SUMMARY OF PRODUCT CHARACTERISTICS

▼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. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Zokinvy 50 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg lonafarnib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule (capsule)

Size 4 hard capsule (5 mm x 14 mm), opaque yellow with “LNF” and “50” printed in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zokinvy is indicated for the 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.

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the treatment of patients with progeroid syndromes or patients with rare genetic metabolic syndromes.

Posology

Starting dose
For all indications, the recommended starting dose is 115 mg/m^2 twice daily. The Du Bois formula was used in clinical trials and should be used to calculate body surface area for dosing. All total daily doses should be rounded to the nearest 25 mg increment and divided into two equal, or near equal, doses (see Table 1). Doses should be taken approximately 12 hours apart from one another (morning and evening).

Table 1: Recommended starting dose and administration schedule for 115 mg/m^2 body surface area-based dosing

Body surface area (m^2)	**Total daily dose rounded to nearest 25 mg**	**Morning dose number of capsule(s)**		**Evening dose number of capsule(s)**	
		lonafarnib 50 mg	**lonafarnib 75 mg**	**lonafarnib 50 mg**	**lonafarnib 75 mg**
0.30 – 0.38	75		1*		1*
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	

* For patients with a body surface area of 0.30 m^2 to 0.38 m^2, the contents of a 75 mg capsule must be mixed with 10 mL of orange juice. Half of the mixture (5 mL) equates to a 37.5 mg dose of lonafarnib. This dose will be prepared and consumed twice daily (see section 6.6).

Maintenance dose
After 4 months of treatment using the starting dose of 115 mg/m^2 twice daily, the dose should be increased to the maintenance dose of 150 mg/m^2 twice daily (morning and evening). All total daily doses should be rounded to the nearest 25 mg increment and divided into two equal, or near equal, doses (see Table 2).

Table 2: Recommended maintenance dose and administration schedule for 150 mg/m^2 body surface area-based dosing

Body surface area (m^2)	Total daily dose rounded to nearest 25 mg	Morning dose number of capsule(s)		Evening dose number of capsule(s)	
		lonafarnib 50 mg	lonafarnib 75 mg	lonafarnib 50 mg	lonafarnib 75 mg
0.30 – 0.37	100	1		1	
0.38 – 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

Missed dose
If a dose is missed, the dose should be taken as soon as possible, up to 8 hours prior to the next scheduled dose with food. If less than 8 hours remain before the next scheduled dose, the missed dose should be skipped and the dose regimen should be resumed at the next scheduled dose.

Patients taking the starting dose of 115 mg/m^2 with a body surface area of 0.30 m^2 to 0.38 m^2
Patients will need to receive a daily dose of 75 mg (37.5 mg twice daily). The contents of a lonafarnib 75 mg capsule should be mixed with 10 mL of orange juice. Only half of the 10-mL mixture will be consumed (see section 6.6).

Dose adjustment for patients with persistent vomiting and/or diarrhoea leading to dehydration or weight loss
For patients who have increased their dose to 150 mg/m^2 twice daily and are experiencing repeated episodes of vomiting and/or diarrhoea resulting in dehydration or weight loss (see section 4.4), the dose may be reduced to the starting dose of 115 mg/m^2 twice daily. All daily doses should be rounded to the nearest 25 mg increment and divided into two equal, or near equal, doses (see Table 1).

Prevention or treatment of vomiting and/or diarrhoea leading to dehydration or weight loss
Prevention or treatment of vomiting and/or diarrhoea with an anti-emetic and/or anti-diarrhoeal medicinal product can be considered (see section 4.4).

Dose adjustment for patients already taking a moderate CYP3A inhibitor (see section 4.5)
When adding lonafarnib to an existing treatment regimen containing a moderate CYP3A inhibitor, a lower starting dose of lonafarnib might be reasonable. If the concomitantly taken moderate CYP3A inhibitor will be discontinued, the lonafarnib dose may be increased (body surface area-based dosing).

Dose adjustment for patients with known dysfunctional polymorphisms in CYP3A4

The patient's daily dose of lonafarnib should be reduced by 50%, and the reduced daily dose should be divided into two equal doses. Each dose should be rounded to the nearest 25 mg increment. The dosing regimen will be either 25 mg twice daily, 50 mg twice daily or 75 mg twice daily. Patients who have a reduced daily dose of 50 mg (25 mg twice daily) should mix the contents of a lonafarnib 50 mg capsule with 10 mL of orange juice to achieve the correct dose. Only half (5 mL) of the 10-mL mixture will be consumed (see section 6.6). QTc monitoring is recommended.

Dose adjustment for patients requiring parenteral midazolam for a surgical procedure
Concomitant use of midazolam is contraindicated (see sections 4.3 and 4.5). Patients requiring parenteral midazolam for a surgical procedure should discontinue lonafarnib for 14 days before and 2 days after administration of midazolam.

