HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOKINVY safely and effectively. See full prescribing information for ZOKINVY.

ZOKINVY™ (lonafarnib) capsules, for oral use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

ZOKINVY is a farnesyltransferase inhibitor indicated in patients 12 months of age and older with a body surface area of 0.39 m² and above (1):

- To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome
- For 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:

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 (1)

DOSAGE AND ADMINISTRATION

- Start at 115 mg/m² twice daily with morning and evening meals (2.1)
- After 4 months, increase to 150 mg/m² twice daily (2.1)
- Round all total daily doses to nearest 25 mg increment (2.1)
- Swallow capsules whole. If unable to swallow capsules, mix contents with Ora Blend SF®, Ora-Plus®, orange juice, or applesauce (2.5).
- See Full Prescribing Information for additional instructions on dosing, preparation and administration (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg and 75 mg (3)

CONTRAINDICATIONS

- Strong or moderate CYP3A inhibitors or inducers (4)
- Midazolam (2.4, 4)
- Lovastatin, simvastatin, and atorvastatin (4)

WARNINGS AND 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 (5.1, 7)
- Laboratory Abnormalities: Monitor for changes in electrolytes, complete blood counts, and liver enzymes (5.2)
- Nephrotoxicity: Caused nephrotoxicity in rats. Monitor renal function at regular intervals (5.3, 13.2)
- 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 (5.4, 13.2)
- 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 (5.5, 13.1, 13.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the risk to a fetus and to use effective contraception (5.6, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥25%) are vomiting, diarrhea, infection, nausea, decreased appetite, fatigue, upper respiratory tract infection, abdominal pain, muscularkeletal pain, electrolyte abnormalities, decreased weight, headache, myelosuppression, increased aspartate aminotransferase, decreased blood bicarbonate, cough, hypertension, and increased alanine aminotransferase (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eiger BioPharmaceuticals, Inc. at 833-267-0545 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Reduce to or continue at 115 mg/m² twice daily with concomitant use of weak CYP3A inhibitors (2.3, 7)
- See Full Prescribing Information for additional information regarding drug interactions (2.4, 4, 5.1, 7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2020

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**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

**ZOKINVY** is indicated in patients 12 months of age and older with a body surface area (BSA) of 0.39 m² 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**

**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.

**2 DOSAGE AND ADMINISTRATION**

Table 1 provides the BSA-based dosage recommendations for the starting dosage of 115 mg/m² twice daily.

**Table 1: Recommended Dosage and Administration for 115 mg/m² Body Surface Area-Based Dosing**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total Daily Dosage Rounded to Nearest 25 mg</th>
<th>Morning Dosing Number of Capsule(s)</th>
<th>Evening Dosing Number of Capsule(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOKINVY 50 mg</td>
<td>ZOKINVY 75 mg</td>
<td>ZOKINVY 50 mg</td>
<td>ZOKINVY 75 mg</td>
</tr>
<tr>
<td>0.39 - 0.48</td>
<td>100</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.49 - 0.59</td>
<td>125</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.6 - 0.7</td>
<td>150</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.71 - 0.81</td>
<td>175</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.82 - 0.92</td>
<td>200</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.93 - 1</td>
<td>225</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2 provides the BSA-based dosage recommendations for the dosage of 150 mg/m² twice daily.

**Table 2: Recommended Dosage and Administration for 150 mg/m² Body Surface Area-Based Dosing**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total Daily Dosage Rounded to Nearest 25 mg</th>
<th>Morning Dosing Number of Capsule(s)</th>
<th>Evening Dosing Number of Capsule(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOKINVY 50 mg</td>
<td>ZOKINVY 75 mg</td>
<td>ZOKINVY 50 mg</td>
<td>ZOKINVY 75 mg</td>
</tr>
<tr>
<td>0.39 - 0.45</td>
<td>125</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.46 - 0.54</td>
<td>150</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.55 - 0.62</td>
<td>175</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.63 - 0.7</td>
<td>200</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.71 - 0.79</td>
<td>225</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0.8 - 0.87</td>
<td>250</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.88 - 0.95</td>
<td>275</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.96 - 1</td>
<td>300</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**2.1 Recommended Dosage**

- The starting dosage of **ZOKINVY** for patients with a BSA of 0.39 m² and above is 115 mg/m² twice daily with morning and evening meals (see Table 1) to reduce the risk of gastrointestinal adverse reactions [see Adverse Reactions (6.1)]. An appropriate dosage strength of **ZOKINVY** is not available for patients with a BSA of less than 0.39 m² [see Indications and Usage (1)].
- After 4 months of treatment, increase the dosage to 150 mg/m² twice daily with morning and evening meals (see Table 2).
- Round all total daily dosages to the nearest 25 mg increment (see Table 1 and Table 2).
- 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.

