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

Joenja 70 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains leniolisib phosphate equivalent to 70 mg leniolisib.

Excipient with known effect

Each film-coated tablet contains 241.16 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval-shaped, biconvex, bevelled edge film-coated tablet debossed with “70” on one side and “LNB” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Joenja is indicated for the treatment of activated phosphoinositide 3-kinase delta (P13Kδ) syndrome (APDS) in adult and paediatric patients 12 years of age and older.

4.2 Posology and method of administration

Testing prior to treatment with Joenja

Pregnancy status in females of reproductive potential should be verified prior to initiating treatment with Joenja (see sections 4.4 and 4.6).

Posology

The recommended dosage of Joenja in adult and paediatric patients 12 years of age and older weighing 45 kg or greater is 70 mg administered orally twice daily approximately 12 hours apart, with or without food. There is no recommended dosage for patients weighing less than 45 kg.

Missed dose
If a dose is missed by more than 6 hours, patients should wait and take the next dose at the usual time.

If vomiting occurs within 1 hour after taking Joenja, patients should take Joenja as soon as possible. If vomiting occurs more than 1 hour after dosing, patients should wait and take the next dose at the usual time.

Interactions
The use of Joenja is not recommended concomitantly with strong or moderate CYP3A4 inhibitors (e.g., clarithromycin, diltiazem, erythromycin, ketoconazole, ritonavir, verapamil, grapefruit juice); strong or moderate CYP3A4 inducers (e.g., carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort); or CYP1A2 metabolized drugs with a narrow therapeutic index (e.g., theophylline, tizanidine) (see section 4.5).

Special populations

Elderly
Because clinical studies of Joenja did not include any patients 65 years of age and older, it cannot be determined whether they respond differently from younger adult patients.

Paediatric population
The safety and effectiveness of Joenja have not been established in paediatric patients below the age of 12 years. There is no recommended dosage for paediatric patients 12 years of age and older who weigh less than 45 kg.

Patients with hepatic impairment
Leniolisib is extensively (60%) metabolized by the liver. The effect of hepatic impairment on the pharmacokinetics of leniolisib has not been studied. The use of Joenja in patients with moderate to severe hepatic impairment is not recommended (see section 5.2).

Method of administration

Oral use.

Joenja can be taken with or without meals. The tablets should be swallowed whole. The tablets should not be split, crushed, or chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Embryo-foetal toxicity

Based on findings in animals, Joenja may cause foetal harm when administered to a pregnant woman. Administration of leniolisib to rats and rabbits during the period of organogenesis caused embryo-foetal toxicity including malformations at exposures that were 2 to 6 times higher than the maximum recommended human dose (MRHD) in APDS patients based on AUC comparisons. The pregnancy status of patients of reproductive potential should be verified prior to starting treatment. Pregnant women should be advised of the potential risk to a foetus. Females of reproductive potential should be advised to use highly effective methods of contraception during treatment and for 1 week after the last dose.

Vaccinations

Live, attenuated vaccinations may be less effective if administered during Joenja treatment.

Excipients with known effect

Lactose content

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption must not take this medicine.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on Joenja

Strong and moderate CYP3A4 inhibitors

Joenja is a substrate of CYP3A4. Leniolisib exposure was increased 2-fold when co-administered with itraconazole, a strong CYP3A4 inhibitor. Physiological based pharmacokinetic (PBPK) model-based simulations predicted a maximum increase of 75% in leniolisib AUC_{0-12} with erythromycin (moderate CYP3A4 inhibitor). Concomitant use of Joenja with strong and moderate CYP3A4 inhibitors (e.g., clarithromycin, cobicistat, danoprevir, dasabuvir, diltiazem, elvitegravir, erythromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telithromycin, tipranavir, troleandomycin, verapamil, voriconazole) should be avoided.

Strong and moderate CYP3A4 inducers

Concomitant use of strong and moderate CYP3A4 inducers may result in reduced leniolisib exposure and thus reduced leniolisib efficacy. PBPK model-based simulations predicted a maximum decrease of 78% and 58% in leniolisib AUC_{0-12} with rifampin (strong CYP3A4 inducer) and efavirenz (moderate CYP3A4 inducer), respectively. Therefore, concomitant use of Joenja with strong and moderate CYP3A4 inducers (e.g., avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort, bosentan, efavirenz, etravirine, modafinil, nafcillin, nevirapine) should be avoided.