Specific interactions with foods and drinks
Lonafarnib should not be taken with foods or juices that contain grapefruit, cranberries, pomegranates or Seville oranges (*e.g.*, orange marmalade), otherwise known as sour or bitter oranges (see section 4.5). Taking lonafarnib with food or drinks containing these fruits or fruit juices may increase adverse reactions associated with lonafarnib.

Special populations

Patients with hepatic impairment
No dose adjustments are required in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively). Lonafarnib is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Patients with renal impairment
Lonafarnib has not been studied in patients with renal impairment. Because lonafarnib and metabolite HM21 are only excreted to a limited extent via urine, no dose adjustments are required in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population
The posology is the same in adults and children 12 months of age and older.

The safety and efficacy of lonafarnib in children less than 12 months of age have not been established. No data are available (see section 5.1).

Method of administration

Lonafarnib is intended for oral use. The capsule should be swallowed whole. The capsule should not be chewed. Each dose is to be taken with food.

For patients unable to swallow the capsule whole, instructions on mixing the capsule contents with orange juice are provided in section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or any other member of the farnesyltransferase class, or to any of the excipients listed in section 6.1.

Concomitant use with strong CYP3A inhibitors (see section 4.5).

Concomitant use of medicinal products that are predominantly metabolised by CYP3A4, such as midazolam, atorvastatin, lovastatin and simvastatin (see sections 4.2, 4.4 and 4.5).

Patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

4.4 Special warnings and precautions for use

4.4 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 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 (see section 5.1).

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

Electrolyte abnormalities (hypermagnesaemia, hypokalaemia, hyponatraemia) have been reported (see section 4.8). The severity of gastrointestinal adverse reactions, especially during the first 4 months of treatment, should be closely monitored. When gastrointestinal adverse reactions occur, monitoring the patient's weight, caloric consumption and fluid 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).

Patients requiring parenteral midazolam for a surgical procedure

Concomitant administration of lonafarnib and midazolam is contraindicated (see sections 4.3 and 4.5) 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). 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). 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). 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).

Concomitant use of CYP3A inhibitors

Concomitant use of lonafarnib and strong CYP3A inhibitors is contraindicated (see section 4.3 and 4.5).

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).

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).

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'.

4.5 Interaction with other medicinal products and other forms of interaction

Lonafarnib is metabolised by CYP3A4 and 3A5 and is also known to be a moderate CYP3A4 inhibitor. Hence, it autoinhibits its metabolism. There is an approximately 4-fold increase in C_{max} following multiple doses of lonafarnib (75 mg twice daily for 6 days) relative to single-dose lonafarnib (75 mg). Based on the C_{max} and AUC values, an accumulation of the active substance at steady state was evident. The same was true for the main metabolite of lonafarnib but with a reduced magnitude.

Lonafarnib as victim

Strong CYP3A inhibitors

When lonafarnib was co-administered with ketoconazole, a strong CYP3A inhibitor, in healthy adult subjects, ketoconazole (200 mg for 5 doses) increased lonafarnib (single dose of 50 mg) C_{max} by 3.7-fold and AUC by 5.3-fold. This may lead to an increased risk of adverse reactions. Therefore, concomitant use of lonafarnib and strong CYP3A inhibitors is contraindicated (see section 4.3).

Moderate CYP3A inhibitors

When fluconazole (200 mg once daily for 4 days), a moderate CYP3A4 inhibitor, is added to a multiple-dose lonafarnib regimen (75 mg twice daily for 6 days then co-administered with fluconazole for 4 days), differences in lonafarnib exposures are not considered clinically relevant (no change in C_{max} and a 1.2-fold decrease in AUC). No further inhibition besides the autoinhibitory effect following multiple-dose lonafarnib is observed when adding the moderate CYP3A4 inhibitor fluconazole to the regimen. However, adding lonafarnib to an existing regimen containing a moderate CYP3A inhibitor requires caution, and a lower starting dose might be reasonable (see sections 4.2 and 4.4).

Weak CYP3A inhibitors

No drug-drug interaction studies have been conducted with a weak CYP3A inhibitor. No dose adjustment is considered necessary; however, if the concomitant use of a

weak CYP3A inhibitor induces a persistent toxicity, the dose of lonafarnib should be reduced by 50% and QTc monitoring is recommended(see sections 4.2 and 6.6).

Strong CYP3A inducers

Co-administration 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 resulted in the C_{max} of lonafarnib being reduced by 12.5-fold and the AUC being reduced by 50-fold, when compared to rifampin alone in healthy adult subjects. There is no efficacy data available that demonstrates lonafarnib remains effective when administered concomitantly with a strong CYP3A inducer. Therefore, the concomitant use of lonafarnib and a strong CYP3A inducer should be avoided, and therapeutic alternatives sought (see section 4.4).

Moderate CYP3A inducers

No interaction studies have been conducted with a moderate CYP3A inducer. There is no efficacy data available demonstrating that lonafarnib remains effective when given concomitantly with a moderate CYP3A inducer. Therefore, the concomitant use of lonafarnib and a moderate CYP3A inducer should be avoided, and therapeutic alternatives sought (see section 4.4).

