New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Zokinvy™ (lonafarnib) [Eiger BioPharmaceuticals]**
Dosage Formulations:	50 mg and 75 mg oral capsules
FDA Approval Date: **FDB File Date:**	FDA: November 20, 2020 FDB: December 27, 2020

Indication:	Indicated in patients 12 months of age and older with a body surface area (BSA) ≥ 0.39 m^2:
	• To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)
	• For the treatment of processing-deficient Progeroid Laminopathies (PLs) with either:
	  ○ Heterozygous *LMNA* mutation with progerin-like protein accumulation
	  ○ Homozygous or compound heterozygous *ZMPSTE24* mutations

Mechanism of Action:	Zokinvy is a farnesyltransferase inhibitor that prevents the buildup of progerin and progerin-like proteins within the inner nuclear membrane
Dose/ Administration:	• Starting dose: 115 mg/m^2 twice daily with morning and evening meals.

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	

• Maintenance dose: 150 mg/m^2 twice daily with morning and evening meals after tolerating 4 months of treatment at starting dose.

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

• Dosage adjustments may be necessary in cases of unavoidable drug interactions involving weak CYP3A inhibitors or repeated episodes of nausea and/or diarrhea resulting in dehydration or weight loss.
• Temporarily discontinue Zokinvy for 10 to 14 days before and 2 days after midazolam administration.
• Administration:
  ○ Each dose should be administered whole with a sufficient amount of water
  ○ Capsules may be opened, and contents mixed with 5 to 10 mL Ora Blend SF®, Ora-Plus®, orange juice, or applesauce. Should not be mixed with grapefruit or Seville oranges
  ○ Mixture must be taken within approximately 10 minutes of mixing

Disease State Clinical Highlights:

- HGPS and PLs are rare, genetic, and inevitably fatal conditions diagnosed between 9-24 months of age following a presumed normalcy during infancy. The characteristic appearance of premature aging is often associated with alopecia, head/facial abnormalities, cardiovascular disease, stroke, joint stiffness, and lipodystrophy. Atherosclerosis, the primary cause of premature death, occurs by age 13 on average but ranges from 8-21 years.
- PLs are even more rare than HGPS. According to the Progeria Research Foundation, as of September 30, 2020 there are 128 individuals worldwide living with HGPS and 51 with PLs; 18 and 13 of which are living within the United States (U.S). Prevalence of HGPS in the U.S is estimated between 1 in 18 and 1 in 20 million people.
- HGPS is one of the most severe disorders among laminopathies (diseases resulting from mutations in the lamin genes which encode for the proteins of the nuclear lamina, a matrix of protein located next to the inner nuclear membrane). Pathogenic variants in the *LMNA* gene which encode for the proteins lamin A and C (lamin A/C) have been identified as the cause of HGPS. The mutation of the *LMNA* gene leads to the activation of a cryptic splice site in exon 11 and resultant deletion of 150 nucleotides from *LMNA* mRNA and the synthesis of a truncated protein, progerin. Progerin, a farnesylated mutant lamin A protein, accumulates within the nuclear envelope. Lamin proteins line the inside of the nuclear membrane and are integral in many cellular functions including genome organization, transcription, DNA replication, and DNA repair. Defects in lamin proteins such as lamin A, lead to cellular instability and premature aging.
- PLs are caused by various mutations in either the *LMNA* gene and/or the *ZMPSTE24* gene. These forms of laminopathies do not result in the production of progerin but are associated with disease characteristics and traits that overlap with Progeria. Although patients with processing-deficient PLs were not adequately represented in the clinical trials, it is assumed that products that show effectiveness in patients with HGPS will likely be effective in patients with processing-deficient PLs.

Drug Clinical Highlights:

- Received Orphan Drug Status, Breakthrough Therapy Designation and Rare Pediatric Disease Designation.
- Clinical Trials: Phase 2, open-label, single-arm
  - Study 1 (n=28): Patients aged 3-16 with a BSA of 0.38-0.75 m^2 were initiated on 115 mg/m^2 twice daily and increased to 150 mg/m^2 twice daily after 4 months if initial dose was tolerated. Treatment duration: 24-30 months.
    - 26 patients with classic HGPS, 1 with non-classic HGPS, and 1 with processing-deficient PL with *LMNA* heterozygous mutation with progerin-like protein accumulation
  - Study 2: Patients aged 2-17 with a BSA of 0.42-0.90m^2. Consisted of 2 study phases and included patients who completed Study 1. Within Phase 1, 26 patients received Zokinvy with additional therapies (zoledronic acid and pravastatin) for 5 years, followed by Phase 2 in which 35 treatment-naïve patients received Zokinvy 150 mg/m^2 twice daily for up to 3 years.
    - 34 patients with classic HGPS and 1 with non-classic HGPS
  - Result: 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 of up to 11 years compared to untreated patients from a separate natural history cohort.