CYP2D6 and P-gp inhibitors

Quinidine (strong P-gp and CYP2D6 inhibitor) had no effect on leniolisib systemic exposure. Leniolisib is not a sensitive substrate of P-gp and CYP2D6.

Effect of Joenja on other drugs

CYP1A2 metabolized drugs with a narrow therapeutic index

Leniolisib inhibits CYP1A2 in a time-dependent manner *in vitro*. Concomitant use of Joenja with drugs that are primarily metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine) should be avoided.

BCRP, OATP1B1, and OATP1B3 substrates

In vitro, leniolisib is a substrate and an inhibitor of the hepatic efflux transporter BCRP and a substrate of P-gp. Leniolisib was identified *in vitro* as a potential inhibitor of the hepatic uptake and efflux transporters OATP1B1/B3 and BCRP. The effect of Joenja on BCRP, OATP1B1, and OATP1B3 substrates has not been studied clinically. Due to a possible increase in systemic exposure of these substrates, concomitant use of Joenja with drugs that are BCRP, OATP1B1, and OATP1B3 substrates (e.g., rosuvastatin, pitavastatin, letermovir) should be avoided.

Oral contraceptives

When combined with a monophasic oral contraceptive containing levonorgestrel and ethinylestradiol, leniolisib increased ethinylestradiol exposure by approximately 25 to 30% in terms of both AUC and C_{max}, but did not affect the C_{max} or AUC of levonorgestrel. Efficacy of a combined oral contraceptive composed of ethinylestradiol and levonorgestrel is not expected to be compromised by concomitant use with leniolisib.

Gastric acid reducing agents

Leniolisib exhibits pH-dependent solubility (pH range of 1.2 to 4), with low solubility at higher pH values (≥ 5). However, PK results from APDS patients did not indicate that acid reducing agents (e.g., H2-antagonists, proton pump inhibitors) have a clinically relevant effect on leniolisib systemic exposure.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should use highly effective methods of contraception during treatment with Joenja and for 1 week after the last dose. Leniolisib can cause foetal harm based on findings from animal studies. Pregnancy status in females of reproductive potential should be verified prior to initiating treatment with Joenja.

Pregnancy

There are no data from the use of leniolisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Joenja is not recommended during pregnancy and in women of childbearing potential not using highly effective methods of contraception.

Breast-feeding

There are no data on the presence of leniolisib or its metabolites in human milk or the effects on the breastfed infant or milk production. Available pharmacokinetic/toxicological data in animals have shown excretion of leniolisib in milk (see section 5.3). Because of the potential for serious adverse reactions from leniolisib in the breastfed child, women should be advised not to breastfeed during treatment with Joenja and for 1 week after the last dose.

4.7 Effects on ability to drive and use machines

Leniolisib has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of Joenja reflects exposure based on 38 adult and paediatric patients 12 years of age and older with activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) from the placebo-controlled portion of Study 2201 and additional open-label clinical safety data. Thirty-seven of 38 patients received Joenja 70 mg orally twice daily for at least 60 weeks and 81% were exposed for 96 weeks or longer. Median duration of Joenja treatment was approximately 3 years, and 5 patients had more than 5 years of Joenja exposure.

The data below are based on the 12-week, placebo-controlled portion of Study 2201 in which either Joenja 70 mg (N=21) or placebo (N=10) was administered twice daily to patients with APDS. Demographics of the patients who participated in this study are summarized in section 5.1. Table 1 presents adverse reactions that occurred in 2 or more patients treated with Joenja and for which the incidence in patients treated with Joenja was greater than the incidence in patients treated with placebo.

The most common adverse reactions (> 10%) were headache, sinusitis, and atopic dermatitis.