**2.2 Dosage Modifications for Gastrointestinal Adverse Reactions**

For patients who have increased their dose of **ZOKINVY** to 150 mg/m² twice daily 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 115 mg/m² twice daily (see Table 1). Ensure **ZOKINVY** is taken with the morning and evening meals and with an adequate amount of water.

**2.3 Dosage Modifications for Drug Interactions**

**CYP3A Inhibitors**

If concomitant use of **ZOKINVY** with a weak CYP3A inhibitor is unavoidable [see Warnings and Precautions (5.1), Drug Interactions (7.1)],

- Reduce to or continue **ZOKINVY** at the starting dosage of 115 mg/m² twice daily (see Table 1).
- Resume the previous **ZOKINVY** dosage 14 days after discontinuing the concomitant use of the weak CYP3A inhibitor.

**2.4 Temporary Discontinuation for Midazolam Use**

Temporarily discontinue **ZOKINVY** for 10 to 14 days before and 2 days after administration of midazolam [see Contraindications (4), Drug Interactions (7.2)].

**2.5 Preparation and Administration Instructions**

Administer **ZOKINVY** orally with the morning and evening meals.
5.2 Laboratory Abnormalities
Some patients treated with ZOKINVY developed laboratory abnormalities [see Adverse Reactions (6.1)]. These included:
• Electrolyte abnormalities (43%), such as hyperkalemia, hypokalemia, hyponatremia, or hypercalcemia
• Myelosuppression (35%), such as reductions in absolute neutrophil count, white blood cell counts, lymphocytes, hemoglobin, or hematocrit
• Increased liver enzymes, such as aspartate aminotransferase (35%), or alanine aminotransferase (27%)
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.

5.3 Nephrotoxicity
Lonafarnib caused nephrotoxicity in rats at plasma drug exposures approximately equal to that achieved with the human dose [see Nonclinical Toxicology (13.2)]. Monitor renal function at regular intervals during ZOKINVY therapy.

5.4 Retinal Toxicity
Lonafarnib caused rod-dependent, low-light vision decline in monkeys at plasma drug exposures similar to that achieved with the human dose [see Nonclinical Toxicology (13.2)]. Perform ophthalmological evaluation at regular intervals and at the onset of any new visual changes during ZOKINVY therapy.

5.5 Impaired Fertility
Lonafarnib caused impaired fertility in female rats at 1.2 times the human dose based on plasma drug exposure [see Nonclinical Toxicology (13.1)].
Lonafarnib caused impaired fertility and testicular toxicity in male rats at 1.5 times the human dose based on plasma drug exposure [see Nonclinical Toxicology (13.1)], and toxicity in the male reproductive tract in monkeys at doses lower than the human dose based on plasma drug exposure [see Nonclinical Toxicology (13.2)].
Advise females and males of reproductive potential of the animal fertility findings, and that the impact on pubertal development and the potential for impaired fertility with ZOKINVY therapy in humans have not been adequately evaluated [see Use in Specific Populations (8.3)].

5.6 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, ZOKINVY can cause embryo-fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lonafarnib in pregnant rats during organogenesis produced embryo-fetal toxicity at plasma drug exposures that were approximately equal to the recommended human dose. In pregnant rabbits, oral administration of lonafarnib during organogenesis produced skeletal malformations and variations at exposures lower than the human exposure. Advise pregnant women of the risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant and to use appropriate effective contraception during treatment with ZOKINVY [see Use in Specific Populations (8.3)].