Weak CYP3A inducers

No interaction studies have been conducted with a weak CYP3A inducer. There is no efficacy data available demonstrating that lonafarnib remains effective when given concomitantly with a weak CYP3A inducer. Therefore, the concomitant use of lonafarnib and a weak CYP3A inducer should be avoided, and therapeutic alternatives sought (see sections 4.2 and 4.4). If co-administration with a weak CYP3A inducer is unavoidable, maintain the current dose of lonafarnib. If the patient has not already been escalated to the maintenance dose of 150 mg/m^2 twice daily, the timing of their scheduled dose increase should be maintained.

Foods and select juices that affect the metabolism of lonafarnib

Grapefruit, cranberries, pomegranate and Seville oranges (*e.g.*, orange marmalade), otherwise known as sour or bitter oranges, inhibit the CYP3A system. Ingestion of food or juices containing these fruits should be avoided while taking lonafarnib (see section 4.2).

Lonafarnib as perpetrator

CYP3A4 substrates

Lonafarnib is an inhibitor of CYP3A4. When lonafarnib was co-administered with CYP3A4 substrate midazolam in healthy adult subjects, multiple-dose lonafarnib (100 mg twice daily for 5 consecutive days) increased midazolam (single 3 mg oral dose) C_{max} by 2.8-fold and AUC by 7.4-fold. This interaction thereby increases the

risk of extreme sedation and respiratory depression. Therefore, concomitant use of lonafarnib and midazolam is contraindicated (see sections 4.2, 4.3 and 4.4).

No interaction studies have been conducted with HMG-CoA reductase inhibitors. The HMG-CoA reductase inhibitors atorvastatin, lovastatin, and simvastatin are all dependent on CYP3A for metabolism. Lonafarnib is a potent *in vivo* CYP3A mechanism-based inhibitor and, when given concomitantly with either atorvastatin, lovastatin, or simvastatin, lonafarnib is expected to increase the plasma concentrations of these statins. This results in an increased risk of myopathy including rhabdomyolysis. Therefore, concomitant use of lonafarnib and atorvastatin, lovastatin and simvastatin are contraindicated (see section 4.3).

Loperamide

When lonafarnib was co-administered with loperamide in healthy adult subjects, multiple -dose lonafarnib (100 mg twice daily for 5 consecutive days) increased loperamide (single 2 mg oral dose) C_{max} by 3.1-fold and AUC by 4.0-fold. The dose of loperamide should not exceed 1 mg daily (see section 4.4). In the event more than 1 mg of loperamide daily is to be administered, the dose should be slowly increased with caution as needed to treat diarrhoea.

CYP2C19 substrates

When lonafarnib was co-administered with the CYP2C19 substrate omeprazole in healthy adult subjects, multiple -dose lonafarnib (75 mg twice daily for 5 consecutive days) increased omeprazole (single 40 mg oral dose) C_{max} by 28% and AUC by 60%. Patients taking medicinal products that are CYP2C19 substrates should be monitored during this period for potential adverse reactions, with dose adjustments made as necessary.

MATE1 and MATE2-K

Based on *in vitro* data, lonafarnib is a MATE1/MATE2-K inhibitor at clinically relevant maximal systemic concentrations and could potentially precipitate a clinically relevant interaction. Currently, the only identified clinically relevant substrate of MATE1/MATE2-K is metformin. Concomitant use of metformin and lonafarnib should be avoided. If metformin is required, clinicians should carefully monitor the patient for interactions with lonafarnib.

P-glycoprotein substrates

When lonafarnib was co-administered with the P-glycoprotein substrate fexofenadine in healthy adult subjects, multiple dose lonafarnib (100 mg twice daily for 5 consecutive days) increased fexofenadine (single 180 mg oral dose) C_{max} by 21% and AUC by 24%. When lonafarnib is co-administered with P-glycoprotein substrates (*e.g.*, digoxin, dabigatran) where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions and reduce the dose of the P-glycoprotein substrate in accordance with its approved product labelling.

OCT1 substrates

In vitro studies indicate that lonafarnib is an OCT1 inhibitor at clinically relevant systemic concentrations. However, the clinical relevance is currently unknown.

Oral contraceptives

There have been no studies assessing the interaction of concomitant lonafarnib and an oral contraceptive. Females of childbearing potential must use effective contraception during treatment with Zokinvy and for at least 1 week after the final dose (see section 4.6).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Females of childbearing potential must use effective contraception during treatment with Zokinvy and for at least 1 week after the final dose. Males with female partners of reproductive potential must use effective contraception during treatment with Zokinvy and for at least 3 months after the final dose.

Effects of Zokinvy on contraceptive steroids have not been studied. A barrier method must be added if systemic steroids are used for contraception.