Adverse reactions are listed in Table 1 by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), and rare (≥ 1/10 000 to < 1/1 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported by 2 or more Joenja-treated patients and more frequently than placebo

System organ class	Adverse reactions	Frequency
Infections and infestations	Sinusitis	Very common
Nervous system disorders	Headache	Very common
Cardiac disorders	Tachycardia[1]	Very common
Gastrointestinal disorders and administration site conditions	Diarrhoea	Very common
Skin and subcutaneous tissue disorders	Dermatitis atopic[2] Alopecia	Very common Very common
Musculoskeletal and connective tissue disorders	Back pain Neck pain	Very common Very common
General disorders and administration site conditions	Fatigue Pyrexia	Very common Very common

[1]Tachycardia: including tachycardia and sinus tachycardia

[2]Dermatitis atopic: including dermatitis atopic and eczema

Description of selected adverse reactions

Laboratory abnormalities

Seven (33%) patients receiving Joenja developed an absolute neutrophil count (ANC) between 500 and 1500 cells/microL (0.5-1.5 x 109/L). No patients developed an ANC < 500 cells/microL (0.5-1.5 x 109/L) and there were no reports of infection associated with neutropenia.

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 Scheme Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

If overdose occurs, the patient should be monitored for any signs or symptoms of adverse reactions. Treatment of overdose with Joenja consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, other immunostimulants, ATC code: L03AX22

Mechanism of action

Leniolisib inhibits PI3K-delta by blocking the active binding site of PI3K-delta. In cell-free isolated enzyme assays, leniolisib was selective for PI3K-delta over PI3K-alpha (28-fold), PI3K-beta (43-fold), and PI3K-gamma (257-fold), as well as the broader kinome. In cell-based assays, leniolisib reduced pAkt pathway activity and inhibited proliferation and activation of B and T cell subsets. Gain-of-function variants in the gene encoding the p110-delta catalytic subunit or loss of function variants in the gene encoding the p85-alpha regulatory subunit each cause hyperactivity of PI3K-delta. Leniolisib inhibits the signalling pathways that lead to increased production of PIP3, hyperactivity of the downstream mTOR/Akt pathway, and to the dysregulation of B and T cells.

Pharmacodynamic effects

Ex vivo pharmacodynamics of leniolisib [proportion of phosphorylated Akt (pAkt)-positive B cells] were assessed intra-individually at 10, 30, and 70 mg twice daily for 4 weeks at each dose level in patients with APDS. Within the explored dose range, higher leniolisib plasma concentrations were generally associated with higher reduction of pAkt-positive B cells and higher doses were associated with a slightly higher peak reduction as well as more sustained reduction. Treatment with Joenja 70 mg twice a day at steady state is estimated to produce time-averaged reduction of pAkt-positive B cells by approximately 80%.

Clinical efficacy and safety

The efficacy of Joenja was evaluated in the placebo-controlled portion of Study 2201, a 12-week blinded, randomized, placebo-controlled study in adult and paediatric

patients 12 years of age and older with confirmed APDS-associated genetic PI3Kδ mutation with a documented variant in either *PIK3CD* or *PIK3R1*. Baseline patient demographics are shown in Table 2.

Table 2 Baseline demographic and disease characteristics in patients with APDS (Study 2201)

Demographics and disease characteristics	**Joenja (N=21)**	**Placebo (N=10)**
Demographics		
Age[1] (Years) Mean (SD)	22.2 (10.00)	26.7 (13.43)
Age categories		
< 18, n (%)	8 (38)	4 (40)
(Min, Max)	(12, 17)	(15, 17)
≥ 18, n (%)	13 (62)	6 (60)
(Min, Max)	(18, 54)	(18, 48)
Sex, n (%)		
Male	11 (52)	4 (40)
Female	10 (48)	6 (60)
Race, n (%)		
Asian	1 (5)	1 (10)
Black	1 (5)	1 (10)
White	18 (86)	7 (70)
Other	1 (5)	1 (10)
Ethnicity, n (%)		
Hispanic or Latino	0	1 (10)
Not Hispanic or Latino	14 (67)	7 (70)
Not reported	7 (33)	2 (20)
Disease characteristics		
APDS 1 (*PIK3CD* variant), n (%)	16 (76)	9 (90)
APDS 2 (*PIK3R1* variant), n (%)	5 (24)	1 (10)
Concomitant glucocorticoids, n (%)	12 (57)	6 (60)
Concomitant immunoglobulin G (IgG), n (%)	14 (67)	7 (70)
Previous rapamycin/sirolimus use, n (%)	4 (19)	3 (30)

[1]Patient age from study Day -4 up to initial Joenja dosing

Patients had nodal and/or extranodal lymphoproliferation, as measured by index nodal lesion selected by the Cheson methodology on CT or MRI and clinical findings and manifestations compatible with APDS (e.g., history of repeated oto-sino-pulmonary infections, organ dysfunction). Immunosuppressive medications or PI3Kδ inhibitors (selective or non-selective) were prohibited within 6 weeks of baseline (Day -1 and the visit prior to first study drug administration) and throughout the study. In addition, patients who had previous or concurrent B cell depleters (e.g., rituximab) within 6 months of baseline were excluded from the study, unless absolute B lymphocytes in the blood were normal. B cell depleters were prohibited throughout the study.