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 84 subjects were treated with at least one dose of ZOKINVY with or without additional therapy, of which 8 were treated at a dosage of at least 115 mg/m² twice daily for greater than or equal to 10 years. The safety profile of ZOKINVY is based on 128 patient-years of treatment exposure (62 patients with HGPS and 1 patient with processing-deficient Progeroid Laminopathy with LMNA heterozygous mutation) and pooled results from two Phase 2 open-label, single-arm trials (n=63: 28 patients from Study 1 and 35 treatment naive patients from Study 2). In Study 1, ZOKINVY treatment was initiated at 115 mg/m² twice daily and increased to 150 mg/m² twice daily after approximately 4 months for a total treatment duration of 24 to 30 months. Treatment naive patients in Study 2 received ZOKINVY 150 mg/m² twice daily for up to 36 months. In both studies,
ZOKINVY was administered orally via capsules or the capsule contents were mixed with Ora Blend SF or Ora-Plus and administered orally as a suspension.

In these two studies, a total of 63 patients received ZOKINVY for a median duration of 2.2 years, with approximately 1.9 years at the recommended dose of 150 mg/m2 twice daily. The population was 2 to 17 years old, with a similar proportion of males (33 [52%] patients) and females (30 [48%] patients). Most patients had classic HGPS (60 [95%] patients) compared to non-classic HGPS (2 [3%] patients) and 1 (2%) patient had Progeroid Laminopathy with LMNA heterozygous mutation.

Table 3 summarizes adverse reactions reported in the clinical trials. 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.

Table 3: Adverse Reactions in ≥5% of Patients in Study 1 and Treatment-Naïve Patients in Study 2 Receiving ZOKINVY

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ZOKINVY n=63, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>57 (90%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51 (81%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (56%)</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>30 (48%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (22%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (6%)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (51%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (14%)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Infection‡</td>
<td>49 (78%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection§</td>
<td>32 (51%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12 (19%)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite (anorexia)</td>
<td>33 (53%)</td>
</tr>
<tr>
<td>Electrolyte abnormalities¶</td>
<td>27 (43%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>Myelosuppression∥</td>
<td>22 (35%)</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>22 (35%)</td>
</tr>
<tr>
<td>Decreased blood bicarbonate</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain¶</td>
<td>30 (48%)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>Cerebral ischemia¶</td>
<td>7 (11%)</td>
</tr>
</tbody>
</table>

†Abdominal pain includes stomach pain and abdominal pain.
‡Infection includes abdominal infection, candidiasis, chicken pox, Clostridium difficile colitis, colitis, croup, dengue fever, flu syndrome, fungal infection, gastroenteritis, gastrointestinal infection, Helicobacter pylori infection, infection, infection viral, influenza, nail infection, otitis media, parotitis, perirectal abscess, pneumonia, small intestine infection, submandibular lymphadenitis, tonsillitis, viral infection.
§Upper respiratory infection includes bronchial infection, bronchitis, sinus infection, and upper respiratory infection.
¶Electrolyte abnormalities includes hypermagnesemia, hypokalemia, hyperkalemia, hypernatremia, hypercalcemia, hyperphosphatemia, hypocalcemia, and hypernatremia.
∥Myelosuppression includes absolute neutrophil count decreased, low total white blood cells, lymphopenia, decreased hemoglobin, and hematocrit low.

As noted in Table 3, gastrointestinal adverse reactions were the most frequently reported adverse reactions. Of the 57 patients who experienced vomiting, 30 (53%) patients had mild vomiting (defined as no intervention required), 26 (46%) patients had moderate vomiting (defined as outpatient intravenous hydration; medical intervention required), and 1 (2%) patient had severe vomiting (defined as tube feeding, total parental nutrition, or hospitalization indicated). Of the 35 patients who experienced nausea, 34 (97%) had mild nausea (defined as loss of appetite without alteration in eating habits) and 1 (3%) patient had moderate nausea (defined as oral intake decreased without significant weight loss, dehydration, or malnutrition). During the first four months of treatment in Study 1, 19 (68%) patients had vomiting and 10 (36%) patients had nausea. By the end of therapy, 4 (14%) patients who were still on ZOKINVY required antiemetics or anti-nauseants. A total of 4 patients discontinued ZOKINVY, mostly due to nausea or vomiting.

