Prescribing Information

Abbreviated Prescribing Information

ZOKINVY ▼ 50 mg, 75 mg hard capsules (lonafarnib) - Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentations

50 mg (yellow) / 75 mg (light orange) lonafarnib hard capsules.

Indications

Treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation.

Posology and method of administration

Starting dose: For all indications, the recommended starting dose is 115 mg/m2 twice daily. The Du Bois formula should be used to calculate body surface area for dosing. Doses should be taken approximately 12 hours apart from one another (morning and evening).
Maintenance dose: After 4 months of treatment using the starting dose of 115 mg/m2 twice daily, the dose should be increased to the maintenance dose of 150 mg/m2 twice daily (morning and evening). Refer to full SmPC for full information on posology and administration.

Contraindications

- Hypersensitivity to active substance or any excipient.
- Concomitant use with strong CYP3A inhibitors.
- Concomitant use of medicinal products that are predominantly metabolised by CYP3A4 (midazolam, atorvastatin, lovastatin and simvastatin.
- Patients with severe hepatic impairment (Child-Pugh Class C).

Special warnings and precautions for use

Age at start of treatment: Treatment with lonafarnib should be initiated as soon as a diagnosis has been made. The expected survival benefit of lonafarnib treatment in Hutchinson-Gilford progeria syndrome (HGPS) patients who started treatment at 10 years of age or above is less compared to those who started at a younger age. Treatment initiation with lonafarnib in older patients should be balanced against the side effects (i.e., vomiting, nausea and diarrhoea) in the first few months of treatment.
Gastrointestinal adverse reactions and dehydration: Closely monitor severity of gastrointestinal adverse reactions, especially during the first 4 months of treatment.
Patients requiring parenteral midazolam for a surgical procedure: Concomitant administration of lonafarnib and midazolam is contraindicated. If midazolam is required, lonafarnib treatment should be discontinued for 14 days before and 2 days after parenteral midazolam is administered.
Abnormal liver function: Increased liver enzymes have been reported. Signs and symptoms of reduced liver function should be assessed on a consistent basis. Liver function should be measured annually or at the onset of any new or worsening signs or symptoms of liver dysfunction.

Nephrotoxicity: Signs and symptoms of reduced renal function should be assessed on a consistent basis. Renal function should be measured annually or at the onset of any new or worsening signs or symptoms associated with renal dysfunction.
Retinal toxicity: An ophthalmological evaluation should be performed annually and at the onset of any new visual disturbances during therapy.
Concomitant use of moderate and strong CYP3A inducers: Concomitant use may reduce the efficacy of lonafarnib, and they should be avoided.
Concomitant use of moderate CYP3A inhibitors: Concomitant use should be avoided. If concomitant use is unavoidable, the dose of lonafarnib should be reduced by 50% and QTc monitoring is recommended.
Concomitant use of weak CYP3A inducers: Concomitant use may reduce the efficacy of lonafarnib and should be avoided. If their use is unavoidable, no dose adjustment of lonafarnib is needed.
Subjects with known dysfunctional polymorphisms in CYP3A4: Subjects with a known dysfunctional polymorphism in CYP3A4 should start therapy at 50% of the indicated dose. QTc monitoring is necessary.
Other progeroid syndromes: Lonafarnib is not expected to be effective for the treatment of progeroid syndromes caused by mutations in genes other than LMNA or ZMPSTE24 and laminopathies not associated with the accumulation of progerin-like proteins. Lonafarnib is not expected to be effective in the treatment of the following progeroid syndromes: Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy and ataxia-telangiectasia.
Excipients with known effect: Zokinvy contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Interaction with other medicinal products and other forms of interaction
Concomitant use with strong CYP3A inhibitors, atorvastatin, lovastatin, simvastatin, midalozam is contraindicated. Concomitant use with moderate CYP3A inhibitors, metformin, strong, moderate or weak CYP3A inducers is not recommended. Ingestion of food or juices containing grapefruit, cranberries, pomegranate or Seville oranges should be avoided. Lonafarnib should be used with caution with concomitant weak CYP3A inhibitors, loperamide, CYP2C19 substrates (omeprazole) and P-glycoprotein substrates (digoxin, dabigatran).

Fertility, pregnancy and lactation
Lonafarnib is not recommended during pregnancy, breast-feeding and in women of childbearing potential not using contraception. Women of childbearing potential must use effective contraception during treatment and for at least 1 week after the final dose. Males with female partners of reproductive potential must use effective contraception during treatment and for at least 3 months after the final dose. A barrier method must be added if systemic steroids are used for contraception. The effect on male and female fertility is unknown.

Effects on ability to drive and use machines
Lonafarnib has a minor influence on the ability to drive and use machines.

Undesirable effects
The most frequently occurring adverse reactions are vomiting, diarrhoea, increased aspartate aminotransferase, increased alanine aminotransferase, decreased appetite, nausea, abdominal pain, fatigue, decreased weight, constipation and upper respiratory tract infection. Most adverse reactions occurred within the first 4 weeks following initiation of treatment and in general steadily decreased

with increasing duration of treatment. The most serious adverse reactions are increased alanine aminotransferase, increased aspartate aminotransferase, cerebral ischaemia, pyrexia and dehydration. Refer to full SmPC for full information on undesirable effects.

Legal Category
Prescription only medicine.

Pack quantities and costs
Pack size of 30 hard capsules.