	Follow-up time censored at 3-years		Last follow-up time	
Summary	**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)	8.9 (6.9, 9.1)
Difference in Mean Survival Time (years) (95% CI)	--	0.24 (-0.03, 0.50)	--	2.5 (0.8, 4.1)
Hazard Ratio for Risk of Death (95% CI)	--	0.30 (0.10, 0.89)	--	0.40 (0.21, 0.77)

- Warnings and Precautions: reduced efficacy or adverse reactions caused drug interactions, laboratory abnormalities, nephrotoxicity, retinal toxicity, impaired fertility, embryo-fetal toxicity
- Contraindicated in patients taking strong or moderate CYP3A inhibitors or inducers, midazolam, lovastatin, simvastatin, or atorvastatin
- Adverse Reactions

Adverse Reactions (≥ 38%)	Zokinvy n=63 n (%)	Adverse Reactions (≥ 21-37%)	Zokinvy n=63 n (%)
Vomiting	57 (90%)	Headache	23 (37%)
Diarrhea	51 (81%)	Weight decreased	23 (37%)
Infection	49 (78%)	Increased aspartate aminotransferase	22 (35%)
Nausea	35 (56%)	Myelosuppression	22 (35%)
Decreased appetite (anorexia)	33 (53%)	Cough	21 (33%)
Fatigue	32 (51%)	Ocular changes	15 (24%)
Upper respiratory tract infection	32 (51%)	Decreased blood bicarbonate	21 (33%)
Abdominal pain	30 (48%)	Hypertension	18 (29%)
Musculoskeletal pain	30 (48%)	Increased alanine aminotransferase	17 (27%)
Electrolyte abnormalities	27 (43%)	Epistaxis	13 (21%)

Price Per Unit (WAC):

- 50 mg bottle (30 capsules): $21,510 WAC
- 75 mg bottle (30 capsules): $32,265 WAC

Total Daily Dose	Recommended Dosing Regimen	Monthly Cost (WAC)	Annual Cost (WAC)
100 mg	Two 50 mg capsules (1 in the morning and 1 in the evening)	$43,020	$516,240
300 mg	Four 75 mg capsules (2 in the morning and 2 in the evening)	$129,060	$1,548,720

Therapeutic Alternatives:

- Zokinvy represents the first FDA-approved disease-modifying treatment for HGPS and PLs. Current treatment options are limited to supportive care directed towards disease complications.
- Pravastatin and zoledronic acid have been shown to inhibit progerin production upstream of the farnesylation seen with Zokinvy via their effect on the mevalonate pathway, also known as the HMG-CoA reductase pathway, and have also been evaluated in small clinical trials but have not been accepted as primary therapy options. Trials have documented an increase in bone mineral density as well as skin aging external markers (wrinkles).
- Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has also been shown to decrease insoluble progerin aggregates, increase proliferation, and correct misshapen nuclei.

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with a geneticist or other specialist in the treated disease state
- Documented diagnosis of HGPS or processing-deficient PLs with either heterozygous *LMNA* mutation with progerin-like protein accumulation or homozygous or compound heterozygous *AMPSTE24* mutations
- Participant is aged ≥ 12 months
- Participant has a BSA ≥ 0.39 m^2
- Participant (female of childbearing age) is not pregnant
- Lack of concurrent therapy with midazolam, lovastatin, simvastatin, or atorvastatin

	Continuation of Therapy: • None **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Baseline and repeated as necessary: ophthalmology and dental exams, audiometry, liver and renal function, vital signs (e.g., blood pressure), lipid panel, electrocardiogram, neurological examination, assessments of daily living • Routine physical and occupational therapy
Implication to State Medicaid Program:	• Phase III clinical trials are ongoing to evaluate the efficacy of lonafarnib in combination with ritonavir with or without peginterferon alfa-2a for the treatment of Hepatitis D. • A Phase I/II Trial of everolimus in combination with lonafarnib in progeria is currently enrolling by invitation.

References:

1. ZOKINVY™ (lonafarnib) [package insert]. Palo Alto, CA: Eiger BioPharmaceuticals, Inc.; November 2020.
2. NIH: U.S. National Library of Medicine. Phase II Trial of Lonafarnib (a Farnesyltransferase Inhibitor) for Progeria. https://clinicaltrials.gov/ct2/show/NCT00425607?term=NCT00425607&draw=2&rank=1. 10 December 2020.
3. National Organization for Rare Disorders (NORD): Hutchinson-Gilford Progeria. https://rarediseases.org/rare-diseases/hutchinson-gilford-progeria/. 10 December 2020.
4. Gordon, L.B, Shappell, H., Massaro, J., et.al. Association of Lonafarnib Treatment vs No Treatment with Mortality Rate in Patients with Hutchinson-Gilford Progeria Syndrome. JAMA. 2018 April 24; 319(16):1687-1695. 10 December 2020.
5. Dorado, B., Ploen G.G., Barettino, A., et al. Generation and characterization of a novel knockin minipig model of Hutchinson-Gilford progeria syndrome. Cell Discovery. https://www.nature.com/articles/s41421-019-0084-z#citeas. 10 December 2020.
6. U.S. Food & Drug Administration (FDA): News Release: FDA Approved First Treatment for Hutchinson-Gilford Progeria Syndrome and Some Progeroid Laminopathies. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-hutchinson-gilford-progeria-syndrome-and-some-progeroid-laminopathies. 10 December 2020.
7. IPD Analytics: New Drug Review: Zokinvy (lonafarnib). Accessed 10 December 2020.
8. Progeria Research Foundation. PRF by the numbers. Published September 30, 2020. Accessed 10 December 2020. https://progeriaresearch.org/wp-content/uploads/2020/10/PRF-By-the-Numbers_-FINAL-October2020.pdf
9. Clements, C.S., Bikkul, M.U., Ofosu, W., et. al. Presence and distribution of progerin in HGPS cells is ameliorated by drugs that impact on the mevalonate and mTOR pathways. Biogerontology. 20, 337-358 (2019). https://doi.org/10.1007/s10522-019-09807-4.
10. IPD Analytics: RxBrief: Hepatitis D – Is It the Next Hepatitis C? Accessed 13 April 2021.