Pregnancy

There are no or limited data from the use of lonafarnib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Lonafarnib is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether lonafarnib is excreted in human milk. Animal studies have shown excretion of lonafarnib in milk (for details see section 5.3). A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue therapy with lonafarnib taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Fertility

There are no data on the effects of lonafarnib on fertility in humans. In animal studies, lonafarnib resulted in changes in the male and female reproductive tracts and resorptions (see section 5.3). The potential effect of lonafarnib on fertility in humans is currently unknown.

4.7 Effects on ability to drive and use machines

Lonafarnib has a minor influence on the ability to drive and use machines. Fatigue may occur following the administration of lonafarnib (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions are: vomiting (86%), diarrhoea (78%), increased aspartate aminotransferase (64%), increased alanine aminotransferase (50%), decreased appetite (41%), nausea (38%), abdominal pain (35%), fatigue (29%), decreased weight (27%), constipation (18%) and upper respiratory tract infection (11%). 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 (3.6%), increased aspartate aminotransferase (3.6%), cerebral ischaemia (3.2%), pyrexia (1.6%) and dehydration (1.6%).

Tabulated list of adverse reactions

Adverse reactions occurring in the clinical trials are presented in Table 3 by System Organ Class and Preferred Term. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency within each System Organ Class.

Table 3: Adverse reactions

System organ class	Very common	Common

Infections and infestations	Upper respiratory tract infection	Infection Rhinitis Gastroenteritis Influenza Oral pustule Perirectal abscess Pneumonia Sinusitis
Blood and lymphatic system disorders	Haemoglobin decreased	White blood cell count decreased
Metabolism and nutrition disorders	Decreased appetite Weight decreased	Dehydration Hypermagnesaemia Hypokalaemia Hypoalbuminaemia Hyponatraemia
Psychiatric disorders		Depressed mood
Nervous system disorders		Cerebral ischaemia Headache Dizziness Paraesthesia
Respiratory, thoracic and mediastinal disorders		Cough Epistaxis Laryngeal/oropharyngeal pain Nasal congestion
Gastrointestinal disorders	Vomiting Diarrhoea Nausea Abdominal pain[a] Constipation	Flatulence Colitis Dyspepsia Gastritis Lower gastrointestinal haemorrhage
Hepatobiliary disorders	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bicarbonate decreased	Blood creatinine decreased

Skin and subcutaneous tissue disorders		Rash Pruritus Dry skin Skin hyperpigmentation
Musculoskeletal and connective tissue disorders		Musculoskeletal pain Back pain Pain in extremity
General disorders and administration site conditions	Fatigue	Fever Chest pain Chills
Injury, poisoning and procedural complications		Tooth fracture

[a] Abdominal pain includes abdominal pain and abdominal pain upper

Description of selected adverse reactions

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions (vomiting [85.7%], diarrhoea [77.8%], nausea [38.1%]) were the most frequently reported adverse reactions. Of the patients with treatment related vomiting, 29 (53.7%) patients had Grade 1 vomiting (defined as no intervention required) and 25 (46.3%) had Grade 2 vomiting (defined as outpatient intravenous hydration; medical intervention required). Of these patients with treatment related nausea, 23 (95.8%) had Grade 1 nausea (defined as loss of appetite without alteration in eating habits) and 1 (4.2%) patient had Grade 2 nausea (defined as oral intake decreased without significant weight loss, dehydration or malnutrition). During the first 4 months of treatment in ProLon1, 19 (67.9%) patients had vomiting and 10 (35.7%) patients had nausea. By the end of therapy, 4 (14.3%) patients required anti-emetics or anti-nauseants (see section 4.4). A total of 4 patients discontinued treatment, mostly due to nausea or vomiting.

Most patients with treatment related diarrhoea (approximately 94%) experienced mild or moderate diarrhoea; 38 (77.6%) patients reported Grade 1 (defined as an increase of less than 4 stools per day over baseline) and 8 (16.3%) patients reported Grade 2 treatment related diarrhoea (defined as an increase of 4 to 6 stools per day over baseline; limiting instrumental activities of daily living). Three (6.1%) patients reported Grade 3 diarrhoea (defined as an increase of 7 or more stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living). During the first 4 months of treatment in ProLon1, 23 (82.1%) patients had diarrhoea; by the end of therapy, 3 (10.7%) patients had diarrhoea. Twelve (42.9%) patients were treated with loperamide.

Electrolyte abnormalities

Electrolyte abnormalities (hypermagnesaemia, hypokalaemia, hyponatraemia) were experienced by 4 (6.3%) patients. Of the 2 patients who experienced hypermagnesaemia, 2 (100%) patients had Grade 1 hypermagnesaemia (defined as > upper limit of normal [ULN] to 3.0 mg/dL; >ULN to 1.23 mmol/L). Of the 2 patients who experienced hypokalaemia, 1 (50%) patient had Grade 1 hypokalaemia (defined as < lower limit of normal [LLN] to 3.0 mmol/L) and 1 (50%) patient had Grade 3 hypokalaemia (defined as <3.0 to 2.5 mmol/L; hospitalisation indicated). Of the 1 patient that experienced hyponatraemia, 1 (100%) patient had Grade 1 hyponatraemia (defined as <LLN to 130 mmol/L). Dehydration was experienced by 3 (4.8%) patients. Of the 3 patients who experienced dehydration, 1 (33.3%) patient had Grade 1 dehydration (defined as increased oral fluids indicated; dry mucous membranes; diminished skin turgor) and 2 (66.7%) patients had Grade 2 dehydration (defined as intravenous fluids indicated).

