ANNEX I

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, approximately 16 mm in length, 6.3 mm in width, and 6.0 mm in thickness.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Joenja is indicated for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more.

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the management of primary immune deficiencies.

Posology

The recommended dose is 70 mg leniolisib twice daily approximately 12 hours apart. Joenja is indicated in adults and adolescents 12 years of age and older and weighing 45 kg or more.

Treatment should be continued as long as a benefit is observed or until unacceptable toxicity occurs.

Missed dose
If a dose is missed by more than 6 hours, the patient should not take the missed dose but resume dosing at the next scheduled time.

If vomiting occurs within 1 hour after taking leniolisib, the patient should take another leniolisib tablet as soon as possible. If vomiting occurs more than 1 hour after dosing, the patient should not take an additional dose.

Special populations

Paediatric population
The safety and efficacy of leniolisib in children aged less than 12 years or below the weight of 45 kg have not yet been established. No data are available.

Elderly
There are no data on patients aged 65 years and older. No dosing modifications are recommended for elderly patients.

Renal impairment
Leniolisib has not been studied in patients with renal impairment (creatinine clearance (CrCL) 15 to 89 mL/min). No dosing modifications are recommended for patients with renal impairment.

Hepatic impairment
Leniolisib has not been studied in patients with hepatic impairment. Use of leniolisib in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C) is not recommended.

Method of administration

Oral use.

Joenja can be taken with or without meals. The tablets should be swallowed whole. Do not split, crush, or chew the tablets.

Gastric acid reducing agents
For patients using locally acting antacids chronically, the antacid should be taken either 2 hours before or 2 hours after leniolisib administration (see section 4.5).

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

Immune-related adverse events

Serious, sometimes fatal, immune-related adverse events such as severe infections, severe cutaneous adverse reactions (SCARs), pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other phosphoinositide 3-kinase delta (PI3Kδ) inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in APDS patients. Joenja is not approved for treatment of haematological or solid cancers.

Combination with CYP3A4 inhibitors

Concomitant therapy with a strong cytochrome P450 (CYP)3A4 inhibitor increased leniolisib exposure. Concomitant use of leniolisib with strong CYP3A4 inhibitors should be avoided (see section 4.5). If use of strong CYP3A4 inhibitors is required, it is recommended that Joenja be discontinued 2 days before administration of CYP3A4 inhibitor. Joenja may be restarted 7 days after CYP3A4 inhibitor discontinuation.

Combination with CYP3A4 inducers

Concomitant use may result in reduced leniolisib exposure and thus reduced leniolisib efficacy. Therefore, concomitant use of leniolisib with strong and moderate CYP3A4 inducers should be avoided (see section 4.5).

Combination with BCRP inhibitors

Concomitant use may result in increased leniolisib exposure, which could lead to an increased risk of adverse reactions. Therefore, concomitant use of leniolisib with strong breast cancer resistance protein (BCRP) transporter inhibitors should be avoided (see section 4.5).

Combination with organic anion transporter (OAT)P1B1, OATP1B3, and breast cancer resistance protein (BCRP) substrates

When co-administered, leniolisib increased rosuvastatin systemic exposure 2-fold. Concomitant use of leniolisib with medicinal products that are substrates of these transporters should be avoided (see section 4.5).

Combination with OAT3 substrates
For OAT3 substrates with a narrow therapeutic index (e.g., methotrexate), monitor patients for adverse events and consider dose adjustments if co-administration cannot be avoided (See section 4.5).

UDP-glucuronosyltransferase (UGT) 1A1 substrates

In vitro, leniolisib is an inhibitor of UGT1A1, and although a relevant clinical interaction is not expected, concomitant administration of leniolisib with a UGT1A1 substrate should be avoided (see section 4.5).

Gastric acid reducing agents

For patients using antacids chronically, the antacid should be taken either 2 hours before or 2 hours after Joenja administration (see section 4.5).

Reproductive toxicity

Women of childbearing potential should use highly effective contraception while taking Joenja and for 1 week after the last dose (see section 4.6). Joenja is not recommended during pregnancy and in women of childbearing potential not using highly effective methods of contraception. Verify pregnancy status in females of reproductive potential prior to initiating treatment with Joenja.

