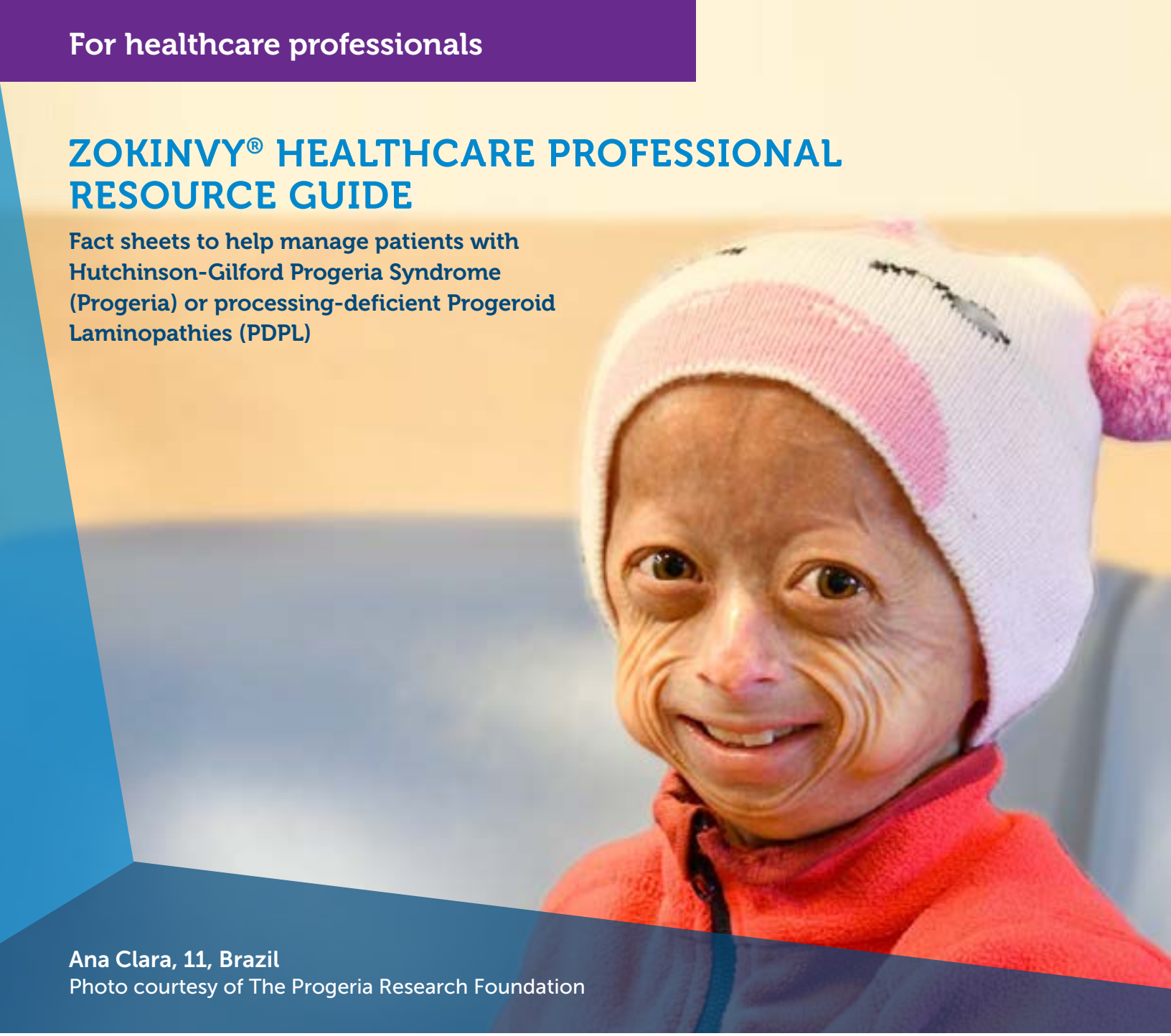
For healthcare professionals

# ZOKINVY® HEALTHCARE PROFESSIONAL RESOURCE GUIDE

**Fact sheets to help manage patients with Hutchinson-Gilford Progeria Syndrome (Progeria) or processing-deficient Progeroid Laminopathies (PDPL)**



**Ana Clara, 11, Brazil**
Photo courtesy of The Progeria Research Foundation

## INDICATION AND USAGE

ZOKINVY® is indicated in adult and pediatric patients 12 months of age and older with a body surface area (BSA) of 0.39 $m^2$ 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

ZOKINVY is not indicated for use in patients with non-HGPS Progeroid Syndromes or with Progeroid Laminopathies known to be processing-proficient. Based upon its mechanism of action, ZOKINVY would not be expected to be effective in these populations.