Thirty-one patients were randomized 2:1 to receive either Joenja 70 mg (N=21) or placebo (N=10) twice a day for 12 weeks. The co-primary efficacy endpoints were improvement in lymphoproliferation as measured by a change from baseline in lymphadenopathy measured by the log10-transformed sum of product diameters and the normalization of immunophenotype as measured by the percentage of naïve B cells out of total B cells. Both co-primary efficacy endpoints were statistically significant (Table 3).

Table 3 Co-primary endpoints in placebo-controlled portion of Study 2201 at Week 12 (Day 85)

	Joenja	**Placebo**

	(N=21)	(N=10)
Log10-transformed SPD of index lesions (excluding patients with 0 lesions at Baseline)[a]		
n[b]	18	8
Baseline Mean (SD)	3.03 (0.42)	3.05 (0.39)
Change from Baseline, LS Mean (SE)	-0.27 (0.04)	-0.02 (0.05)
Difference vs. Placebo (95% CI)		-0.25 (-0.38, -0.12)
p-value		0.0006
Percentage of naïve B cells out of total B cells (patients with < 48% of naïve B cells at Baseline)[c]		
n[d]	8	5
Baseline[e] Mean (SD)	27.16 (13.16)	30.51 (7.97)
Change from Baseline, LS Mean (SE)	37.39 (5.34)	0.09 (6.66)
Difference vs. Placebo (95% CI)		37.30 (24.06, 50.54)
p-value		0.0002

CI=confidence interval; SD= Standard deviation; SE=standard error; SPD=sum of product diameters; vs=versus; LS Mean: Least-squares mean

Note: The LS mean change from baseline, difference in LS mean change from baseline between Joenja and placebo and its p-value were obtained from an Analysis of Covariance model with treatment, glucocorticoids use and immunoglobulin replacement therapy at baseline, and baseline measurement as covariates.

[a]Change in index lesion size was measured using the log10 transformed sum of the product of diameters (SPD) of the largest lymph nodes (maximum of 6) identified as per the Cheson criteria on CT/MRI.

[b]The analysis excluded 2 patients from each treatment group due to protocol deviations and 1 Joenja patient having complete resolution of the index lesion identified at baseline.

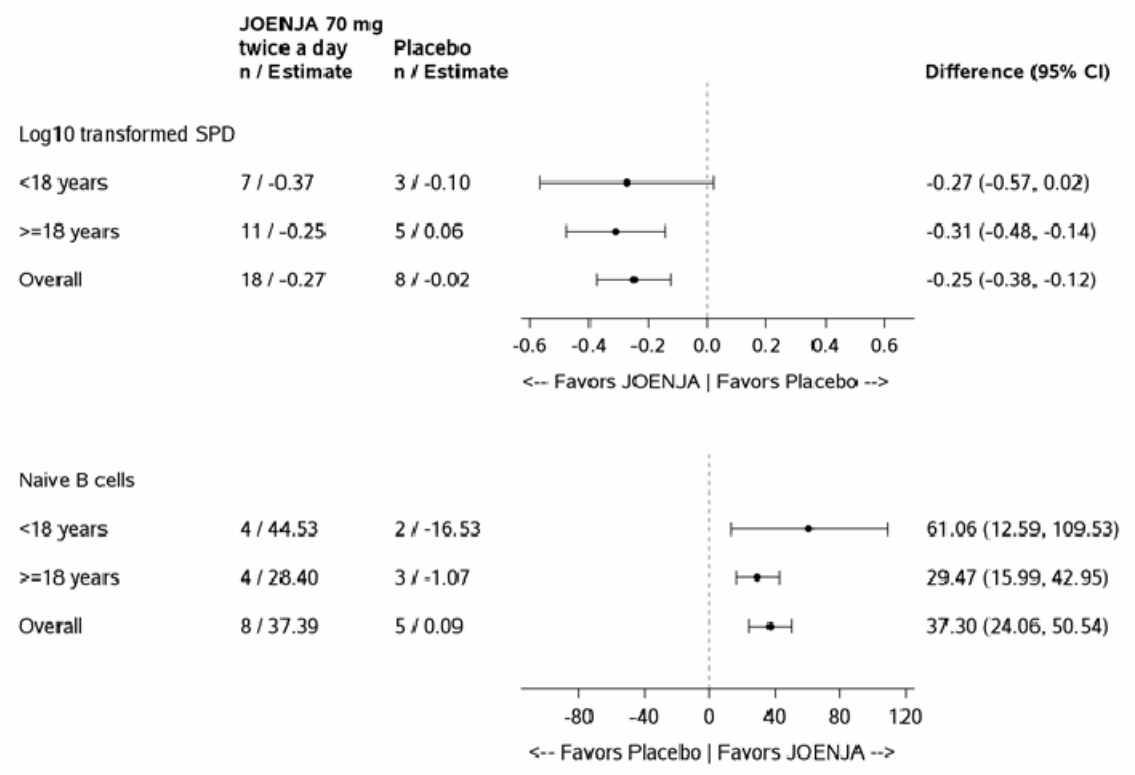
[c]Cell surface markers used to distinguish naïve B cells on flow cytometry were CD19+CD27-CD10-.