Of the 51 patients who experienced diarrhea, the majority of patients (approximately 92%) experienced mild or moderate diarrhea; 38 (75%) patients reported mild diarrhea (defined as an increase of less than 4 stools per day over baseline) and 9 (18%) patients reported moderate diarrhea (defined as an increase of 4 to 6 stools per day over baseline; limiting instrumental activities of daily living). Four (8%) patients reported severe diarrhea (defined as an increase of seven or more stools per day; hospitalization indicated).
over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living). During the first four months of treatment in Study 1, 23 (82%) patients had diarrhea; by the end of therapy, 3 (11%) patients had diarrhea. Twelve (43%) patients were treated with loperamide.

Alanine Aminotransferase and Aspartate Aminotransferase Elevations
Increased alanine aminotransferase was commonly reported (17 [27%] patients). Of the 17 patients with increased alanine aminotransferase, 14 (82%) patients had mild increases (defined as greater than upper limit of normal (ULN) to 3.0 times ULN if baseline was normal; 1.5 to 3.0 times ULN if baseline was abnormal), 1 (6%) patient had moderate increases (defined as greater than 3.0 to 5.0 times ULN if baseline was normal or abnormal), and 2 (12%) patients had severe increases (defined as greater than 5.0 to 20.0 times ULN if baseline was normal or abnormal). Increased aspartate aminotransferase was also commonly reported (22 [35%] patients). Of the 22 patients with increased aspartate aminotransferase, 21 (95%) patients had mild increases (defined as greater than ULN to 3.0 times ULN if baseline was normal; 1.5 to 3.0 times ULN if baseline was abnormal) and 1 (5%) patient had a severe increase (defined as greater than 5.0 to 20.0 times ULN if baseline was normal or abnormal). One patient with alanine and aspartate aminotransferase elevations also experienced hypertriglyceridemia and hyperglycemia resulting in discontinuation of ZOKINVY.

Hypertension
Increases in blood pressure have been documented in patients treated with ZOKINVY. At baseline 22 (35%) patients had either a systolic blood pressure or a diastolic blood pressure or both above the 95th percentile. Over the course of the trials, 18 (29%) patients had hypertension based on systolic blood pressure or diastolic blood pressure measurements above the 95th percentile on 3 or more occasions. Five (8%) patients who were normotensive at baseline had either systolic blood pressure or diastolic blood pressure above the 95th percentile at the end of treatment.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on ZOKINVY
Table 4 presents clinically significant drug interactions involving drugs that affect ZOKINVY.

<table>
<thead>
<tr>
<th>CYP3A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td><strong>Prevention or Management</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP3A Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td><strong>Prevention or Management</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2C9 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td><strong>Prevention or Management</strong></td>
</tr>
</tbody>
</table>
Lonafarnib is a strong CYP3A mechanism-based inhibitor. Coadministration of ZOKINVY with a CYP3A substrate increases the AUC and C\text{max} of the CYP3A substrate [see Clinical Pharmacology (12.3)] which may increase the risk of the CYP3A substrate’s adverse reactions, including myopathy or rhabdomyolysis (with statins), or extreme sedation or respiratory depression (with midazolam).

### Prevention or Management

**HMG CoA reductase inhibitors (“Statins”)**
Coadministration of ZOKINVY with lovastatin, simvastatin, or atorvastatin is contraindicated [see Contraindications (4)].

**Midazolam**
Coadministration of ZOKINVY with midazolam is contraindicated [see Contraindications (4)]. Temporarily discontinue ZOKINVY for 10-14 days before and 2 days after administration of midazolam [see Dosage and Administration (2.4)].

**Other sensitive CYP3A substrates**
Avoid coadministration of ZOKINVY with sensitive CYP3A substrates. As noted above, use with lovastatin, simvastatin, or atorvastatin, and midazolam is contraindicated [see Contraindications (4)]. If coadministration of other sensitive CYP3A substrates is unavoidable, monitor for adverse reactions and reduce the dosage of those sensitive CYP3A substrate(s) in accordance with their approved product labeling.

**Certain CYP3A substrates**
When ZOKINVY is coadministered 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 in accordance with its approved product labeling.

### Loperamide

Lonafarnib is a weak inhibitor of P-gp and strong inhibitor of CYP3A. Coadministration of ZOKINVY with loperamide increases the AUC and C\text{max} of loperamide [see Clinical Pharmacology (12.3)] which may increase the risk of loperamide’s adverse reactions.