Excipients with known effect

Lactose content
This medicinal product contains lactose monohydrate. 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

Medicinal products affecting the pharmacokinetics of leniolisib

CYP3A4 inhibitors
Leniolisib is cleared primarily through oxidative metabolism (primarily hydroxylation and dealkylation) by CYP isoenzymes (predominantly CYP3A4, 95.4%). In a study of healthy adults, co-administration of leniolisib and itraconazole, a strong CYP3A4 inhibitor, resulted in a 2-fold increase in leniolisib exposure. Concomitant use of leniolisib with strong CYP3A4 inhibitors (e.g., cobicistat, danoprevir, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telithromycin, tipranavir, troleandomycin,

voriconazole) should be avoided (see sections 4.4 and 5.2).

CYP3A4 inducers
No interaction studies have been conducted with leniolisib and strong and moderate CYP3A4 inducers. Concomitant use may result in reduced leniolisib exposure and thus reduced leniolisib efficacy. Therefore, concomitant use of leniolisib with strong and moderate CYP3A4 inducers (e.g., avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's Wort, bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided (see section 4.4).

BCRP inhibitors
Leniolisib is a substrate of BCRP transporters. No interaction studies have been conducted with leniolisib and strong BCRP inhibitors. Concomitant use may result in increased leniolisib exposure, which could lead to an increased risk of adverse effects. Therefore, concomitant use of leniolisib with strong BCRP inhibitors (e.g., curcumin, cyclosporine) should be avoided (see section 4.4).

Gastric acid reducing agents
Leniolisib exhibits pH-dependent solubility, with lower solubility at higher pH-values. Locally acting antacids (e.g., magnesium-, aluminum-, and calcium-based antacids, sodium bicarbonate) should be taken 2 hours before or 2 hours after leniolisib administration (see sections 4.2 and 4.4).

Medicinal products that have their exposure altered by leniolisib

OATP1B1, OATP1B3, and BCRP substrates
When co-administered, leniolisib increased rosuvastatin exposure 2-fold. Avoid concomitant use of leniolisib with medicinal products that are OATP1B1, OATP1B3, and BCRP substrates (e.g., rosuvastatin, pitavastatin, letermovir).

OAT3 substrates
Leniolisib is an OAT3 inhibitor and may increase systemic exposure to OAT3 substrates (e.g., adefovir, baricitinib, bumetanide, cefaclor, ceftizoxime, ciprofloxacin, famotidine, furosemide, methotrexate, oseltamivir carboxylate, benzylpenicillin [penicillin G], tenofovir). When co-administered, leniolisib increased furosemide exposure 1.4-fold. Avoid concomitant use of leniolisib with medicinal products that are OAT3 substrates with a narrow therapeutic index (e.g., methotrexate).

UDP-glucuronosyltransferase (UGT) 1A1 substrates
In vitro, leniolisib is an inhibitor of UGT1A1, and although a relevant clinical interaction is not expected, concomitant administration of leniolisib with a UGT1A1 substrate (e.g., irinotecan) should be avoided.

Hormonal contraceptives
Administration of leniolisib with a single dose oral contraceptive containing ethinylestradiol and levonorgestrel increased ethinylestradiol exposure by approximately 30% with no effect on levonorgestrel exposure. The increase in ethinylestradiol exposure is unlikely to reduce the effectiveness of a combined oral contraceptive composed of ethinylestradiol and levonorgestrel.

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 (see section 5.3). Verify pregnancy status in females of reproductive potential 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

It is unknown whether leniolisib and its metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of leniolisib in milk (see section 5.3). A risk to breastfed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Joenja.

Fertility

No human data on the effect of leniolisib on fertility are available. Studies in animals have shown effects on the male reproductive organs (see section 5.3).

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

Summary of safety profile

The most commonly reported adverse reactions during leniolisib treatment were headache (32%), vomiting (16%), weight increase (13%), and alopecia (11%). Based on laboratory data from the clinical studies, 33% of patients experienced a decrease in neutrophil counts.

Tabulated list of adverse reactions

The safety of leniolisib was evaluated in 38 adolescent and adult patients with APDS who participated in the placebo-controlled portion of Study 2201, and an open label safety study. Thirty-seven of 38 patients received leniolisib 70 mg orally twice daily for at least 60 weeks and 84% were exposed for 108 weeks or longer. Median duration of leniolisib treatment was approximately 4 years, and 10 patients had more than 5 years of leniolisib exposure.

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience. Adverse reactions in Table 1 are listed 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 frequency.

