PDL DRUG REVIEW

Proprietary Name: Zokinvy®
Common Name: lonafarnib
PDL Category: Progeria Treatments

Summary

Pharmacology/Usage: Lonafarnib, the active ingredient of Zokinvy®, is a farnesyltransferase inhibitor. It inhibits farnesyltransferase to prevent farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane.

Indication: In patients 12 months of age and older with a body surface area (BSA) of 0.39m^2 and above:

- To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)
- For the 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 include that Zokinvy® is not indicated for 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies, Zokinvy® can cause embryofetal harm when administered to a pregnant woman. There are no human data on Zokinvy® use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the risk to a fetus. The safety and efficacy of use in the pediatric population younger than 12 months of age have not been established.

Dosage Form: Capsules: 50mg, 75mg

Recommended Dosage: The starting dosage for patients with a BSA of 0.39m^2 and above is 115mg/m^2 BID with morning and evening meals to reduce the risk of GI adverse reactions. An appropriate dosage strength of Zokinvy® is not available for patients with a BSA of less than 0.39m^2. After 4 months of treatment, increase the dosage to 150mg/m^2 BID with morning and evening meals. Round all total daily dosages to the nearest 25mg increment. Refer to the prescribing information regarding specific BSA-based dosage recommendations for both the starting dose and the titrated dose.

If a dose is missed, take the dose as soon as possible with food, up to 8 hours prior to the next scheduled dose. If less than 8 hours remains before the next scheduled dose, skip the missed dose, and resume taking Zokinvy® at the next scheduled dose.

For patients who have increased the dose to 150mg/m^2 BID and are experiencing repeated episodes of vomiting and/or diarrhea resulting in dehydration or weight loss, Zokinvy® can be dose reduced to the starting dose of 115mg/m^2 BID. Ensure Zokinvy® is taken BID with meals and an adequate amount of water. For patients who are

unable to swallow capsules, the entire contents of the capsules can be mixed with Ora Blend SF or Ora-Plus or, for patients unable to access or tolerate Ora Blend SF or Ora-Plus, the contents of the capsule can be mixed with orange juice (5-10ml per capsule) or applesauce (1-2 teaspoonfuls per capsule). Do not mix with juice containing grapefruit or Seville oranges. The mixture must be prepared fresh for each dose and be taken within about 10 minutes of mixing.

Zokinvy® has not been studied in patients with renal or hepatic impairment.

Drug Interactions: Use of Zokinvy® with a strong or moderate CYP3A inhibitor is contraindicated. Avoid consumption of grapefruit or Seville oranges. Avoid coadministration of Zokinvy® with weak CYP3A inhibitors; however, if coadministration is unavoidable, reduce to or continue Zokinvy® at a dosage of 115mg/m^2. During coadministration, closely monitor for arrhythmias and events such as syncope and heart palpitations. Resume previous Zokinvy® dosage 14 days after discontinuing the weak CYP3A inhibitor.

Use of Zokinvy® with a strong or moderate CYP3A inducer is contraindicated. No Zokinvy® dosage adjustment is recommended if use concomitantly with weak CYP3A inducers.

Avoid coadministration of Zokinvy® with CYP2C9 inhibitors. If coadministration is unavoidable, closely monitor patients for arrhythmias and events such as syncope and heart palpitations.

Coadministration of Zokinvy® with the CYP3A substrates midazolam, lovastatin, simvastatin, or atorvastatin is contraindicated, as coadministration of Zokinvy® with a CYP3A substrate increases the AUC and Cmax of the CYP3A substrate, which may increase the risk of the CYP3A substrate's adverse reactions. Avoid coadministration of Zokinvy® with sensitive CYP3A substrates. If coadministration of 11 other sensitive CYP3A substrates is unavoidable, monitor for adverse reactions and reduce the dosage of these sensitive CYP3A substrates per the approved product label. When Zokinvy® is co-administered with certain CYP3A substrates where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions, and reduce the dosage of the CYP3A substrate per its approved product labeling.

Loperamide is contraindicated in patients less than 2 years of age. When Zokinvy® is used concomitantly with loperamide, do not exceed loperamide 1mg QD when first co-administered. Slowly increase loperamide dosage with caution.