### Prevention or Management

Loperamide is contraindicated in patients less than 2 years of age. When ZOKINVY is coadministered with loperamide, do not exceed loperamide 1 mg once daily when first coadministered. Slowly increase loperamide dosage with caution in accordance with its approved product labeling.

### CYP2C19 Substrates

Lonafarnib is a moderate CYP2C19 inhibitor. Coadministration of ZOKINVY with a CYP2C19 substrate increases the AUC and C\text{max} of the CYP2C19 substrate [see Clinical Pharmacology (12.3)] which may increase the risk of the CYP2C19 substrate’s adverse reactions.

### Prevention or Management

Avoid coadministration of ZOKINVY with CYP2C19 substrates. If coadministration is unavoidable, monitor for adverse reactions and reduce the dosage of the CYP2C19 substrate in accordance with its approved product labeling.

### P-gp Substrates

Lonafarnib is a weak P-gp inhibitor. Coadministration of ZOKINVY with a P-gp substrate increases the AUC and C\text{max} of the P-gp substrate [see Clinical Pharmacology (12.3)], which may increase the risk of the P-gp substrate’s adverse reactions.

### Prevention or Management

When ZOKINVY is coadministered with P-gp substrates (e.g., digoxin, dabigatran) where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions and reduce the dosage of the P-gp substrate in accordance with its approved product labeling.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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 evaluate 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.

In animal reproduction studies, oral administration of lonafarnib to pregnant rats during organogenesis produced embryo-fetal toxicity at exposures...
that were 1.2-times the human exposure at the recommended dose of 150 mg/m² twice daily. In pregnant rabbits, oral administration of lonafarnib during organogenesis produced skeletal malformations and variations at exposures lower than the human exposure at 150 mg/m² twice daily, and maternal toxicity at 26 times the human exposure at 150 mg/m² twice daily (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, oral administration of lonafarnib during organogenesis produced an increase in post-implantation loss (resorptions) and decreases in fetal body weight and number of live fetuses at 30 mg/kg/day (1.2 times the AUC [area under the plasma concentration-time curve] in humans at the recommended dose of 150 mg/m² twice daily). No effects on embryo-fetal development in rats were observed at systemic exposures lower than the human AUC at 150 mg/m² twice daily.

In rabbits, oral administration of lonafarnib during organogenesis resulted in skeletal malformations and variations at systemic exposures lower than the human AUC at the recommended dose of 150 mg/m² twice daily, and maternal toxicity (body weight loss and abortion) at 120 mg/kg/day (26 times the human AUC at 150 mg/m² twice daily).

No effects in offspring were observed in a pre- and postnatal development study in rats with maternal administration of up to 20 mg/kg/day orally (AUC lower than the human AUC at 150 mg/m² twice daily) during organogenesis through lactation.

8.2 Lactation

Risk Summary

There are no data on the presence of ZOKINVY in human milk, the effects on the breastfed infant, or the effects on milk production. Lonafarnib is excreted in rat milk (see Data). When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOKINVY and any potential adverse effects of the breastfed infant from ZOKINVY or from the underlying maternal condition.

Data

Lonafarnib is excreted in milk following oral administration in lactating rats, with a mean milk to plasma concentration ratio of 1.5 at 12 hours.

8.3 Females and Males of Reproductive Potential

Contraception

ZOKINVY can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use appropriate effective contraception during treatment with ZOKINVY.

Infertility

Based on findings in rats, ZOKINVY may reduce fertility in females and males of reproductive potential [see Warnings and Precautions (5.5), Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in pediatric patients 12 months of age and older. Use of ZOKINVY for these indications is supported by adequate and well controlled studies in pediatric patients 2 years of age and older [see Clinical Studies (14)].

The safety and effectiveness of ZOKINVY in pediatric patients less than 12 months of age have not been established.

8.6 Adult Use

The safety and effectiveness of ZOKINVY for the treatment of HGPS and processing-deficient Progeroid Laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations) have been established in adults. Use of ZOKINVY in adults for these indications is based on adequate and well controlled studies in pediatric patients 2 years of age and older [see Clinical Studies (14)].

