NEW DRUG APPROVAL

Brand Name	Zokinvy™
Generic Name	lonafarnib
Drug Manufacturer	Eiger Biopharmaceuticals

New Drug Approval

FDA Approval Date: November 20, 2020

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity

Dispensing Restriction: Specialty only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PLs) are premature aging diseases. 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. PLs, however, are due to various mutations either in the LMNA gene and/or the ZMPSTE24 gene. The mutant protein produced in these conditions is distinct from progerin; however, it is also permanently farnesylated, like progerin. The clinical manifestations of HGPS include a general failure to thrive and progressive growth retardation noticed in the first years of life. The condition is also characterized by dental abnormalities, dermatologic manifestations including a loss of adipose tissue and skin that appears abnormally aged (dry, wrinkled, and taut), and progressive musculoskeletal manifestations including osteoporosis, joint contractures, and skeletal dysplasia. Finally, the finding that is primarily responsible for the mortality of these patients is premature, widespread arteriosclerosis, which can lead to heart failure, myocardial infarction, stroke, or a transient ischemic attack. Patients with HGPS and PLs have a significantly reduced life span, with a range of approximately 8 to 21 years of age and the average age of death being 13 to 14 years.

The Progeria Research Foundation (PRF) estimated in September 2020 that there are approximately 18 HGPS patients and 13 patients with PLs (including processing deficient and processing-sufficient) currently living in the United States. The PRF estimated the prevalence of HGPS in the United States is 1 in 20 million. According to Eiger Biopharmaceuticals, the prevalence of PLs is 1 in 36 million worldwide.

Efficacy

The approval of Zokinvy™ was based on a retrospective survival analysis named the Observational Cohort Survival Study. This study compared survival data from two single-arm, Phase 2 studies (Study 1 and Study 2) of Zokinvy™ to data from matched, untreated patients from a separate natural history cohort.

Study 1 (NCT00425607): Zokinvy™ was evaluated in 28 patients. Of these patients, 26 had classic HGPS, 1 had non-classic HGPS, and 1 had processing-deficient PL with an LMNA heterozygous mutation. Twenty-seven of the 28 patients were included in the Observational Cohort Survival Study. 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.

Study 2 (NCT00916747): Study 2 had two phases. Phase 1 enrolled 26 patients following their completion of Study 1, where the patients continued to receive Zokinvy™ in conjunction with additional therapies for 5 years. The additional therapies included zoledronic acid and pravastatin. Phase 2 of Study 2 enrolled 35 treatment-naïve patients, all of whom were included in the Observational Cohort Survival Study. Thirty-four patients had classic HGPS and 1 had non-classic HGPS. Patients in Phase 2 received Zokinvy™ at a dose of 150 mg/ m^2 twice daily for up to 3 years. Baseline characteristics included:

- 13 females; 22 males
- Median age: 6 years (range, 2–17 years)
- Body weight range: 6.7 kg–22 kg
- BSA range: 0.42 m2–0.90 m2

The Observational Cohort Survival Study collected mortality data from Study 1 and Study 2 (62 patients total) and compared it to data from matched, untreated patients from a separate natural history cohort. This included only HGPS patients. Patients were matched by mutation status, sex, and continent of residence using a fixed 50th percentile matching algorithm. Follow-up time for the matched pairs began at the age the treated patient began receiving Zokinvy™. The survival analysis is summarized in the table below.

Observational Cohort Survival Study Results

	Follow-up time at 3 years		Last follow-up time (up to 11 years)	
	Untreated (n=62)	Zokinvy (n=62)	Untreated (n=62)	Zokinvy (n=62)
Number of deaths (%)	12 (19.4)	5 (8.1)	25 (40.3)	21 (33.9)
Mean survival time (years) (95% CI)	2.6 (2.4, 2.8)	2.8 (2.7, 3.0)	5.5 (4.3, 6.8)	8.0 (6.9, 9.1)
Difference in mean survival time (years) (95% CI)		0.24 (–0.03, 0.50)		2.5 (0.8, 4.1)

Source: Zokinvy Prescribing Information

Key Trial Takeaways: 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. It is important to note that while the longest follow-up time and treatment duration with Zokinvy™ was 11 years for a small number of patients, the median duration of Zokinvy™ exposure varied from patient to patient, with the shortest follow-up time ranging only a few years. Taking this into account, the above results may understate the true survival benefit of Zokinvy™.

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥25%) are 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.

WARNINGS & PRECAUTIONS

- **Risk of Reduced Efficacy or Adverse Reactions Due to Drug Interactions:** Prior to and during treatment, consider potential for drug interactions and review concomitant medications; monitor for adverse reactions.
- **Laboratory Abnormalities:** Monitor for changes in electrolytes, complete blood counts, and liver enzymes.

- **Nephrotoxicity:** Caused nephrotoxicity in rats. Monitor renal function at regular intervals.
- **Retinal Toxicity:** Caused rod-dependent, low-light vision decline in monkeys. Perform ophthalmological evaluation at regular intervals and at the onset of any new visual changes.
- **Impaired Fertility:** Caused impaired fertility in female rats, impaired fertility and testicular toxicity in male rats, and toxicity in the male reproductive tract in monkeys. Advise females and males of reproductive potential of the animal fertility findings.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

- Strong or moderate CYP3A inhibitors or inducers
- Midazolam.
- Lovastatin, simvastatin, and atorvastatin

Clinical Pharmacology

MECHANISMS OF ACTION

Lonafarnib inhibits farnesyltransferase to prevent farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane.

Dose & Administration

ADULTS

In patients 12 months of age and older and with a body surface area of 0.39 m^2 and above: Starting dose of 115 mg/m^2 twice daily and increase dose after 4 months to 150 mg/m^2 twice daily. Round all total daily doses to nearest 25 mg increment.

Table 1 provides the BSA-based dosage recommendations for the starting dosage of 115 mg/m^2 twice daily.

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 provides the BSA-based dosage recommendations for the dosage of 150 mg/m^2 twice daily.

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

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PEDIATRICS

The safety and effectiveness of Zokinvy™ in pediatric patients less than 12 months of age have not been established. If older than 12 month of age, refer to adult dosing.

GERIATRICS

Following a single oral dose of 100 mg lonafarnib in healthy subjects, the plasma lonafarnib AUC and Cmax were 59% and 27% higher in subjects ≥65 years, respectively, compared to subjects 18 to 45 years of age. The observed higher exposure in geriatric subjects is not considered clinically relevant.

RENAL IMPAIRMENT

Zokinvy™ has not been studied in patients with renal impairment.

HEPATIC IMPAIRMENT

Zokinvy™ has not been studied in patients with hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 50 mg and 75 mg.