Zokinvy™
(lonafarnib)
capsules 50 mg/75 mg

**Please see Important Safety Information throughout and on pages 14 through 16, and full Prescribing Information at Zokinvy.com/hcp**

# Table of contents

Zokinvy™ (lonafarnib) capsules 50 mg/75 mg

# Welcome to the Zokinvy® HCP Resource Guide

**Inside, you will find detailed information to support the following key facts and findings:**

Progeria, also known as Hutchinson-Gilford Progeria Syndrome (HGPS), is caused by a single-point mutation in the *LMNA* gene that results in symptoms of premature aging. **Left untreated, the average age of survival is 14.6 years.**[1] A related disease with similar characteristics is processing-deficient Progeroid Laminopathies (PDPL), which is caused by a heterozygous mutation in *LMNA* or compound heterozygous *ZMPSTE24* mutations.[2]

Zokinvy **prevents farnesylation** and the subsequent accumulation of progerin or progerin-like proteins within cells.[3] This accumulation impairs tissue repair functions and further damages cells as they age, which can lead to early mortality.[1,2,4]

In clinical studies, treatment with Zokinvy resulted in **increased mean survival of 2.5 years** and a **60% reduction in risk of mortality**.[3]

The most commonly reported adverse reactions were **gastrointestinal** (vomiting, diarrhea, and nausea); most were **mild to moderate** and generally decreased over time.[3,5]

## IMPORTANT SAFETY INFORMATION

### Contraindications

**ZOKINVY is contraindicated in patients taking:**

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

### Warnings and Precautions

**QTc Interval Prolongations**

- ZOKINVY prolongs the QTc interval. Prolongation of the QTc interval increases the risk of Torsade de pointes, other serious arrhythmias, and sudden death.

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Progeria and processing-deficient Progeroid Laminopathies (PDPL)

# Ultra-rare, genetic, and multisystemic diseases of premature aging[1,2]

Though there are distinct differences, Progeria and PDPL are often grouped together as types of laminopathies that result in accelerated morbidity and mortality.[2,6]

## Similarities of Progeria and PDPL

### Low prevalence rates

- In the United States, the prevalence of Progeria is **1 in 20 million**,[1] and the prevalence of progeroid laminopathies, which include both processing-deficient and processing-proficient, is **1 in 36.4 million**.[7]

### Shared disease pathophysiology processes

- Both diseases are caused by genetic mutations, with Progeria caused by a mutation in *LMNA* and PDPL caused by a constellation of mutations in *LMNA* and/or *ZMPSTE24*. These affect the same nuclear architecture pathway, resulting in **accumulation of harmful progerin or progerin-like proteins, damaging tissues and multiple organs and leading to early mortality**.[1,2]

### Accelerated morbidity and mortality

- Cardiovascular manifestations are commonly seen in both Progeria and PDPL, though the course of disease, select manifestations, and severity can vary between the two.[7] In Progeria, patients often experience **accelerated atherosclerosis leading to cardiovascular disease, stroke, and early mortality** primarily caused by heart failure at a mean age of 14.6 years.[1]

**Patients with Progeria age at a rapid rate, 8 to 10 times faster than healthy people of the same age.[6]**

## IMPORTANT SAFETY INFORMATION

### QTc Interval Prolongations (cont'd)

- Avoid use of ZOKINVY in patients with a history of cardiac arrhythmias, as well as in other circumstances that may increase the risk of the occurrence of Torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia, or hypomagnesemia. Avoid use of ZOKINVY in combination with other drugs known or suspected to prolong the QTc interval *[see Drug Interactions]*.
- Monitor ECGs prior to initiating ZOKINVY, during treatment, and as clinically indicated. If QTc interval is greater than 500 msec, withhold ZOKINVY until QTc interval is less than 470 msec, then resume ZOKINVY at same dosage.
- Obtain serum electrolytes prior to initiating ZOKIVNY and during treatment as clinically indicated. Correct serum electrolyte abnormalities.

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# The underlying cause: persistent nuclear accumulation of progerin or progerin-like proteins[1,2]

Left untreated, the accumulation of progerin or progerin-like proteins supports the likelihood of progressive cardiovascular disease.[1]

Due to the genetic mutation(s) in Progeria and PDPL, prelamin A, a protein crucial to many cellular functions, is **enzymatically modified** to form progerin or progerin-like proteins.[2,8]

Increased accumulation of progerin (or a similar protein) inside cellular nuclei drives a **cascade of cellular pathologies** that negatively affect tissues and organs throughout the body.[1,2]

Zokinvy® **prevents farnesylation** and the subsequent accumulation of progerin or progerin-like proteins within cells.[3] This accumulation impairs tissue repair functions and further damages cells as they age, which can lead to early mortality.[1,2,4]

**The root cause of premature aging in Progeria and PDPL is the enzymatic modification of prelamin A or a downstream protein.[1]**

## IMPORTANT SAFETY INFORMATION

### Laboratory Abnormalities

Some patients treated with ZOKINVY developed laboratory abnormalities. 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%), and 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.