Aminotransferase increases

Increased alanine aminotransferase was recorded for 14 (50.0% of patients) ProLon1 patients. Of the patients with increased alanine aminotransferase, 11 (78.6%) patients experienced a Grade 1 increase (defined as greater than ULN to 3.0 times ULN if baseline was normal; 1.5 to 3.0 times baseline if baseline was abnormal), 1 (7.1%) patient experienced a Grade 2 increase (defined as >3.0 to 5.0 times ULN if baseline was normal; >3.0 to 5.0 x baseline if baseline was abnormal), and 2 (14.3%) patients experienced a Grade 3 increase (defined as >5.0 to 20.0 x ULN if baseline was normal; >5.0 to 20.0 x baseline if baseline was abnormal).

Increased aspartate aminotransferase was recorded for 18 (64.3%) ProLon1 patients. Of these patients, 17 (94.4%) patients experienced a Grade 1 increase (defined as greater than ULN to 3.0 times ULN if baseline was normal; 1.5 to 3.0 times baseline if baseline was abnormal) and 1 (5.6%) patient experienced a Grade 3 increase (defined as >5.0 to 20.0 x ULN if baseline was normal; >5.0 to 20.0 x baseline if baseline was abnormal).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Reporting site at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of acute overdose, supportive medical care should be given as clinically indicated, including fluid replacement to avoid electrolyte imbalance and close monitoring of vital signs. There is no antidote to lonafarnib to reverse overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16AX20

Mechanism of action

Lonafarnib is a disease modifying agent that prevents farnesylation, thereby reducing the accumulation of aberrant progerin and progerin-like proteins in the cell's inner nuclear membrane. This results in maintaining cell integrity and normal function. The accumulation of progerin and progerin-like proteins in the cells within the walls of large blood vessels causes inflammation and fibrosis.

Clinical efficacy and safety

The clinical efficacy and safety of lonafarnib have been evaluated in two Phase 2 studies (ProLon1 and ProLon2). Both studies were single-centre, open-label, single-arm trials that evaluated the efficacy and safety of lonafarnib in patients with genetically confirmed HGPS or a processing-deficient progeroid laminopathy. Analysis was done by combining the studies into a pooled analysis to evaluate differences in survival between those HGPS patients treated with lonafarnib and those that were lonafarnib-naïve. Survival analyses were conducted at 1, 2 and 3 years based upon the period of lonafarnib monotherapy in either ProLon1 or ProLon2 and using vital status as of August 1, 2021, otherwise called last follow-up.

There were 28 patients in ProLon1 (26 patients with classic HGPS, 1 patient with non-classic HGPS and 1 patient with a progeroid laminopathy with a *LMNA* heterozygous mutation with progerin-like protein accumulation). Patients received lonafarnib over 24 to 30 months. Patients initiated treatment with lonafarnib 115 mg/m^2 twice daily. After 4 months of treatment, patients who tolerated treatment had an increase in dose to 150 mg/m^2 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). At the start of the study all patients were less than 18 years of age.

There were 35 patients in ProLon2 (34 patients with classic HGPS and 1 patient with non-classic HGPS). Patients received lonafarnib over 12 to 36 months. Patients were treated with lonafarnib 150 mg/m^2 twice daily. Among the 35 patients treated, all were included in the survival assessment. The median age at treatment initiation was 6.0 years (range: 2 to 17 years). At the start of the study all patients were less than 18 years of age.

Of the 63 patients in ProLon1 and ProLon2, 15 (24%) required some form of dosing adjustment. One (2%) patient discontinued, 11 (17%) patients had their dose

interrupted, and 3 (5%) patients reduced dose. For 10 patients (10/63, 16%), the action taken was associated with a gastrointestinal disturbance, a known and common side-effect of lonafarnib.

The retrospective 3-year survival analysis was based on the mortality data from 62 HGPS patients (27 treatment-naïve patients in ProLon1 and 35 treatment-naïve patients in ProLon2) treated with lonafarnib monotherapy and data from matched, untreated patients in a separate natural history cohort.

The mean lifespan of HGPS patients treated with lonafarnib increased by an average of 0.44 to 0.47 years (without and with adjustment for age at start of treatment, respectively) through the first 3 years of follow-up. However due to the uncertainties of the available data this might be as low as 2.4 months.

At last follow-up time (*i.e.*, August 1, 2021) the mean lifespan of HGPS patients treated with lonafarnib increased by an average of 4.3 years. Given the limited information in the datasets this can be as low as 2.6 years. The results for the last follow-up time should be interpreted with some caution as patients underwent additional (potentially beneficial) treatments.