[d]The analysis excluded 2 patients from each treatment group due to protocol deviations, 5 Joenja patients and 3 placebo patients with more than or equal to 48% naïve B cells at baseline, 5 Joenja patients with no Day 85 measurement, and 1 Joenja patient with no baseline measurement.

[e]Baseline is defined as the arithmetic mean of the Baseline and Day 1 values when both were available, and if either value was missing, the existing value was used.

Figure 1 represents the co-primary endpoints grouped by age (< 18 years of age vs ≥ 18 years of age).

Figure 1 Difference from baseline in log10 transformed SPD of index lesions and percentage of naïve B cells out of total B cells (patients with < 48% of naïve B cells at Baseline) by age group



Paediatric population

For adolescents aged 12 to 17 years, please see above. The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with leniolisib in one or more subsets of the paediatric population in APDS (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The systemic drug exposure (AUC and C_{max}) of leniolisib increased dose proportionally within the studied range of doses (20 to 140 mg twice a day dosing and single doses of 10 to 400 mg). During twice daily dosing approximately 12 hours apart, leniolisib accumulates approximately 1.4-fold (range of 1.0 to 2.2) in achieving steady-state, consistent with an effective half-life ($t_{1/2}$) of approximately 7 hours. Steady state drug concentrations can be expected to be reached after approximately 2 to 3 days of Joenja treatment. The pharmacokinetics of leniolisib are similar between healthy participants and APDS patients.

Absorption

In a placebo controlled, single and multiple ascending dose study in healthy participants, leniolisib median time to maximum plasma concentration (T_{max}) occurred at about 1 hour postdose. T_{max} appeared independent of dose and was not altered after multiple oral doses. Food is unlikely to have a clinically meaningful effect on the systemic exposure of leniolisib during Joenja treatment (see section 4.2).