### Nephrotoxicity

- Lonafarnib caused nephrotoxicity in rats at plasma drug exposures approximately equal to that achieved with the human dose. Monitor renal function at regular intervals during ZOKINVY therapy.

Zokinvy™ (lonafarnib) capsules 50 mg/75 mg

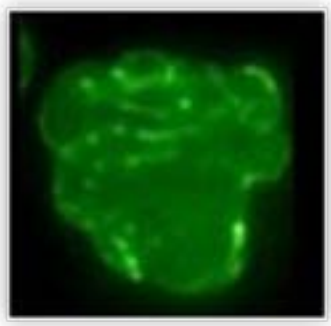
# Zokinvy® is a farnesyltransferase inhibitor that prevents the accumulation of cellular progerin or progerin-like proteins[3]

By inhibiting farnesylation, Zokinvy targets a key step in the pathophysiology of Progeria and PDPL.[1,3]

### Normal cell[7]

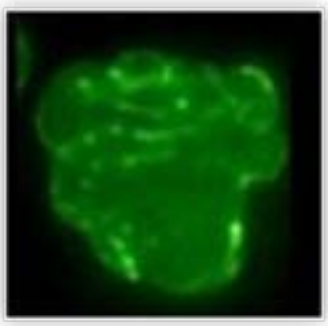
Lamin A, a normal *LMNA* protein product, is critical to many cellular functions.[1]

### Progeria cell[7]



Left untreated, farnesylated *LMNA* mutations will incorporate into the inner nuclear membranes of cells.[1,8]

### Progeria cell after treatment with Zokinvy[7]



Zokinvy inhibits farnesyltransferase to prevent farnesylation and subsequent accumulation of progerin or progerin-like proteins in the inner nuclear membrane.[3]

Photos courtesy of The Progeria Research Foundation

**Zokinvy prevents the accumulation of progerin and progerin-like proteins, resulting in restoration of nuclear morphology.[3]**

## IMPORTANT SAFETY INFORMATION

### Retinal Toxicity

- Lonafarnib caused rod-dependent, low-light vision decline in monkeys at plasma 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.

### Impaired Fertility

- Based on findings in rats, ZOKINVY may reduce fertility. Advise males and females of reproductive potential of the animal findings and that the impact on pubertal development and the potential for impaired fertility with ZOKINVY have not been adequately evaluated.

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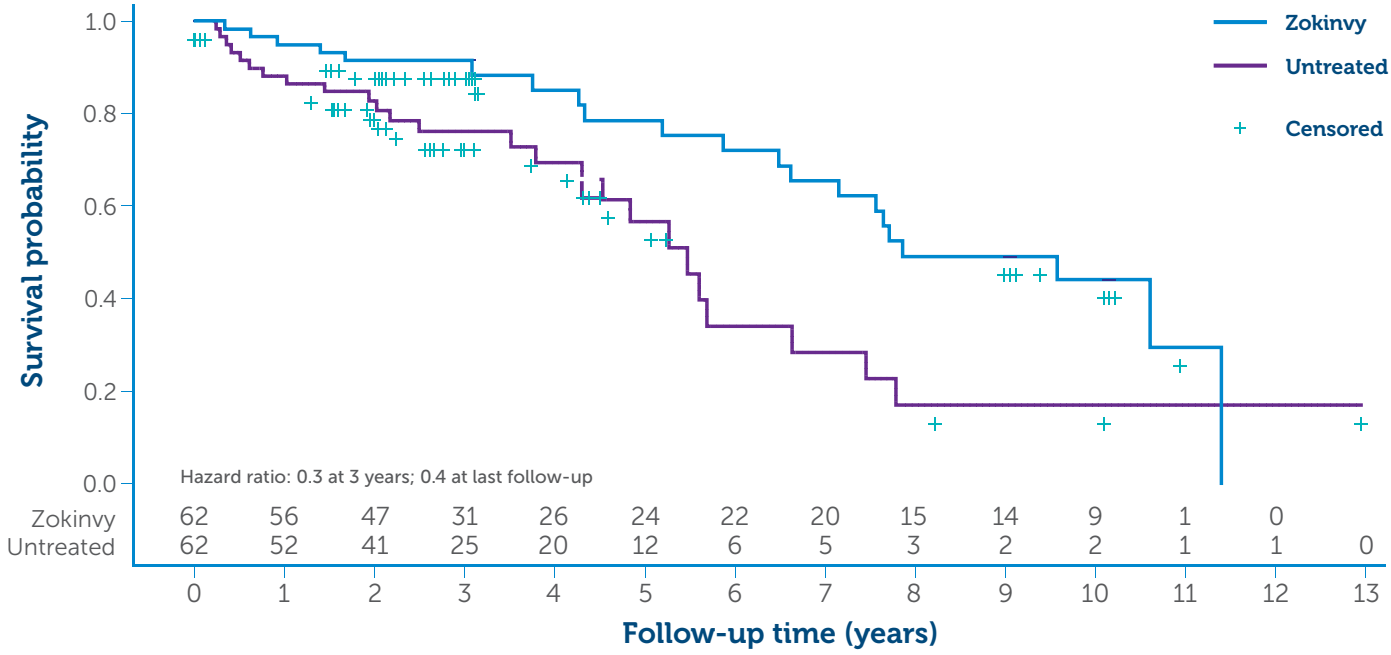
# Zokinvy® reduces the risk of mortality, adding years to patients' lives[3]