11 DESCRIPTION

ZOKINVY (lonafarnib) is a farnesyltransferase inhibitor. The chemical name for lonafarnib is 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[1,2]cyclohepta [2,4-b]pyridin-11-yl]piperidin-1-yl][2-oxoethyl]piperidine-1-carboxamide. Its molecular formula is C_{27}H_{31}Br_{2}ClN_{4}O_{2}, molecular mass is 638.8 g/mol, and its chemical structure is depicted below.
Table 6: Summary of Pharmacokinetic Parameters of Lonafarnib at Steady State after Oral Administration Twice Daily to Patients with HGPS

<table>
<thead>
<tr>
<th>Lonafarnib Dose</th>
<th>Median (range) t&lt;sub&gt;max&lt;/sub&gt; (hr)</th>
<th>Mean (SD) C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>Mean (SD) AUC&lt;sub&gt;0-8hr&lt;/sub&gt; (ng*hr/mL)</th>
<th>Mean (SD) AUC&lt;sub&gt;tau&lt;/sub&gt; (ng*hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115 mg/m²</td>
<td>N 23</td>
<td>23</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Results</td>
<td>2 (0, 6)</td>
<td>1777 (1083)</td>
<td>9869 (6327)</td>
<td>12365 (9135)</td>
</tr>
<tr>
<td>150 mg/m²</td>
<td>N 18</td>
<td>18</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Results</td>
<td>4 (0, 12)</td>
<td>2695 (1090)</td>
<td>16020 (4978)</td>
<td>19539 (6434)</td>
</tr>
</tbody>
</table>

Absorption
The absolute bioavailability of lonafarnib following oral administration has not been determined. Following oral administration of lonafarnib 75 mg and 100 mg twice daily in healthy subjects under fasted conditions, the geometric mean (CV%) maximum peak plasma concentrations of lonafarnib were 834 (32%) ng/mL and 964 (32%) ng/mL, respectively.

Effect of Food
Following a single oral dose of 75 mg lonafarnib in healthy subjects, the C<sub>max</sub> decreased 55% and AUC decreased 29% with a high-fat meal (approximately 43% fat of the total 952 calories) compared to fasted conditions. C<sub>max</sub> decreased 25% and AUC decreased 21% with a low-fat meal (approximately 12% fat of the total 421 calories) compared to fasted conditions.

Distribution
In vitro plasma protein binding of lonafarnib was greater than or equal to 99% over the concentration range between 0.5 to 40.0 μg/mL. The apparent volumes of distribution were 87.8 L and 97.4 L, respectively, at steady state following oral administration of lonafarnib 100 mg and 75 mg twice daily in healthy subjects.

Elimination
The mean half-life was approximately 4 to 6 hours following oral administration of lonafarnib 100 mg twice daily in healthy subjects.

Metabolism
Lonafarnib is primarily metabolized by CYP3A and to a lesser extent by CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1 in vitro.

Excretion
Following an oral administration of 104 mg [14C]-lonafarnib under fasted conditions in healthy subjects, approximately 62% of the total radiolabeled dose was recovered in feces and <1% of the total radiolabeled dose was recovered in urine up to 240 hours post-dose. The two most predominant metabolites were HM17 and HM21 (an active metabolite) accounting for 15% and 14% of plasma radioactivity, respectively.

Specific Populations
Patients with Renal Impairment or Hepatic Impairment
ZOKINVY has not been studied in patients with renal impairment or in patients with hepatic impairment.

Male and Female Patients
Following a single oral dose of 100 mg lonafarnib in healthy subjects, the plasma lonafarnib AUC and C<sub>max</sub> were 44% and 26% higher in female subjects, respectively, compared to male subjects. The observed exposure difference by sex in healthy subjects is not considered clinically meaningful.

Geriatric Patients
Following a single oral dose of 100 mg lonafarnib in healthy subjects, the plasma lonafarnib AUC and C<sub>max</sub> 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.

Drug Interaction Studies
CYP3A inhibitors
Lonafarnib is a CYP3A substrate and a potent CYP3A time-dependent and mechanism-based inhibitor. Lonafarnib is an inhibitor of CYP2C8 and CYP2C19. Lonafarnib is not considered an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, or CYP2D6. Lonafarnib is unlikely to be an inducer of CYP1A2, CYP2B6, and CYP3A.

CYP2C9 inhibitors
Coadministration with CYP2C9 inhibitors may increase lonafarnib AUC and C<sub>max</sub>. A drug-drug interaction study of ZOKINVY with CYP2C9 inhibitors has not been conducted.