Distribution
The systemic decay in leniolisib plasma concentration over time is bi-exponential, indicating a distribution delay towards peripheral tissues. The apparent terminal elimination $t_{1/2}$ is approximately 10 hours. The volume of distribution of leniolisib is estimated to be 28.5 L in patients with APDS. Leniolisib was highly bound (94.5%) to plasma proteins.
Biotransformation
Leniolisib was 60% metabolized by the liver, with CYP3A4 being the most predominant enzyme involved (95.4%) in the primary oxidative metabolism of leniolisib with minor contribution from other enzymes (3.5% CYP3A5, 0.7% CYP1A2 and 0.4% CYP2D6). Intestinal secretion by BCRP as well as extrahepatic CYP1A1 cannot be excluded as excretion routes.
Elimination
The mean recovery of total 14C-radioactivity following a single oral dose of 70 mg 14C-leniolisib was 92.5% (67.0% and 25.5% recovered via faeces and urine, respectively) 168 hours postdose. Unchanged leniolisib (6.32%) was the predominant drug-related material recovered in urine.
Paediatric patients
Following a single 70 mg oral dose of leniolisib in APDS patients, leniolisib systemic exposures were comparable between paediatric patients (12 to 17 years of age) and adults (≥ 18 years of age), with median T_{max} (ranging from 1 to 5 hours) reached approximately 3 hours post-dose in patients 12 to 17 years of age. The observed difference in the median T_{max} between paediatric patients (12 to 17 years of age) and adults (≥ 18 years of age) is not clinically relevant given the PK variability and comparable concentration-time profiles between the two age groups.
Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of leniolisib has not been evaluated. As leniolisib is metabolized to a large extent by the liver (60%), use of Joenja is not recommended in patients with moderate to severe hepatic impairment.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity
Carcinogenicity studies have not been conducted with leniolisib.
Leniolisib was not genotoxic in the *in vitro* Ames assay, *in vitro* chromosomal aberration assay in human lymphocytes, or micronucleus assays in TK6 cells (*in vitro*) and rats (*in vivo*).
Reproductive and developmental toxicity
In a fertility study, male rats had decreased round spermatids and decreased spermatocytes in the testis at an oral dose of 90 mg/kg/day (approximately 2 times the MRHD on an AUC basis). Leniolisib had no effect on fertility in female rats at oral doses up to 90 mg/kg/day (approximately 4 times the MRHD on an AUC basis). No effects on male or female fertility and reproductive performance indices were observed up to the maximum dose administered of 90 mg/kg/day (approximately 2 to 4 times the MRHD on an AUC basis).
Leniolisib was administered orally to pregnant rats at doses of 10, 30, and 120 mg/kg/day during the period of organogenesis from gestation Day 6 to Day 17. Leniolisib at a dose of 120 mg/kg/day was associated with decreased foetal body weight, visceral and skeletal variations, and external, visceral, and skeletal malformations (eye bulge, microphthalmia, anophthalmia, and reduction in orbital socket size) in the presence of maternal toxicity (decrease in body weight gain) at exposures approximately 6 times the MRHD on an AUC basis. No developmental

toxicity was observed in rats at an exposure approximately 2 times the MRHD (on an AUC basis at a maternal oral dose of 30 mg/kg/day).
Leniolisib was administered orally to pregnant rabbits at doses of 10, 30, and 100 mg/kg/day during the period of organogenesis from gestation Day 7 to Day 20. Leniolisib at a dose of 100 mg/kg/day was associated with skeletal variations as well as visceral and skeletal malformations (microphthalmia and reduction in orbital socket size) in the presence of maternal toxicity (decrease in body weight gain) at exposures approximately 2 times the MRHD on an AUC basis. No developmental toxicity was observed in rabbits at an exposure approximately 0.3 times the MRHD (on an AUC basis at a maternal oral dose of 30 mg/kg/day).
In the pre- and postnatal developmental rat toxicity study, adverse effects on the progeny during the preweaning period, manifested as reduced pup survival and persistently lower pup weight during postweaning, were seen at maternal doses of 90 mg/kg/day. Leniolisib was detected in all lactation study samples, with leniolisib concentrations increasing in a dose-dependent manner resulting in a concentration that was approximately 2 to 3-fold higher than the maternal plasma concentration at 10 to 30 mg/kg/day.
Juvenile animal toxicity data
Studies were conducted with leniolisib in juvenile rats starting at postnatal day (PND) 7 (the equivalent of a human newborn) to PND 77 (the equivalent of a human adult). Death was observed in juvenile rats that received 90 mg/kg/day, approximately 9 times the MRHD on an AUC basis (measured after the first dose) and occurred primarily during the pre-weaning period (PND 9 to PND 15). Changes in the onset of puberty (delays in males and accelerations in females) were observed in juvenile rats at equal to or greater than 30 mg/kg/day leniolisib, which is one half to equivalent to, the MRHD on an AUC basis. A no effect dose level was identified at an exposure approximately 0.1 to 1.0 times the MRHD on an AUC basis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Sodium starch glycolate
Magnesium stearate
Colloidal anhydrous silica

Tablet film-coating

Hypromellose
Titanium dioxide
Iron oxide monohydrate yellow
Iron oxide red
Talc
Polyethylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate.

6.5 Nature and contents of container

High density polyethylene bottles with aluminium induction seal and child resistant polypropylene screw cap.
Each pack contains 1 bottle with 60 tablets.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharming Technologies B.V.
Darwinweg 24
2333 CR Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 33010/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/09/2024

10 DATE OF REVISION OF THE TEXT

27/08/2025