The efficacy of Zokinvy was based on results from the Observational Cohort Survival Study, which retrospectively compared survival data from two phase 2 studies in patients with Progeria with those from an untreated cohort.[3] (For additional details on the study designs, please visit **Zokinvy.com/hcp**)

- **Primary end point:** all-cause mortality compared with historical control patient data matched by age at start of treatment, gender, and continent[3,7]
- At last follow-up, treatment with Zokinvy resulted in **increased mean survival of 2.5 years** and a **60% reduction in risk of mortality**[3]

**Kaplan-Meier survival curves for follow-up time censored at last follow-up for patients with HGPS[3]**




**At a 3-year follow-up, there was a 70% reduction in risk of mortality. At last follow-up, the reduction was 60%.[3]**

## IMPORTANT SAFETY INFORMATION

### Adverse Reactions

- The most common adverse reactions were vomiting (90%), diarrhea (81%), infection (78%), nausea (56%), decreased appetite (53%), fatigue (51%), upper respiratory tract infection (51%), abdominal pain (48%), musculoskeletal pain (48%), electrolyte abnormalities (43%), headache (37%), decreased weight (37%), increased aspartate aminotransferase (35%), myelosuppression (35%), cough (33%), decreased blood bicarbonate (33%), hypertension (29%), and increased alanine aminotransferase (27%).

### Gastrointestinal Adverse Reactions

- Gastrointestinal adverse reactions were the most frequently reported adverse reactions. Of the 57 patients (90%) that experienced vomiting, 30 (53%) patients had mild vomiting, 26 (46%) patients had moderate vomiting, and 1 (2%) patient had severe vomiting. (*continues*)

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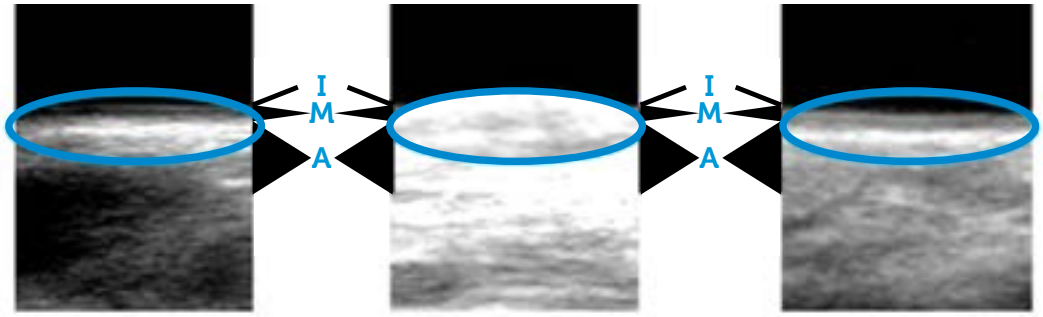
# Zokinvy® improves cardiovascular outcomes in patients with Progeria or PDPL[1,5,7]

In clinical studies, Zokinvy was shown to reduce.[1,5,7]

- Carotid artery echodensity, suggestive of a reduction in vascular wall inflammation and fibrosis
- Pulse wave velocity, a measure of arterial stiffness

## Zokinvy decreases the stiffness of arterial walls, which may lower the likelihood of developing hypertension[5,9]




Control patient[10] | Before Zokinvy[10] | After Zokinvy[10]

Earlier treatment with Zokinvy results in greater reduction in mortality risk.[7]

- In patients who died, a 3.5-year delay in starting treatment increased the probability of death by 152.9%[7]
- Conversely, decreasing the baseline age of starting treatment by 5 years is expected to reduce the probability of death by 78.7%[7]

**Zokinvy offers patients more time to do what matters most to them.[3]**

## IMPORTANT SAFETY INFORMATION

### Gastrointestinal Adverse Reactions (cont'd)

- Of the 35 patients (56%) that experienced nausea, 34 (97%) patients had mild nausea and 1 (3%) patient had moderate nausea.
- Of the 51 patients (81%) that experienced diarrhea, the majority of patients (92%) experienced mild or moderate diarrhea; 38 (75%) patients reported mild diarrhea and 9 (18%) patients reported moderate diarrhea. Four (8%) patients reported severe diarrhea.
- Loss of fluids and dehydration can be severe, leading to hospitalization. As a result, patients should receive therapy for diarrhea at the earliest signs in order to avoid possible severe complications.