Avoid the coadministration of Zokinvy® with CYP2C19 substrates. If coadministration is unavoidable, monitor for adverse reactions and reduce the dosage of the CYP2C19 substrate per its approved product label.

When Zokinvy® is co-administered with P-gp substrates (e.g. digoxin, dabigatran) where minimal concentration changes may lead to serious toxicities, monitor for adverse reactions, and reduce the dosage of the P-gp substrate in accordance with its approved label.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zokinvy®). Please note that there was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included vomiting (90%), diarrhea (81%), nausea (56%), abdominal pain (48%), constipation (22%), flatulence (6%), fatigue (51%), pyrexia (14%), infection (78%), upper respiratory tract infection (51%), rhinitis (19%), decreased appetite (anorexia; 53%), electrolyte abnormalities (43%), weight decrease (37%), myelosuppression (35%), increased aspartate aminotransferase (35%), decreased blood bicarbonate (33%), hypertension (29%), increased alanine aminotransferase (27%), dehydration (5%), musculoskeletal pain (48%), headache (37%), cerebral ischemia (11%), ocular changes (24%), depressed mood (5%), cough (33%), epistaxis (21%), rash (11%), pruritus (8%), and mucositis (8%).

As noted above, laboratory abnormalities developed with Zokinvy® treatment. These laboratory abnormalities often improved while continuing Zokinvy®, but it is not possible to exclude Zokinvy® as a cause of the abnormalities. Periodically monitor electrolytes, complete blood counts, and liver enzymes, and manage abnormalities accordingly.

Lonafarnib caused nephrotoxicity in animals at drug exposures about equal to that achieved with the human dose. Monitor renal function at regular intervals during Zokinvy® treatment.

Lonafarnib caused rod-dependent, low-light vision decline in animals at drug exposures similar to that achieved with the human dose. Perform ophthalmological evaluation at regular intervals and at the onset of any new visual changes during Zokinvy® therapy.

Contraindications: In patients taking

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

Manufacturer: Eiger Biopharmaceuticals, Inc

Analysis: 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 study that assessed the efficacy of Zokinvy® in patients (N=28; 26 with classic HGPS, one with non-classic HGPS, and one with Progeroid Laminopathy with *LMNA* heterozygous mutation with progerin-like protein accumulations) who were treated for 24 to 30 months. Among the 28 patients treated, 27 patients with HGPS (16 females, 11 males) were included in the survival analysis. The median age at treatment initiation was 7.5 years for the 27 patients (range 3 to 16 years), while the body weight range was 6.6 to 17.6kg and the BSA range was 0.38 to 0.75m^2.

After completion of study 1, 26 patients enrolled in a second phase 2 open-label, single-arm study (study 2) that consisted of 2 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® 150mg/m^2 BID for a period of up to 3 years. There were 35 treatment naïve patients with HGPS enrolled into the second phase of study 2. Of the 35 treated patients (22 males, 13 females), 34 patients had classic HGPS and 1 patient had non-classic HGPS. The median age of included patients was 6 years (range 2 to 17 years), while the body weight range was 6.7 to 22kg and the BSA range was 0.42 to 0.9m^2.

The retrospective survival analysis was based on the mortality data from 62 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 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. The survival analysis can be seen in the table below, which was adapted from the prescribing information.

	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	2.6	2.8	5.5	8.0
Difference in mean survival time, years	-	0.24	-	2.5
HR for risk of death	-	0.30	-	0.40

^ Includes 27 patients in study 1 and 35 treatment-naïve patients in study 2

Place in Therapy: Zokinvy® is an oral farnesyltransferase inhibitor indicated in patients 12 months of age and older with a body surface area (BSA) of 0.39m^2 and above to reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS) and for the treatment of processing-deficient Progeroid Laminopathies with either 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. Based on its mechanism of action, Zokinvy® would not be expected to be effective in these populations. The efficacy of Zokinvy® is based on results from the Observational Cohort Survival study, retrospectively comparing survival data from two phase 2 studies in patients with HGPS to those from a natural history cohort. There were fewer deaths in the Zokinvy® group than the untreated group, and the mean survival time increased 2.5 years through the last follow-up time (11 years) compared to untreated patients.

It is recommended that Zokinvy® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Zokinvy [package insert]. Alto, CA: Eiger Biopharmaceuticals, Inc; 2020.