Table 1 Adverse reactions

System organ class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity*	Not known
Nervous system disorders	Headache	Very common
Gastrointestinal disorders	Vomiting	Very common
	Dyspepsia	Common
Skin and subcutaneous tissue disorders	Alopecia	Very common
	Atopic dermatitis**	Common
	Rash	Common

System organ class	Adverse reaction	Frequency
General disorders and administration site conditions	Fatigue	Common
Investigations	Weight increased	Very common
	Neutrophil count decreased	Very common

*Hypersensitivity: including itching, skin redness, hives, rash, difficulty breathing or swallowing (from post-marketing use of Joenja)
**Atopic dermatitis: including dermatitis atopic and eczema

Description of selected adverse reactions

Neutrophil count decreased
Seven (33%) patients receiving leniolisib developed a transient absolute neutrophil count (ANC) between 500 and 1500 cells/µL. No patients developed an ANC < 500 cells/µL and there were no reports of infection associated with neutropenia. One case of Grade 3 neutrophil count decrease considered related to leniolisib was reported.

Hypersensitivity
Hypersensitivity reactions have been identified during post-marketing use of Joenja.

Paediatric population

Thirteen patients aged 12 to 17 were treated with leniolisib in the clinical trials. Frequency, type, and severity of adverse reactions were similar to adults.

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 national reporting system listed in Appendix V.

4.9 Overdose

If overdose occurs, the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with leniolisib 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 and pharmacodynamic effects

Leniolisib selectively inhibits PI3Kδ by blocking the active binding site of PI3Kδ. Gain-of-function variants in the gene encoding p110δ catalytic subunit (resulting in APDS1) or loss-of-function variants in the p85α regulatory subunit (resulting in APDS2) both lead to hyperactive PI3Kδ signalling leading to increased production of phosphatidylinositol 3,4,5 trisphosphate and downstream phosphorylated protein kinase B (pAkt). Through inhibiting PI3Kδ thus decreasing production of PIP3, hyperactivity of the downstream Akt/mammalian target of rapamycin (mTOR) pathway is reduced, subsequent deficiencies and dysregulation of B and T cell populations normalise.

Clinical efficacy and safety

The efficacy of leniolisib was assessed in Study 2201, a 12-week randomised, blinded, placebo-controlled phase 2/3 study in 31 patients with confirmed APDS-associated pathogenic variant in either *PIK3CD* or *PIK3R1*. Patients were randomized 2:1 to receive either leniolisib 70 mg or placebo twice a day. Patient demographics at baseline are presented in Table 2.

Table 2 Baseline demographic and disease characteristics (Study 2201)

Demographics and disease characteristics	**Leniolisib 70 mg (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)

SD – standard deviation
[1]Patient age from study Day -4 up to initial 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). mTOR inhibitors and PI3Kδ inhibitors (selective or non-selective) were prohibited within 6 weeks of baseline and throughout the study. In addition, patients treated with previous or concurrent B cell depleting agents (e.g., rituximab) within 6 months of baseline were excluded from the study, unless absolute B lymphocytes in the blood were normal. B cell depleting agents were prohibited throughout the study.

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 (SPD) of index lesions, and the normalisation of immunophenotype as measured by the percentage of naïve B cells out of total B cells. Table 3 presents the results for the co-primary endpoints.

Table 3 Primary analysis of change from baseline at Week 12 (Day 85)

	Leniolisib (N=21)	**Placebo (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)	-0.30 (0.04)	-0.06 (0.06)
Difference vs. placebo (95% CI)		-0.24 (-0.37, -0.11)
p-value		0.0012
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)	34.76 (3.08)	-5.37 (3.95)
Difference vs. placebo (95% CI)		40.13 (28.51, 51.75)
p-value		<0.0001

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 leniolisib and placebo, and its p-value were obtained from an Analysis of Covariance model with treatment as a fixed effect and log10-transformed baseline SPD as a covariate. The use of both glucocorticoids and IV Ig at baseline was included as categorical (yes/no) covariates.

[a]Change in index lesion size was measured using the log10 transformed 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 patient on leniolisib having complete resolution of the index lesion identified at baseline.

[c]Only patients with a reduced percentage of naïve B cells at baseline (defined as below 48% being the lowest value across all ages in literature) were included in the analysis.

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

Paediatric population

The European Medicines 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).

Exceptional circumstances

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

The pharmacokinetics of leniolisib have been studied in healthy subjects and adult and adolescent patients with APDS. Steady state drug concentrations can be expected to be reached after approximately 2 to 3 days of leniolisib treatment. The pharmacokinetics of leniolisib are similar between healthy participants and APDS patients.