### 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, 1 (6%) patient had moderate increases, and 2 (12%) patients had severe increases. (*continues*)

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# Zokinvy® has a well-studied safety profile[3]

In clinical studies, the most commonly reported adverse reactions were gastrointestinal (such as vomiting, diarrhea, and nausea).[3]

- To date, more than **90 young people** have been treated with Zokinvy, resulting in **414 patient-years of treatment exposure**[7]
- In the Progeria and PDPL clinical studies, **only 4 patients (6%) discontinued due to adverse reactions**[3]

**Adverse reactions in ≥5%[a] of patients in Study 1 and treatment-naïve patients in Study 2 receiving Zokinvy[3,b]**

| Adverse reactions | Zokinvy N=63 n (%) |
|---|---|
| **Gastrointestinal disorders** | |
| Vomiting | 57 (90%) |
| Diarrhea | 51 (81%) |
| Nausea | 35 (56%) |
| Abdominal pain[c] | 30 (48%) |
| Constipation | 14 (22%) |
| Flatulence | 4 (6%) |
| **General disorders and administration site conditions** | |
| Fatigue | 32 (51%) |
| Pyrexia | 9 (14%) |
| **Infections and infestations** | |
| Infection[d] | 49 (78%) |
| Upper respiratory tract infection[e] | 32 (51%) |
| Rhinitis | 12 (19%) |
| **Investigations** | |
| Decreased appetite (anorexia) | 33 (53%) |
| Electrolyte abnormalities[f] | 27 (43%) |
| Weight decreased | 23 (37%) |
| Myelosuppression[g] | 22 (35%) |
| Increased aspartate aminotransferase | 22 (35%) |
| Decreased blood bicarbonate | 21 (33%) |

| Adverse reactions | Zokinvy N=63 n (%) |
|---|---|
| **Investigations (cont'd)** | |
| Hypertension | 18 (29%) |
| Increased alanine aminotransferase | 17 (27%) |
| Dehydration | 3 (5%) |
| **Musculoskeletal and connective tissue disorders** | |
| Musculoskeletal pain[h] | 30 (48%) |
| **Nervous system disorders** | |
| Headache | 23 (37%) |
| Cerebral ischemia[i] | 7 (11%) |
| **Ophthalmic** | |
| Ocular changes[j] | 15 (24%) |
| **Psychiatric disorders** | |
| Depressed mood | 3 (5%) |
| **Respiratory, thoracic and mediastinal disorders** | |
| Cough | 21 (33%) |
| Epistaxis | 13 (21%) |
| **Skin and subcutaneous tissue disorders** | |
| Rash | 7 (11%) |
| Pruritus | 5 (8%) |
| Mucositis | 5 (8%) |

[a]Adverse reactions greater than or equal to a lower threshold of 5% are provided for greater context.
[b]One patient had progeroid laminopathy with *LMNA* heterozygous mutation.[3]
[c]Abdominal pain includes stomach pain and abdominal pain.[3]
[d]Infection includes abdominal infection, candidiasis, chicken pox, Clostridium difficile colitis, colitis, croup, dengue fever, flu syndrome, flu-like symptoms, 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, and viral infection.[3]
[e]Upper respiratory infection includes bronchial infection, bronchitis, sinus infection, and upper respiratory infection.[3]
[f]Electrolyte abnormalities includes hypermagnesemia, hypokalemia, hyperkalemia, hyponatremia, hypercalcemia, hypokalemia, hyperphosphatemia, hypocalcemia, and hypernatremia.[3]
[g]Myelosuppression includes absolute neutrophil count decreased, low total white blood cells, lymphopenia, decreased hemoglobin, and hematocrit low.[3]
[h]Musculoskeletal pain includes arthritis, back pain, bone pain, foot pain, intercostal pain, joint pain, knee pain, leg pain, musculoskeletal pain, pain in ankle/extremity/fingers/hip/leg/limb/lower limbs/left arm, shoulder pain, unilateral leg pain. Excluded is musculoskeletal pain for abdomen.[3]
[i]Cerebral ischemia includes central nervous system hemorrhage and ischemia cerebrovascular.[3]
[j]Ocular changes includes visual acuity change, corneal clouding, conjunctivitis, watering eyes, keratitis.[3]

**Please see Important Safety Information throughout and on pages 14 through 16, and full Prescribing Information at Zokinvy.com/hcp**

Zokinvy™ (lonafarnib) capsules 50 mg/75 mg

## Although ProLon1 (Study 1) had a lower starting dosage than ProLon2 (Study 2), adverse reactions were reduced in both studies over time[3]

Analysis of clinical data from both studies indicates that[7]