Marketing Authorisation Holder
EigerBio Europe Ltd., 1 Castlewood Avenue, Rathmines, D06 H685, Ireland

Marketing Authorisation Numbers
EU/1/22/1660/001-002
Adverse events should be reported. Reporting forms and information can be found by ringing 0800 4565992. Adverse events should also be reported to MedInfo_Eiger@IQVIA.com
Date of last revision of the API text
8/1/2022
Reporting adverse events

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Ring **0800 4565992** for how to report adverse reactions.

Adverse reactions should also be reported to Eiger BioPharmaceuticals on **MedInfo_Eiger@IQVIA.com**.

Indication and Usage

Therapeutic indications
Zokinvy is indicated for the treatment of patients 12 months of age and older with a genetically confi rmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-defi cient progeroid laminopathy associated with either a heterozygous *LMNA* mutation with progerin- like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation.
Limitations of Use
ZOKINVY is not indicated for use in patients with non-HGPS Progeroid Syndromes or with Progeroid Laminopathies known to be processing-profi cient. Based upon its mechanism of action, ZOKINVY would not be expected to be eff ective in these populations.

IMPORTANT SAFETY INFORMATION
Contraindications
Hypersensitivity to the active substance or any other member of the farnesyltransferase class, or to any of the excipients listed in the SmPC. Concomitant use with strong CYP3A inhibitors. Concomitant use of medicinal products that are predominantly metabolised by CYP3A4, such as midazolam, atorvastatin, lovastatin and simvastatin.

Special warnings and precautions for use

Age at start of treatment

Treatment with lonafarnib should be initiated as soon as a diagnosis has been made. The clinical data indicate that the expected survival benefi t of lonafarnib treatment in Hutchinson-Gilford progeria syndrome (HGPS) patients who started treatment at 10 years of age or above is less compared to those who started at a younger age (see section 5.1 of SmPC). Treatment initiation with lonafarnib in older patients should be balanced against the side eff ects (*i.e.*, vomiting, nausea and diarrhoea) in the fi rst few months of treatment.

Gastrointestinal adverse reactions and dehydration

Electrolyte abnormalities (hypermagnesaemia, hypokalaemia, hyponatraemia) have been reported (see section 4.8 of SmPC). The severity of gastrointestinal adverse reactions, especially during the fi rst 4 months of treatment, should be closely monitored. When gastrointestinal adverse reactions occur, monitoring the patient's weight, caloric consumption and fl uid volume intake should be done on a regular basis. In some cases, persistent diarrhoea can result in hypovolaemia, which should be treated by infusion or orally. Patients experiencing diarrhoea and treated with the anti-diarrhoeal loperamide should be monitored for adverse reactions associated with increased exposure to loperamide (see section 4.5 of SmPC).

Patients requiring parenteral midazolam for a surgical procedure

Concomitant administration of lonafarnib and midazolam is contraindicated (see sections 4.3 and 4.5 of SmPC) due to an increased risk of extreme sedation and respiratory depression. For patients requiring midazolam as a component of anaesthesia for a surgical procedure, lonafarnib treatment should be discontinued for 14 days before and 2 days after parenteral midazolam is administered.

Abnormal liver function

Increased liver enzymes, such as aspartate aminotransferase or alanine aminotransferase, have been reported (see section 4.8 of SmPC). Signs and symptoms of reduced liver function should be assessed on a consistent basis. Liver function should be measured annually or at the onset of any new or worsening signs or symptoms of liver dysfunction.

Nephrotoxicity

Lonafarnib caused nephrotoxicity in rats with clinical chemistry and urinalysis changes, at plasma exposures approximately equal to the human dose (see section 5.3 of SmPC). Signs and symptoms of reduced renal function should be assessed on a consistent basis. Renal function should be measured annually or at the onset of any new or worsening signs or symptoms associated with renal dysfunction.

Retinal toxicity

Lonafarnib caused rod-dependent, low-light vision decline in monkeys at plasma exposures similar to the human dose (see section 5.3 of SmPC). An ophthalmological evaluation should be performed annually and at the onset of any new visual disturbances during therapy.

Concomitant use of moderate and strong CYP3A inducers Concomitant use of moderate and strong CYP3A inducers may reduce the efficacy of lonafarnib and they should be avoided (see section 4.5 of SmPC). *Concomitant use of moderate CYP3A inhibitors* Concomitant use of lonafarnib and moderate CYP3A inhibitors should be avoided. If concomitant use is unavoidable, the dose of lonafarnib should be reduced by 50% and QTc monitoring is recommended (see sections 4.2 and 4.5 of SmPC).

Concomitant use of weak CYP3A inducers

Concomitant use of weak CYP3A inducers may reduce the efficacy of lonafarnib and should be avoided. If their use is unavoidable, no dose adjustment of lonafarnib is needed (see section 4.5 of SmPC).

Subjects with known dysfunctional polymorphisms in CYP3A4

Subjects with a known dysfunctional polymorphism in CYP3A4 should start therapy at 50% of the indicated dose. QTc monitoring is necessary (see section 4.2 and 4.5 of SmPC).

Other progeroid syndromes

Lonafarnib is not expected to be effective for the treatment of progeroid syndromes caused by mutations in genes other than LMNA or ZMPSTE24 and laminopathies not associated with the accumulation of progerin-like proteins. Lonafarnib is not expected to be effective in the treatment of the following progeroid syndromes: Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy and ataxia-telangiectasia.

Excipients with known effect

Zokinvy contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.