CYP3A inducers
With coadministration of a single oral dose of 50 mg lonafarnib following 200 mg ketoconazole (a strong CYP3A inhibitor) once daily for 5 days, the C<sub>max</sub> and AUC of lonafarnib were increased by 270% and 425%, respectively, as compared to lonafarnib administered alone in healthy subjects.

CYP3A Substrates
Lonafarnib is a strong inhibitor of CYP3A. With coadministration of a single oral dose of 3 mg midazolam with multiple oral doses of 100 mg lonafarnib twice daily for 5 days in healthy subjects, the C<sub>max</sub> of midazolam was reduced by 92% and the AUC was reduced by 98%, as compared to without rifampin coadministration in healthy subjects.

Clinical Studies: Effects of other Drugs on Lonafarnib
Clinical Studies: Effects of other Drugs on Lonafarnib
CYP3A inhibitors
Lonafarnib is a sensitive substrate for CYP3A. With coadministration of a single oral dose of 50 mg lonafarnib following 200 mg ketoconazole (a strong CYP3A inhibitor) once daily for 5 days, the C<sub>max</sub> and AUC of lonafarnib were increased by 270% and 425%, respectively, as compared to lonafarnib administered alone in healthy subjects.

CYP2C9 inhibitors
Coadministration with CYP2C9 inhibitors may increase lonafarnib AUC and C<sub>max</sub>. A drug-drug interaction study of ZOKINVY with CYP2C9 inhibitors has not been conducted.

CYP3A inducers
With coadministration of a single oral dose of 50 mg lonafarnib (combined with a single oral dose of 100 mg ritonavir) following 600 mg rifampin once daily for 8 days, the C<sub>max</sub> of lonafarnib was reduced by 92% and the AUC was reduced by 98%, as compared to without rifampin coadministration in healthy subjects.

Clinical Studies: Effects of Lonafarnib on other Drugs
CYP3A Substrates
Lonafarnib is a strong inhibitor of CYP3A. With coadministration of a single oral dose of 3 mg midazolam with multiple oral doses of 100 mg lonafarnib twice daily for 5 days in healthy subjects, the C<sub>max</sub> of midazolam was increased by 180% and 639%, respectively.
at systemic exposures approximately equal to the AUC in humans at 150 mg/m² twice daily. No retinal toxicity was observed at 20 mg/kg/day (2.1 times the human AUC at 150 mg/m² twice daily). However, in a follow-up study of lonafarnib effects on visual function in monkeys as evaluated by electroretinography, oral administration of 15 mg/kg/day for 13 weeks or 60 mg/kg/day for 6 weeks produced adverse effects on rod-dependent, low-light vision. The effects were observed at several time-points throughout the treatment period. No histological changes in the retina were observed at study termination [see Warnings and Precautions (5.4)].

14 CLINICAL STUDIES
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 (NCT00425607) 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/m² twice daily. After 4 months of treatment, patients who tolerated treatment had an increase in dose to 150 mg/m² 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 m² (ZOKINVY is not indicated in patients with a BSA less than 0.39 m² 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, NCT00916747) 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/m² 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 m².

Throughout Study 1 and Study 2, ZOKINVY was administered orally via capsules or the capsule contents were mixed with Ora Blend SF or Ora-Plus 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. The survival analysis summary is provided in Table 7 and Figure 1.
Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Dosing
[see Dosage and Administration (2.1)]
• Advise patients and caregivers that ZOKINVY should be taken twice daily with the morning and evening meals.
• Inform patients and caregivers that if a dose is missed, the next dose should be given as soon as possible up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next scheduled dose, the patient should skip the missed dose and resume taking ZOKINVY at the next scheduled dose.

Preparation and Administration
[see Dosage and Administration (2.5), Drug Interactions (7)]
• Advise patients to swallow the capsule whole with water. The capsules should not be chewed.
• For patients unable to swallow capsules, advise patients and caregivers that the contents of ZOKINVY can be mixed with Ora Blend SF or Ora-Plus. For patients unable to access or tolerate Ora Blend SF or Ora-Plus, the contents of ZOKINVY can be mixed with orange juice or applesauce. Advise patients not to mix the contents of ZOKINVY with juice containing grapefruit or Seville oranges. Advise patients and caregivers to read and carefully follow the instructions for administering the capsule contents in Ora Blend SF, Ora-Plus, orange juice or applesauce [see Instructions for Use]. Advise patient and caregivers to call their healthcare provider or pharmacist if they have any questions.