- After the first 4 months of treatment, the number of adverse reactions **decreased by 70%-80%**
- **94% of patients** treated with Zokinvy® continued beyond the initial 4-month period
- The longest treatment duration is ≥10 years

| Frequency of treatment-emergent adverse events (TEAEs) in 2-week increments: pooled populations of ProLon1 and ProLon2[7] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Weeks | 0-2 | 3-4 | 5-6 | 7-8 | 9-10 | 11-12 | 13-14 | 15-16 | 17-18 |
| At least 1 TEAE | 81.0% | 60.3% | 34.9% | 33.3% | 27.0% | 30.2% | 25.4% | 47.6% | 14.3% |

## Adverse reactions may be managed with supportive care

Adverse reactions, including gastrointestinal issues, can be successfully managed with supportive care and generally decrease over time.[7]

- Prophylactic administration of loperamide is allowed[3]
  - When Zokinvy is coadministered with loperamide, **do not exceed** loperamide 1 mg once daily when first coadministered[3]
  - **Slowly increase loperamide dosage** with caution in accordance with its approved product labeling[3]

**Adverse events may be reduced by reverting to the starting dosage of 115 mg/m² twice daily of Zokinvy.[3]**

## IMPORTANT SAFETY INFORMATION

### Alanine Aminotransferase and Aspartate Aminotransferase Elevations (cont'd)

- Increased aspartate aminotransferase was also commonly reported (22 [35%] patients). Of the 22 patients with increased aspartate aminotransferase, 21 (95%) patients had mild increases and 1 (5%) patient had a severe increase.

### Hypertension

- Increases in blood pressure have been documented in patients treated with ZOKINVY. In clinical trials the incidence of hypertension was 8.1%.

Zokinvy™ (lonafarnib) capsules 50 mg/75 mg

# Zokinvy® offers flexible dosing for your patients[3]

Recommended dosage of Zokinvy is based on body surface area (BSA).[3]


**Zokinvy 50-mg and 75-mg capsules[3]**

## Starting dosage of Zokinvy

For patients with a BSA ≥0.39 $m^2$, the starting dosage is 115 mg/$m^2$ twice daily with morning and evening meals. An appropriate dosage strength of Zokinvy is not available for patients with a BSA below 0.39 $m^2$.[3]

| Recommended dosage and administration for 115 mg/$m^2$ twice daily[3] | | | | | |
|---|---|---|---|---|---|
| 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 | |

## After 4 months of treatment

Increase the dosage to 150 mg/$m^2$ twice daily. Round all total daily doses to the nearest 25-mg increment.[3]

| Recommended dosage and administration for 150 mg/$m^2$ twice daily[3] | | | | | |
|---|---|---|---|---|---|
| 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 |

## IMPORTANT SAFETY INFORMATION

### Drug Interactions

- Strong CYP3A inhibitors
  - ZOKINVY administration with strong CYP3A inhibitors, including herbal supplements, can increase exposures of ZOKINVY resulting in risk of clinically significant adverse events.
  - Do not mix the contents of ZOKINVY with any food or juice containing grapefruit or Seville oranges.

**Please see Important Safety Information throughout and on pages 14 through 16, and full Prescribing Information at Zokinvy.com/hcp**

## If a dose is missed

- Instruct the patient to take the dose as soon as possible, with food, up to 8 hours prior to the next scheduled dose[3]
- If fewer than 8 hours remain before the next scheduled dose, skip the missed dose and resume taking Zokinvy® at the next scheduled dose[3]

## Administration options

Depending on the patient's ability to swallow, Zokinvy can be taken alone or mixed with Ora-Blend SF®, Ora-Plus®, orange juice, or applesauce. Do not mix with any juice containing grapefruit or Seville oranges. Ensure that the mixture is taken within approximately 10 minutes of mixing.[3]

## Adverse reactions

For unmanageable adverse reactions, dosing of Zokinvy can be reduced to the starting dosage (115 mg/m$^2$ twice daily).[3]

## Use with loperamide

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.[3]

## Use with midazolam

Discontinue Zokinvy for 10 to 14 days before and 2 days after administration of midazolam.[3]

## IMPORTANT SAFETY INFORMATION

### Drug Interactions (cont'd)

- Strong or moderate CYP3A inducers
  - ZOKINVY administration with CYP3A inducers, including herbal supplements, can decrease exposure of ZOKINVY, which may impact efficacy.
- QTc Prolongation Drugs
  - Concomitant use of ZOKINVY with other products that prolong the QTc interval may result in a greater increase of the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrythmias, and sudden death.

# Support from Sentynl Cares | Zokinvy

Co-pay assistance and personalized support are available for patients prescribed Zokinvy®.

**Starting and staying on Zokinvy matters. So enroll your patient today.**
Sentynl Cares I Zokinvy helps patients and their caregivers with access to a dedicated, specialized team. Each member of this team is focused on the care and needs of patients with Progeria or PDPL. Download an enrollment form at **Zokinvy.com/hcp**.