The survival analysis summary is provided in Table 4.

Table 4: Survival analysis summary for patients with Hutchinson-Gilford progeria syndrome (lonafarnib treated versus external natural history cohort)

	Difference in RMST* in years (95%-CI)	**Hazard ratio* (95%-CI)**
3-year follow-up	0.466 (0.204, 0.728) P1+P2 0.414 (0.042, 0.785) P1 0.172 (-0.101, 0.445) P2	0.28 (0.107, 0.756) P1+P2 0.15 (0.017, 1.263) P1 0.71 (0.199, 2.556) P2
last follow-up (August 1, 2021)	4.338 (2.551, 6.126) P1+P2	0.28 (0.154, 0.521) P1+P2
2-year follow-up	0.237 (0.074, 0.401) P1+P2	0.29 (0.097, 0.838) P1+P2
1-year follow-up	0.094 (0.034, 0.154) P1+P2	0.20 (0.054, 0.732) P1+P2

CI = confidence interval; P1 = ProLon1; P2 = ProLon2; RMST = restricted mean survival time

There were 27 patients in ProLon1 and 35 patients in ProLon2.

* Estimates are based on matching as follows: for each lonafarnib patient a random match untreated patient was selected with the same sex and same continent. Lonafarnib patients were matched sequentially from the lonafarnib patient with oldest age at start to the youngest. The age at start of treatment of the untreated patient within a matched pair was set to that of the lonafarnib patient. If an untreated patient had a longer follow-up than the lonafarnib treated patient in a matched pair, then this follow-up was censored at the length of the follow-up of the lonafarnib treated patient. Regression analysis for the RMST and Cox proportional hazard regression for the hazard ratio had sex and continent as stratification factors and age at start of treatment as covariate.

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Absolute bioavailability has not been assessed. Lonafarnib is absorbed via the oral route. The median time to maximum peak concentration (t_{max}) was 2 to 4 hours. Following multiple dose administration of lonafarnib (100 mg twice daily for 5 days) in healthy volunteers, the mean maximum peak concentration was 964 ng/mL observed at a median time of 4 hours (2 to 5 hours range).

In healthy volunteers, the exposure following a single oral dose of 75 mg lonafarnib taken as an intact capsule was compared to the exposure following a single oral dose of 75 mg lonafarnib capsule contents mixed with orange juice (for instructions on mixing the capsule contents with orange juice see section 6.6). When the capsule contents were mixed with orange juice the C_{max} of lonafarnib was reduced by 9% and the AUC was reduced by 8% as compared to when administered as an intact capsule.

In healthy volunteers, following a single oral dose of 100 mg lonafarnib, food decreased the absorption of lonafarnib and the relative oral bioavailability under fed conditions as compared to fasted conditions was 48% and 77% based on C_{max} and AUC, respectively. Multiple-dose administration of lonafarnib with food in healthy adult subjects did not have a significant effect on bioavailability and resulted in lower inter-subject variability (~16%).

In healthy volunteers, the accumulation ratio is estimated to be 4.46 for AUC_{TAU}/AUC_{0-12} and 3.36 for C_{max}.

The intra-individual variability is 20.79% for C_{max} and 21.13% for AUC_{TAU} and the inter-individual variability is 36.92% for C_{max} and 50.75% for AUC_{TAU}.

Distribution

In vitro plasma protein binding of lonafarnib was ≥99% over the concentration range between 0.5 to 40.0 micrograms/mL. The blood-to-plasma ratio was 0.992 to 1.56.

Lonafarnib exhibits time-dependent pharmacokinetics. Comparing studies in healthy adult volunteers of single-dose 75 mg lonafarnib to 75 mg lonafarnib twice daily for

5 days shows the lonafarnib apparent volume of distribution is reduced by 60% (242 L and 97.4 L, respectively) following multiple dose lonafarnib for 5 days.

Biotransformation

Lonafarnib is extensively metabolised via hepatic means. Lonafarnib accounted for 50% to 57% of the profiled plasma radioactivity. Total plasma recovery for the two metabolites of interest: HM17 (15.1%) and HM21 (13.9%); therefore, a total of 79% to 86% of the plasma radioactivity was recovered. The common metabolic pathways included oxidation, dehydrogenation and combinations of these two processes. Most of the metabolites resulted from structural changes in the pendant piperidine ring region of lonafarnib.

HM21 is a pharmacologically active metabolite. Following oral administration of 100 mg lonafarnib twice daily for 5 days, HM21 has a peak plasma concentration of 94.8 ng/mL occurring after approximately 4 hours (range: 3 to 6), with an AUC_{TAU} of 864 ng·h/mL. Following oral administration of 75 mg lonafarnib twice daily for 5 days, HM21 has a peak plasma concentration of 82.1 ng/mL after approximately 3 hours (range: 3 to 5), with an AUC_{TAU} of 767 ng·h/mL.