Absorption

In a placebo-controlled, ascending single and multiple dose study in healthy participants, leniolisib was rapidly absorbed in the fasted state, with median time to maximum plasma concentration (t_{max}) at about 1 hour post dose. T_{max} appeared independent of dose and was not altered after multiple oral doses.

Food effect
Co-administration of a single 70 mg dose of leniolisib with a high fat meal delayed the rate of absorption (T_{max}) by 3 hours (0.64 h [fasting] to 3.51 h [fed]) and decreased C_{max} on average by 41% but not the extent of absorption (area under the curve [AUC]). The impact of food on the absorption of leniolisib is not expected to be clinically relevant (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 (estimate from steady-state drug washout). The median oral volume of distribution during the terminal phase ranged from 33 L to 57 L, indicating that leniolisib has a moderate-to-low volume of distribution. In humans, the *in vitro* blood/plasma ratio is 0.643.

Biotransformation

Leniolisib was 60% metabolized by the liver, with CYP3A4 as 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). The strong activity of recombinant CYP1A1 suggests a possible involvement of this enzyme in the biotransformation of leniolisib in extra-hepatic tissues. Intestinal secretion by BCRP and extrahepatic CYP1A1 cannot be excluded as excretion routes.

Elimination

The mass balance of an oral dose of 70 mg ^{14}C-leniolisib was 92.5% (standard deviation: 2.3%) 168 hours post dose (morning of Day 8).

^{14}C-leniolisib was excreted predominately via faeces (67.0%), while excretion via urine was approximately 25.5%. Approximately 70% of the ^{14}C-leniolisib was recovered within 48 hours. During twice daily dosing approximately 12 hours apart, leniolisib accumulates approximately 1.4-fold in achieving steady state (range of 1.0 to 2.2), consistent with an effective half-life ($t_{1/2}$) of approximately 7 hours.

Linearity/non-linearity
Dose proportionality analysis of systemic drug exposure (AUC and maximum plasma concentration [C_{max}]) indicates that the pharmacokinetics of leniolisib are linear with respect to both dose (20 to 140 mg twice a day dosing and single doses of 10 to 400 mg/day) and time.

Pharmacokinetic/pharmacodynamic relationship(s)

Ex vivo pharmacodynamics of leniolisib (proportion 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 leniolisib 70 mg twice a day at steady state is estimated to produce time-averaged reduction of pAkt-positive B cells by approximately 80%.

5.3 Preclinical safety data

Repeated dose toxicity

The effects observed in the repeat dose toxicity studies were primarily in the haemolymphopoietic system related to the immunomodulatory properties of leniolisib and the gastrointestinal tract in mice, rats, and monkeys. Leniolisib caused depletion/decreased activity in lymphoid tissues and inhibited the T cell dependent antibody response (TDAR) in rats. As a result of immunosuppression, an increase in opportunistic skin infections (in rats) and gastrointestinal toxicity (i.e., inflammation/infections in mice and monkeys) were observed, leading to severe diarrhoea and emesis (monkeys only). At the NOAELs of rats and monkeys in the chronic toxicity studies, the combined male/female plasma exposure ($AUC_{0\text{-}24h,u}$) was similar to the human exposure at the therapeutic dose.

Genotoxicity and carcinogenicity

Leniolisib did not show mutagenic, clastogenic, or aneugenic potential in the genotoxicity studies. No signs of carcinogenic potential (e.g., hyperplasia/neoplasia) were found in repeated dose toxicity studies. Long-term animal studies to evaluate the carcinogenic potential of leniolisib have not been conducted.

Reproductive and developmental toxicity

In the 26-week rat study, lower prostate weights correlated with a decreased secretion seen microscopically. In this study and the 10-week juvenile rat study, lower testes and epididymis weights and lower sperm counts were linked to decreases in the germinal epithelium and round spermatids and loss of spermatocytes. These histological findings occurred at 90 and ≥40 mg/kg/day, respectively (corresponding to 2.4- and 1.5-fold the maximum human recommended dose based on AUC). No effects on male or female fertility or reproductive performance was noted in rats up to 90 mg/kg/day (corresponding to 2.4- to 3.8-fold the maximum human recommended dose based on AUC).

Embryonic and foetal development studies in rats and rabbits showed microphthalmia as well as reduced orbital socket size (rats and rabbits) and anophthalmia (rats only) at the highest dose levels (120 and 100 mg/kg/day, respectively). In rabbits, aglossia was also reported from 30 mg/kg/day. The NOAELs for embryo-foetal development were 30 mg/kg/day in rats and 10 mg/kg/day in rabbits corresponding to approximately 1.7- and 0.1-fold, respectively, the maximum recommended human dose based on AUC. Therefore, based on submitted data, it can be concluded that leniolisib is teratogenic in rats and rabbits and it could represent a clinical potential risk.