**Your patient's specialized Zokinvy support team can help by**

- Investigating insurance coverage
- Assisting with financial support options
- Assisting with eligibility criteria and enrollment in financial assistance programs
- Connecting them to the Zokinvy pharmacy

## Contact Sentynl Cares | Zokinvy

Call **1-888-251-2800**
Monday through Friday, 8 AM-8 PM ET.

SENTYNL CARES | Zokinvy™ (lonafarnib) capsules 50 mg/75 mg

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- To reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS)
- For the treatment of processing-deficient Progeroid Laminopathies with either:
  - o Heterozygous *LMNA* mutation with progerin-like protein accumulation
  - o Homozygous or compound heterozygous *ZMPSTE24* mutations

### Limitations of Use

ZOKINVY is not indicated for use in patients with non-HGPS Progeroid Syndromes or with Progeroid Laminopathies known to be processing-proficient. Based upon its mechanism of action, ZOKINVY would not be expected to be effective in these populations.

## IMPORTANT SAFETY INFORMATION

### Contraindications

### ZOKINVY is contraindicated in patients taking:

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

### Warnings and Precautions

### QTc Interval Prolongation

- ZOKINVY prolongs the QTc interval. Prolongation of the QTc interval increases the risk of Torsade de pointes, other serious arrhythmias, and sudden death.
- Avoid use of ZOKINVY in patients with a history of cardiac arrhythmias, as well as in other circumstances that may increase the risk of the occurrence of Torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia, or hypomagnesemia. Avoid use of ZOKINVY in combination with other drugs known or suspected to prolong the QTc interval *[see Drug Interactions]*.
- Monitor ECGs prior to initiating ZOKINVY, during treatment, and as clinically indicated. If QTc interval is greater than 500 msec, withhold ZOKINVY until QTc interval is less than 470 msec, then resume ZOKINVY at same dosage.
- Obtain serum electrolytes prior to initiating ZOKIVNY and during treatment as clinically indicated. Correct serum electrolyte abnormalities.

### Laboratory Abnormalities

Some patients treated with ZOKINVY developed laboratory abnormalities. 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%), and 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.

### Nephrotoxicity

- Lonafarnib caused nephrotoxicity in rats at plasma drug exposures approximately equal to that achieved with the human dose. Monitor renal function at regular intervals during ZOKINVY therapy.

### Retinal Toxicity

- Lonafarnib caused rod-dependent, low-light vision decline in monkeys at plasma 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.

## Impaired Fertility

- Based on findings in rats, ZOKINVY may reduce fertility. Advise males and females of reproductive potential of the animal findings and that the impact on pubertal development and the potential for impaired fertility with ZOKINVY have not been adequately evaluated.

## Adverse Reactions

- The most common adverse reactions were vomiting (90%), diarrhea (81%), infection (78%), nausea (56%), decreased appetite (53%), fatigue (51%), upper respiratory tract infection (51%), abdominal pain (48%), musculoskeletal pain (48%), electrolyte abnormalities (43%), headache (37%), decreased weight (37%), increased aspartate aminotransferase (35%), myelosuppression (35%), cough (33%), decreased blood bicarbonate (33%), hypertension (29%), and increased alanine aminotransferase (27%).

## Gastrointestinal Adverse Reactions

- Gastrointestinal adverse reactions were the most frequently reported adverse reactions. Of the 57 patients (90%) that experienced vomiting, 30 (53%) patients had mild vomiting, 26 (46%) patients had moderate vomiting, and 1 (2%) patient had severe vomiting.
- Of the 35 patients (56%) that experienced nausea, 34 (97%) patients had mild nausea and 1 (3%) patient had moderate nausea.
- Of the 51 patients (81%) that experienced diarrhea, the majority of patients (92%) experienced mild or moderate diarrhea; 38 (75%) patients reported mild diarrhea and 9 (18%) patients reported moderate diarrhea. Four (8%) patients reported severe diarrhea.
- Loss of fluids and dehydration can be severe, leading to hospitalization. As a result, patients should receive therapy for diarrhea at the earliest signs in order to avoid possible severe complications.

## 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, 1 (6%) patient had moderate increases, and 2 (12%) patients had severe increases.
- Increased aspartate aminotransferase was also commonly reported (22 [35%] patients). Of the 22 patients with increased aspartate aminotransferase, 21 (95%) patients had mild increases and 1 (5%) patient had a severe increase.

## Hypertension

- Increases in blood pressure have been documented in patients treated with ZOKINVY. In clinical trials the incidence of hypertension was 8.1%.