In vitro metabolism studies indicate that CYP3A4 and CYP3A5 are mainly responsible for the oxidative metabolism of lonafarnib and that lonafarnib is an *in vivo*-sensitive CYP3A4 substrate.

Twenty-one metabolites were characterised/identified in urine and faeces. No single uncharacterised metabolite represented greater than 5% of the dose.

Transporters

Based on the *in vitro* data, lonafarnib is most likely a substrate of P-glycoprotein and not a substrate of BCRP, OCT1, OATP1B1 and OATP1B3.

Elimination

A ^{14}C- absorption, metabolism and excretion trial conducted in healthy volunteers following single-dose administration of lonafarnib revealed that drug-derived radioactivity was primarily excreted via the faeces. Mean cumulative excretion of radioactivity was 61% in faeces and less than 1% in urine up to 24 hours post-dose (total recovery was ~62% in the mass balance study).

Lonafarnib exhibits time-dependent pharmacokinetics. Comparing studies in healthy adult volunteers of single-dose 75 mg lonafarnib to 75 mg lonafarnib twice daily for 5 days shows lonafarnib clearance was reduced by 75% (48.2 L/h and 12.1 L/h, respectively) and the $t_{1/2}$ increased by 60% (3.5 h versus 5.6 h, respectively) following multiple dose lonafarnib for 5 days.

Special populations

Hepatic impairment

Lonafarnib has not been studied in patients with hepatic impairment. Co-administration of a single oral dose of 50 mg lonafarnib (combined with a single oral dose of 100 mg ritonavir) in mild and moderate hepatically impaired subjects showed similar lonafarnib exposures relative to the matched normal control group (normal hepatic function). These results indicate no dose adjustments are warranted in patients with mild or moderate hepatic impairment (see section 4.2). Lonafarnib is contraindicated in patients with severe hepatic impairment (see section 4.3) due to the predicted safety issue of decompensation due to the risk of diarrhoea (see sections 4.4 and 4.8). Lonafarnib (and most likely HM21) is extensively metabolised in the liver. Therefore, decreased hepatic function will most likely lead to an increase in exposure to lonafarnib (effect on HM21 is unknown) (see section 4.4).

Renal impairment

Lonafarnib has not been studied in patients with renal impairment (see section 4.4). Lonafarnib and HM21 are only excreted to a limited extent via urine. Therefore, it is not expected that renal impairment will affect the exposure to lonafarnib and HM21.

Gender

In healthy volunteers, following a single oral dose of 100 mg lonafarnib, the pharmacokinetic data suggest lonafarnib exposures ($AUC_{0\text{-}inf}$) are higher in female subjects (44% higher) as compared to male subjects. Gender had less of an effect (26%) on the C_{max} as compared with $AUC_{0\text{-}inf}$.

Age

In healthy volunteers, following a single oral dose of 100 mg lonafarnib, the pharmacokinetic data show lonafarnib exposures ($AUC_{0\text{-}inf}$) are higher in elderly subjects (59% higher in those aged 65 years or older) as compared to younger subjects aged 18 to 45 years. Age had less of an effect (27%) on the C_{max} as compared with $AUC_{0\text{-}inf}$.

5.3 Preclinical safety data

Lonafarnib had no effects on QT or QTc interval in guinea pigs and no electrocardiogram (ECG) changes were observed in monkeys. Lonafarnib produced modest and isolated effects on the QT interval of ECG in rats at estimated exposures similar to that seen in humans.

A no-observed-adverse-effect level (NOAEL) could not be established in studies of up to 1-year duration in monkeys. Systemic toxicity was observed in 3-month and 1-year toxicity studies in rats and monkeys following repeated oral administration of lonafarnib at doses ≥30 and ≥10 mg/kg/day, respectively, corresponding to exposures

lower than what is seen in patients. Toxicity findings included bone marrow suppression, testicular toxicity and lymphoid toxicity in rats and monkeys; kidney changes in rats (vacuolisation, mineralisation and necrosis of the inner renal medulla); and diarrhoea and electroretinographic changes in monkeys. In a 3-month toxicity study in monkeys, acute morbidity due to haemorrhage in multiple organs was observed in a small number of monkeys administered 60 mg/kg/day, corresponding to exposures similar to that seen in humans (at 150 mg/m^2 twice daily). In toxicity studies in monkeys, ocular findings of single cell necrosis of retinal photoreceptors were observed at ≥40 mg/kg/day. In a 3-month follow up study, changes in electroretinography were noted at ≥15 mg/kg/day, including substantial changes in scotopic amplitudes at 60 mg/kg/day indicating perturbation of rod cells and impairment of night vision. The NOAEL for ocular toxicity for lonafarnib was considered to be 20 mg/kg/day, corresponding to exposures similar to those seen in humans (at 150 mg/m^2 twice daily).