In the pre- and postnatal developmental rat toxicity study, adverse reactions 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.

In the 10-week juvenile rat study initiated in 7 days old animals, an increase in mortality rate was reported during the preweaning period at 90 mg/kg/day (AUC levels measured after the first dose were 9.5-fold those at the maximum human recommended dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose (E460)
Hypromellose (E464)
Sodium starch glycolate (Type A)
Magnesium stearate (E572)
Colloidal anhydrous silica (E551)

Tablet film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Iron oxide monohydrate yellow (E172)
Iron oxide red (E172)
Talc (E553b)
Polyethylene glycol (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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)

EU/1/26/2034/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of leniolisib in the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.	Annually (with annual reassessment) Final CSR after 10-year follow up
In order to ensure adequate monitoring of safety and efficacy of leniolisib in the treatment of APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of leniolisib.	Annually (with annual reassessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Joenja 70 mg film-coated tablets
leniolisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole. Do not split, crush, or chew the tablets.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2034/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Joenja 70 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Joenja 70 mg film-coated tablets
leniolisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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2333 CR Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2034/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Joenja 70 mg film-coated tablets
leniolisib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Joenja is and what it is used for

Joenja contains the active substance leniolisib, which belongs to a group of medicines called immunostimulants (medicines that increase the ability of the immune system, the body's natural defences, to fight infection and disease).

Joenja is used in adults and adolescents aged 12 years and older, and who weigh 45 kg or more, to treat activated phosphoinositide 3-kinase delta syndrome (APDS). In people with APDS, the immune system does not work properly, leaving them unable to fight infections.

The active substance in Joenja, leniolisib, blocks the activation of a protein known as phosphoinositide 3-kinase delta (PI3Kδ), which is involved in regulating the immune system. In people with APDS there is excessive activity of PI3Kδ. By blocking the excessive activity of PI3Kδ, leniolisib helps to normalise the immune system, thereby potentially slowing down disease progression.

2. What you need to know before you take Joenja

Do not take Joenja
- if you are allergic to leniolisib or any of the other ingredients of this medicine (listed in section 6 “Contents of the pack and other information”)

Warnings and precautions
Tell your doctor right away if you become ill while taking Joenja.

Serious and sometimes fatal infections, severe skin reactions (rash, itching, peeling of the skin), breathing difficulties, severe diarrhoea or colitis (inflammation of the intestines), and liver problems have occurred in patients receiving other PI3Kδ inhibitors for the treatment of conditions other than APDS. These serious events were not reported in the Joenja clinical trials.

Children and adolescents
Do not give Joenja to children under 12 years or below the weight of 45 kg because it has not been studied in this age group.

Other medicines and Joenja
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Tell your doctor or pharmacist if you are taking any of the following medicines as they should not be taken with Joenja:

The following medicines may increase the risk of side effects with Joenja by increasing the levels of Joenja in the blood:

- cobicistat, elvitegravir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir – used to treat human immunodeficiency virus (HIV) infection
- curcumin – an herbal medicine for inflammation
- cyclosporine – used to treat organ rejection post-transplant
- danoprevir, ombitasvir, paritaprevir – used to treat hepatitis C (HCV)
- itraconazole, ketoconazole, posaconazole, voriconazole – used to treat fungal infections
- telithromycin, troleandomycin – used to treat bacterial infections

The following medicines may decrease how well Joenja works by decreasing the amount of Joenja in the blood:

- antacid (aluminium-, magnesium-, and calcium-based antacids, sodium bicarbonate) – for heartburn or indigestion due to excess stomach acid (see section 3, “How to take Joenja”)
- avasimibe – used to treat build-up of cholesterol plaque in the arteries
- bosentan – used to treat pulmonary artery hypertension (PAH)
- carbamazepine, phenobarbital, phenytoin – used to treat epilepsy
- efavirenz, etravirine – used to treat human immunodeficiency virus (HIV) infection
- mitotane – cancer therapy
- modafinil – for the treatment of excessive daytime sleepiness (narcolepsy)
- nafcillin, rifabutin, rifampicin – for bacterial infections
- St. John’s Wort (Hypericum perforatum) – an herbal medicine for depression and sleep problems