## Drug Interactions

- Strong CYP3A inhibitors
  - ZOKINVY administration with strong CYP3A inhibitors, including herbal supplements, can increase exposures of ZOKINVY resulting in risk of clinically significant adverse events.
    - Do not mix the contents of ZOKINVY with any food or juice containing grapefruit or Seville oranges.
- Strong or moderate CYP3A inducers
  - ZOKINVY administration with CYP3A inducers, including herbal supplements, can decrease exposure of ZOKINVY, which may impact efficacy.
- QTc Prolongation Drugs
  - Concomitant use of ZOKINVY with other products that prolong the QTc interval may result in a greater increase of the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrythmias, and sudden death.

- 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. Do not exceed loperamide 1 mg once daily when first coadministered with ZOKINVY. Slowly increase loperamide dosage with caution as needed to treat diarrhea 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 concentration of the P-GP substrate which may increase the risk of the P-gp substrate's adverse reactions.
- CYP2C19 substrates
  - Lonafarnib is a moderate CYP2C19 inhibitor. 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.

## Use in Specific Populations

*Patients who are pregnant or lactating:* Based on findings from animal studies, ZOKINVY can cause embryofetal harm. 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 females of reproductive potential to use effective contraception during treatment with ZOKINVY. There are no data on the presence of ZOKINVY in human breast milk, the effects on the breastfed infant, or the effects on milk production. 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.

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

**Please see full Prescribing Information at Zokinvy.com/hcp.**

**Sources:** **1.** ZOKINVY [package insert]. Palo Alto, CA: Eiger BioPharmaceuticals Inc; Revision 3/ 2024. **2.** Gordon LB, 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;319(16):1687-1695. doi:10.1001/jama.2018.3264.

Zokinvy™ (lonafarnib) capsules 50 mg/75 mg

# Zokinvy® adds years to the lives of patients with Progeria and PDPL, empowering them to do more[3]

- Zokinvy **prevents the accumulation** of progerin or progerin-like proteins within cells.[3] This accumulation impairs tissue repair functions and further damages cells as they age, which can lead to early mortality.[1,2,4]
- In clinical studies, treatment with Zokinvy resulted in **increased mean survival of 2.5 years** and a **60% reduction in risk of mortality** at last follow-up.[3]
- The most commonly reported adverse reactions were **gastrointestinal** (vomiting, diarrhea, and nausea); most were **mild to moderate** and generally decreased over time.[3,5]
- Zokinvy is available in 50-mg and 75-mg capsules, allowing for **dosing flexibility**.[3]
- Sentynl Cares | Zokinvy offers **personalized support**, educational information, verification of insurance coverage, identification of possible options for financial assistance, and direct pharmacy access.

**Please contact Sentynl Cares | Zokinvy for support for patients treated with Zokinvy and their caregivers.**

**Contact Sentynl Cares | Zokinvy**
Call 1-888-251-2800
Monday through Friday, 8 AM-8 PM ET

## IMPORTANT SAFETY INFORMATION

### Drug Interactions (cont'd)

- 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.

**Please see Important Safety Information throughout and on pages 14 through 16, and full Prescribing Information at Zokinvy.com/hcp**

**References:** **1.** Gordon LB, 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;319(16):1687-1695. doi:10.1001/jama.2018.3264. **2.** Marcelot A, Worman HJ, Zinn-Justin S. Protein structural and mechanistic basis of progeroid laminopathies [published online August 16, 2020]. *FEBS J*. doi:10.1111/febs.15526. **3.** Zokinvy [package insert]. Palo Alto, CA: Eiger BioPharmaceuticals Inc; 2020. **4.** Pacheco LM, Gomez LA, Dias J, Ziebarth NM, Howard GA, Schiller PC. Progerin expression disrupts critical adult stem cell functions involved in tissue repair. *Aging (Albany NY)*. 2014;6(12):1049-1063. doi:10.18632/aging.100709. **5.** Gordon LB, Kleinman ME, Miller DT, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci U S A*. 2012;109(41):16666-16671. doi:10.1073/pnas.1202529109. **6.** Devi AS, Thokchom S, Devi AM. Children living with progeria. *Nurs Care Open Acces J*. 2017;3(4):275-278. doi:10.15406/ncoaj.2017.03.00077. **7.** Data on file. Sentynl Therapeutics, Inc. **8.** Goldman RD, Shumaker DK, Erdos MR, et al. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci U S A*. 2004;101(24):8963-8968. doi:10.1073/pnas.0402943101. **9.** Le VP, Knutsen RH, Mecham RP, Wagenseil JE. Decreased aortic diameter and compliance precedes blood pressure increases in postnatal development of elastin-insufficient mice. *Am J Physiol Heart Circ Physiol*. 2011;301(1):H221-H229. doi:10.1152/ajpheart.00119.2011. **10.** Gordon LB, Shappell H, Massaro J, et al. Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford progeria syndrome [supporting information]. *JAMA*. 2018;319(16):1-9. doi:10.1073/pnas.1202529109.

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