Drug Interactions
[see Dosage and Administration (2.3, 2.4), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7)]
• Advise patients and caregivers to report the patient's use of all prescription and nonprescription medications, including nutritional supplements and vitamins.

Gastrointestinal Adverse Reactions
[see Dosage and Administration (2.2), Adverse Reactions (6.1)]
Inform patients and caregivers that gastrointestinal adverse reactions are common with ZOKINVY. These include, but are not limited to, vomiting, diarrhea, and nausea. Advise patients and caregivers to contact their healthcare provider if these adverse reactions persist.

16 HOW SUPPLIED/STORAGE AND HANDLING
ZOKINVY is supplied as:
• 50 mg capsules: Size 4 hard capsule, opaque yellow with “LNF” and “50” printed in black.
  Bottles of 30 capsules each (NDC 73079-050-30)
• 75 mg capsules: Size 3 hard capsule, opaque light orange with “LNF” and “75” printed in black.
  Bottles of 30 capsules each (NDC 73079-075-30)

Note: The Kaplan-Meier (KM) survival curve for the ZOKINVY-treated patients is indicated with a solid line; the curve for the untreated patients is indicated with a dashed line. The shaded regions in blue and red represent the 95% confidence bands for the treated and untreated KM survival curves, respectively.

Table 7: Survival Analysis Summary for Patients with HGPS

<table>
<thead>
<tr>
<th>Summary</th>
<th>Follow-up time censored at 3-years</th>
<th>Last follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated (n=62)</td>
<td>ZOKINVY [1] (n=62)</td>
</tr>
<tr>
<td>Number of Deaths (%)</td>
<td>12 (19.4)</td>
<td>5 (8.1)</td>
</tr>
<tr>
<td>Mean Survival Time (years) [2] (95% CI)</td>
<td>2.6 (2.4, 2.8)</td>
<td>2.8 (2.7, 3.0)</td>
</tr>
<tr>
<td>Difference in Mean Survival Time (years) (95% CI)</td>
<td>0.24 (-0.03, 0.50)</td>
<td>--</td>
</tr>
<tr>
<td>Hazard Ratio for risk of death [3] (95% CI)</td>
<td>0.30 (0.10, 0.89)</td>
<td>--</td>
</tr>
</tbody>
</table>

[1] Includes 27 patients in Study 1 and 35 treatment-naïve patients in Study 2. [2] Based on the area under the survival curves up to 11 years of follow-up. [3] Based on a Cox regression model (with treatment as the only covariate) stratified by continent of residency.

Figure 1: Kaplan-Meier Survival Curves for Follow-up Time Censored at Last Follow-up for Patients with HGPS

Note: The Kaplan-Meier (KM) survival curve for the ZOKINVY-treated patients is indicated with a solid line; the curve for the untreated patients is indicated with a dashed line. The shaded regions in blue and red represent the 95% confidence bands for the treated and untreated KM survival curves, respectively.
Inform patients and caregivers that blood pressure may increase while taking ZOKINVY. Symptoms of hypertension may include headaches, shortness of breath, nosebleeds, flushing, dizziness, or chest pain. Advise patients and caregivers to contact their healthcare provider if these adverse reactions occur.

Nephrotoxicity
[see Warnings and Precautions (5.3), Nonclinical Toxicology (13.2)]
Inform the patient and caregiver of the risk of kidney damage.

Retinal Toxicity
[see Warnings and Precautions (5.4), Nonclinical Toxicology (13.2)]
Inform the patient and caregiver of the risk of developing difficulty with night vision. Advise patients and caregivers to contact their healthcare provider if they experience a change in vision.

Impaired Fertility
[see Warnings and Precautions (5.5), Nonclinical Toxicology (13.1)]
Inform females and males of reproductive potential that ZOKINVY may impact pubertal development and impair fertility.

Embryo-Fetal Toxicity
[see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.3)]
Inform pregnant women and female patients of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZOKINVY.