Gilford Progeria Syndrome (HGPS); AND**
         i. Member has genetic test confirmation of a lamin A gene mutation; **OR**
      2. **Processing-deficient Progeroid Laminopathies (PL); AND**
         i. Member has genetic test confirmation of:
            a. Heterozygous LMNA mutation with progerin-like protein accumulation; **OR**
            b. Homozygous or compound heterozygous ZMPSTE24 mutations.

II. Lonafarnib (Zokinvy) is considered <u>experimental and investigational</u> when criteria above are not met and/or when used for:
   A. Processing-proficient Progeroid Laminopathies
   B. Other than above mentioned Progeroid Syndromes
      i. Wiedemann-Rautenstrauch syndrome
      ii. Werner syndrome
      iii. Bloom syndrome
      iv. Rothmund-Thomson syndrome
      v. Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy
      vi. Fanconi anaemia
      vii. Seckel syndrome
      viii. Ataxia telangiectasia
      ix. Dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics or metabolic disorders; **AND**
IV. Documentation of members body surface area (BSA) measured in the past three months; **AND**
V. Provider attests the member has exhibited improvement or stability of disease symptoms [e.g., cardiovascular status (e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography), bone mineral density].

Supporting Evidence

I. The safety and efficacy of lonafarnib (Zokinvy) has not been studied in pediatric patients less than 12 months of age. The activity of cytochrome P450 (CYP)3A4 and CYP3A5 is low in newborns, approximately 5% to 15% of that of an adult and only achieves full activity at six months of age. Considering these enzymes play a key role in the metabolism of lonafarnib (Zokinvy), it is expected that the clearance would be reduced and there is an increased risk of commonly observed treatment emergent adverse events (TEAEs).

II. The safety and efficacy of lonafarnib (Zokinvy) has only been studied in patients with the body surface area (BSA) ranging from 0.38 m^2 to 0.75 m^2. Due to the lack of clinical trial data on safety and efficacy, and unknown dosage strength, it is not indicated in patients with the BSA less than 0.39m^2.

III. Hutchinson-Gilford Progeria Syndrome (HPS) and processing-deficient PLs are rare and fatal genetic diseases. Considering the complexity of the disease state it is necessary for lonafarnib (Zokinvy) to be prescribed by or in consultation with a specialist in progeroid syndromes, genetics, or metabolic disorders.

IV. Patients with HGPS and processing-deficient PLs experience hypertension, strokes, angina, enlarged heart, and heart failure. Progressive atherosclerosis is common, generally leading to death from myocardial infarction or stroke at the age of approximately 15 years. It is crucial to monitor the cardiovascular status [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]. In a study that sought to better understand cardiovascular disease associated with HGPS, elevated PWVcf, increased intima-media and adventitia echodensity, abnormal ABI, and increased ICA mean flow velocity were identified as pervasive disease features in HGPS. Researchers noted that non-invasive measures including PWVcf, carotid wall echodensity and ICA flow velocity offer quantitative insights into accelerated vasculopathy with HGPS and may therefore, provide indicators of disease progression or remission with therapies.

V. The safety and efficacy of lonafarnib (Zokinvy) have been studied in a observational cohort survival study, which retrospectively compared survival data from two, open-label, single-arm, Phase 2 trials (Study 1 and Study 2) in 62 patients to those from a natural history cohort in 62 patients with HGPS.

- The primary efficacy outcome was all-cause mortality. Among the 62 patients in the treatment group four died (6.3%) and among the 62 patients in the matched untreated group 17 died (27%). None of these deaths were considered by investigators to be treatment related.
- Through the first three years of follow up, the mean lifespan of HGPS patients treated with lonafarnib increased by three months, and increased by two and a half years through the last follow-up time (11 years) compared to untreated patients.
- Study 1 included 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient PL with an LMNA heterozygous mutation). Treatment was initiated with 115mg/m^2 twice daily and after four months of treatment patients who were tolerating treatment had a dose increase to 150 mg/m^2 twice daily.
    - The primary efficacy endpoint of the achievement of at least a 50% increase in the annual rate of weight gain over the rate documented at study entry by the study team, was met by eleven of 28 patients (39.3%).
    - The secondary outcome was change in carotid artery ultrasonography and corrected PWVcf. Echodensity of the carotid artery intima media (10th and 50th percentile), adventitia deep near wall (10th and 50th percentile), and adventitia

luminal near wall (50th percentile) all decreased statistically significantly from baseline to end of therapy (all p<0.05). PWVcf improved with a median percent decrease from baseline of 15.3% (range: -43.6%, 34.1%; p=0.0028).

- Study 2 consisted of two phases. In the first phase patients received lonafarnib (Zokinvy) in conjunction with zoledronic acid and pravastatin for five years. In the second phase patients received lonafarnib (Zokinvy) at a dose of 150mg/m^2 twice daily for three years.
  - The study enrolled 26 patients from Study 1 and 13 treatment naïve patients.
  - The primary efficacy endpoint of weight gain (at least 10% increase in the annual rate) or echodensity was met by 22 (71%) of patients.
- 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

VI. Progeroid laminopathies (PLs) are due to various mutations either in the LMNA gene and/or the ZMPSTE24 gene. The processing-deficient PLs are specifically due to heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. These conditions are more rare than HGPS, and were underrepresented in the clinical trials.

Investigational or Not Medically Necessary Uses

I. Lonafarnib (Zokinvy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Progeroid syndromes (Wiedemann-Rautenstrauch syndrome, Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy, Fanconi anaemia, Seckel syndrome, Ataxia telangiectasia, Dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome) are a group of very rare genetic disorders that are characterized by clinical features that mimic physiological ageing, such as hair loss, short stature, skin tightness, cardiovascular diseases and osteoporosis. But considering the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.
   B. Processing-proficient Progeroid Laminopathies – considering the pathophysiology of the disease state and the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021