Joenja may increase the risk of side effects of the following medicines by increasing the amount of these medicines in the blood:

- adefovir –used to treat hepatitis B (HBV)
- baricitinib – used to treat rheumatoid arthritis
- benzylpenicillin (penicillin G), cefaclor, ceftizoxime, ciprofloxacin – for bacterial infections
- bumetanide, furosemide – used to rid your body of salt (sodium) and water
- famotidine – used to prevent and treat heartburn or indigestion due to excess stomach acid
- irinotecan – for treatment of colon or rectal cancer
- letermovir – to prevent cytomegalovirus (CMV) infection
- methotrexate – cancer therapy
- oseltamivir carboxylate – used to treat the influenza virus
- rosuvastatin, pitavastatin – for lowering cholesterol

- tenofovir – used to treat HBV and HIV

If you are not sure if the above applies to you, ask your doctor.

Pregnancy, breast-feeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Your doctor will do a test to see if you are pregnant before beginning treatment with Joenja.

Pregnancy
Joenja is not recommended during pregnancy. Animal studies suggest that this medicine may cause harm to your unborn baby. There is no information about the safety of this medicine in pregnant women.

Joenja is not recommended for women who could become pregnant, unless they are using highly effective methods of contraception during treatment, and for at least 1 week after the last dose of Joenja. Ask your doctor about suitable methods of contraception.

If you think you may be pregnant after starting treatment with Joenja, tell your doctor immediately.

Breast-feeding
Do not breast-feed while taking Joenja. If you are breast-feeding or are planning to breast-feed, tell your doctor before taking this medicine. This is because it is not known if Joenja can pass into your breast milk or if this would affect your baby.

Fertility
No human data on the effect of leniolisib on fertility are available. Animal studies suggest a possible risk of Joenja affecting male fertility. Tell your doctor before taking this medicine.

Driving and using machines
This medicine has no or negligible influence on your ability to drive or use machines.

Joenja contains lactose monohydrate
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Joenja contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take Joenja

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is
One 70 mg tablet twice daily, approximately 12 hours apart in adult and adolescent patients from 12 years or older who weigh more than 45 kg.

If vomiting occurs within 1 hour after taking the tablet, take another tablet right away. If you vomit more than 1 hour after taking the tablet, wait and take the next dose at your usual scheduled time.

Joenja is for oral use. This medicine can be taken with or without meals. The tablets should be swallowed whole. Do not split, crush, or chew the tablets.

Take antacids 2 hours before or 2 hours after taking Joenja. Joenja may interact with other medicines (see section 2, "Other medicines and Joenja").

If you take more Joenja than you should
Contact your doctor or nearest emergency department immediately for advice if this occurs. Keep the bottle and this leaflet with you so that you can easily describe what you have taken.

If you forget to take Joenja
If you forget to take Joenja at your usual time, take the tablet as soon as you remember. Do not take a tablet if you miss a dose by more than 6 hours. Wait and take the next dose at your usual scheduled time. Do not take a double dose to make up for a missed dose.

If you stop taking Joenja
Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects may occur with following frequencies:
Very common (may affect more than 1 in 10 people)
- headache
- vomiting
- hair loss
- increased weight
- decrease in levels of neutrophils, a type of white blood cell

Common (may affect up to 1 in 10 people)
- dyspepsia (indigestion)
- rash
- atopic dermatitis (itchy, red, and dry skin in people prone to allergies)
- tiredness

Not known (frequency cannot be estimated from the available data)
- allergic reaction (hypersensitivity) including itching, skin redness, hives, rash, difficulty breathing or swallowing

Additional side effects in adolescents
Side effects were similar between adolescent and adult patients in the clinical trials of Joenja.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Joenja

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Joenja contains

- The active substance is leniolisib. Each film-coated tablet contains leniolisib phosphate equivalent to 70 mg leniolisib.
- The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), hypromellose (E464), sodium starch glycolate (Type A), magnesium stearate (E572), colloidal anhydrous silica (E551), titanium dioxide (E171), iron oxide monohydrate yellow (E172), iron oxide red (E172), talc (E553b), polyethylene glycol (E1521) (see section 2 “Joenja contains lactose and sodium”).

What Joenja looks like and contents of the pack

Joenja 70 mg film-coated tablets are yellow, oval-shaped, biconvex, bevelled edge film-coated tablets, debossed with “70” on one side and “LNB” on the other side.

Each pack contains 1 bottle with 60 tablets.

Marketing Authorisation Holder and Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.