Lonafarnib increased pre- and post-implantation loss and decreased the number of live foetuses in female rats at doses ≥30 mg/kg/day. Decreased maternal body weight and lower foetal body weights were also observed at this dose level. The NOAEL for maternal toxicity and F1 litters was considered 10 mg/kg/day, with an estimated exposure level lower than what is seen in humans at 150 mg/m^2 twice daily.

Reproductive organ toxicity was observed in male rats and monkeys, including lower testicular and epididymal weight, aspermia, altered spermatogenesis and spermatogonial debris in male rats at ≥90 mg/kg/day, and lower testes weights in male monkeys at the lowest tested dose 10 mg/kg/day. The NOAEL or the lowest tested dose regarding these effects corresponds to exposure levels lower than what is seen in humans at 150 mg/m^2 twice daily.

Lonafarnib demonstrated teratogenic potential at clinically relevant exposures in rabbits in the absence of maternal toxicity, with increased incidence of malformations and variations in foetal skeletal development observed at the lowest tested dose 10 mg/kg/day, corresponding to an exposure level lower than what is seen in humans at 150 mg/m^2 twice daily. Maternal toxicity was observed at ≥40 mg/kg/day and both maternal and embryofoetal toxicity, including abortion, discoloured urine, body weight loss, increased post-implantation loss and decreased foetal body weight, were observed at 120 mg/kg/day, corresponding to exposures greater than those seen in humans (~2- and 25-times the human exposure at 150 mg/m^2 twice daily, respectively). In rats, lonafarnib had no adverse effects on F1 and F2 generations in a pre- and post-natal development study. 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.

Overall, lonafarnib does not represent a genotoxic concern based on results of *in vitro* tests, including bacterial reverse mutation assays and a chromosome aberration assay using human peripheral blood lymphocytes. In the *in vivo* mouse bone micronucleus assay, lonafarnib was not genotoxic at doses up to 50 and 60 mg/kg/day (intraperitoneal injection) in male and female mice, respectively. However, these dose levels are lower than the clinical relevant dose.

The carcinogenic potential of lonafarnib has not been studied.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Povidone
Poloxamer
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Gelatin (E 171)
Titanium dioxide
Yellow iron oxide (E 172)
Sunflower lecithin (E 322)

Black ink

Shellac
Iron oxide black (E 172)
Propylene glycol
Ammonia solution
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package. Keep the bottle tightly closed in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

HDPE bottle, containing desiccant in a cannister and capsules, with induction seal and polypropylene cap. Pack size of 30 hard capsules.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Patients unable to swallow capsules whole

If capsules cannot be swallowed whole, capsules can be opened and the contents of the capsule can be mixed with orange juice.

Step 1: Using a clean medicine cup, measure either 5 mL or 10 mL of orange juice. You can choose to use 5 mL or 10 mL of orange juice.

Step 2: Pour the orange juice measured in **Step 1** into a clean cup.

Step 3: Hold a capsule above the cup containing the orange juice. Hold the capsule between your thumb and forefinger on both sides. Gently twist and pull apart the capsule.

Step 4: Empty the contents of the capsule directly into the cup containing the orange juice.

Step 5: Using a clean spoon, mix the capsule contents and orange juice well. If only 1 capsule is to be taken, skip to **Step 7**. If 2 capsules are to be taken proceed to **Step 6**.

Step 6: If 2 capsules will be taken, repeat Steps 1 through 5 for the second capsule. After finishing, go to **Steps 7, 8 and 9**.

Step 7: Take all of the mixture with food within about 10 minutes of preparing. Each dose must be mixed and consumed within 10 minutes. The mixture should only be prepared at the time it is to be consumed.

Step 8: Rinse the medicine cup used to measure the orange juice and fill it with 5 mL of water for each capsule mixed with orange juice.

Step 9: Pour the water measured in **Step 8** into the cup used to mix the Zokinvy and orange juice. Gently swirl the water around the cup. Consume the water.

Patients requiring a reduced daily dose of Zokinvy

Step 1: Use a clean medicine cup and fill it with 10 mL of orange juice.

Step 2: Pour the orange juice measured in **Step 1** into a clean cup for mixing.

Step 3: Depending on your doctor's direction, hold a Zokinvy 50 mg capsule above the cup containing the orange juice. Hold the capsule between your thumb and forefinger on both sides. Gently twist and pull apart the capsule.

Step 4: Empty the contents of the capsule directly into the cup containing the orange juice.

Step 5: Using a clean spoon, mix the capsule contents and orange juice well.

Step 6: Pour 5 mL of the orange juice and mixture from the mixing cup into a clean medicine cup.

Step 7: Take the 5-mL mixture with food and within about 10 minutes of preparing. Each dose must be mixed and consumed within 10 minutes. The mixture should only be prepared at the time it is to be consumed.

Step 8: Fill the medicine cup used to consume the mixture with 5 mL of water.

Step 9: Gently swirl the water around the medicine cup. Consume the water.

7 MARKETING AUTHORISATION HOLDER

EigerBio Europe Ltd.

1 Castlewood Avenue

Rathmines, D06 H685, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 56709/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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