Product Monograph

Including Patient Medication Information

PrJOENJA®

Leniolisib tablets

For oral use

70 mg leniolisib (as leniolisib phosphate)

Other Immunostimulants

Pharming Technologies BV
Darwinweg 24
2333 CR Leiden
The Netherlands

Date of Authorization:
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Recent Major Label Changes

Not applicable.

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Health Professional Information

1 Indications

JOENJA (leniolisib) is indicated for:

- the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adults and pediatric patients 12 years of age and older.

1.1 Pediatrics

Pediatrics (≥ 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of JOENJA in pediatric patients ≥ 12 years of age and weighing ≥ 45 kg has been established. Therefore, Health Canada has authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age):

Clinical studies of JOENJA did not include any patients 65 years of age and older, thus it is not known if these patients respond differently from younger adult patients.

2 Contraindications

- Leniolisib is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4 Dosage and Administration

4.1 Dosing Considerations

Verify pregnancy status in female patients of reproductive potential prior to initiating treatment with JOENJA.

Due to the potential for drug interactions with JOENJA, a washout period may be required prior to concomitant dosing with certain medications (see 9 Drug Interactions).

The safety of JOENJA has not been established in patients with recent or concurrent use of immunosuppressive medications.

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

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage for JOENJA in adult and pediatric patients 12 years of age and older, and weighing 45 kg or more is 70 mg orally twice daily, approximately 12 hours apart. There is no recommended dosage for patients weighing less than 45 kg.

Geriatrics (> 65 years of age): The safety and efficacy of JOENJA in patients over the age of 65 years have not been established.

Pediatrics (< 12 years of age): The safety and efficacy of JOENJA in pediatric patients less than 12 years of age and/or below the weight of 45 kg have not been established.

Hepatic impairment: JOENJA has not been studied in patients with hepatic impairment. Use of JOENJA in patients with moderate to severe hepatic impairment is not recommended (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

4.4 Administration

JOENJA is for oral use only.

The film-coated tablet can be taken with or without food.

4.5 Missed Dose

If a dose is missed by less than 6 hours the patient should take the dose then resume the normal dosing schedule. 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.

5 Overdose

If overdose occurs, the patient must be monitored for evidence of toxicity. 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Tablet/ 70 mg leniolisib (as leniolisib phosphate)	colloidal silicon dioxide, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate (Type A), talc, titanium dioxide

Description

JOENJA 70 mg is available as a yellow, oval-shaped, biconvex, bevelled edge film-coated tablet debossed with "70" on one side and "LNB" on the other side. The product is supplied in bottles of 60 tablets.

7 Warnings and Precautions

General

Due to the limited information about APDS, management should be implemented in coordination with health professionals experienced in treating the condition. A registry (the European Society for Immunodeficiencies [ESID]-APDS) has been established to collect data on the natural history of disease, treatment, and outcome of patients with APDS. Information is available at https://esid.org/Working-Parties/Registry-Working-Party/ESID-Registry.

Reproductive Health

- **Fertility**

  There are no data on the effects of JOENJA on human fertility.

  Results from animal studies indicate that JOENJA may impair male fertility (see 16 Non-Clinical Toxicology).

  Verify pregnancy status in females of reproductive potential prior to initiating treatment with JOENJA. Advise pregnant women of the potential risk to a fetus. JOENJA is not recommended in women of childbearing potential not using highly effective methods of contraception. Advise females of reproductive potential to use highly effective methods of contraception during treatment and for 1 week after the last dose.

7.1 Special Populations

7.1.1 Pregnancy

There are no data on the use of JOENJA in pregnant women or on human embryofetal development. JOENJA may cause fetal harm based on findings from animal studies.

In animal reproduction studies, oral administration of leniolisib to pregnant rats and rabbits during the period of organogenesis at exposures approximately 2-6 times the human exposure based on the steady state $AUC_{0\text{-}24h}$ total at the recommended dose of 70 mg twice a day produced embryofetal toxicity, including malformations.

JOENJA is not recommended during pregnancy. Advise pregnant women of the potential risk to a fetus (see 16 Non-Clinical Toxicology).

7.1.2 Breastfeeding

There are no data on the use of JOENJA in lactating women. It is unknown whether leniolisib or its metabolites are excreted in human milk, or its effect on milk production or the breastfed child.

Animal studies have shown excretion of leniolisib in milk at higher concentrations than those found in maternal blood samples. During the preweaning period, adverse effects including decreased survival, reduced weight, and delayed growth were observed in rat pups (see 16 Non-Clinical Toxicology).

Due to the potential of serious adverse reactions from leniolisib, a risk to newborns/infants cannot be excluded. Advise women not to breastfeed during treatment with JOENJA and for 1 week after the last dose.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): Safety and efficacy of JOENJA have not been established in pediatric patients less than 12 years of age and/or weighing less than 45 kg.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): The safety and efficacy of JOENJA in patients over the age of 65 years have not been established.

8 Adverse Reactions

8.1 Adverse Reaction Overview

The most commonly reported adverse events (> 15%) during leniolisib treatment in Study 2201 (including the up-titration, dose-finding portion [Part 1]; the randomised portion [Part 2]; and the open-label extension [2201E1]) were COVID-19 (28.9%), headache (28.9%), upper respiratory tract infection (28.9%), sinusitis (23.7%), pyrexia (21.1%), diarrhea, otitis externa, and vomiting (15.8% each).

The most common serious adverse events (> 5%) reported were abdominal pain and pneumonia (2 patients [5.4%] each).

Skin rash is a known class effect of PI3K inhibitors. Leniolisib-associated skin rashes were primarily observed in healthy participants and non-APDS patients in the leniolisib clinical development program.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of JOENJA was evaluated in adult and pediatric patients ≥ 12 years of age with APDS in the randomised, phase 3, placebo-controlled portion of Study 2201. All patients were treated with 70 mg leniolisib (N=21) or placebo (N=10) twice daily for 12 weeks. The study enrolled 19 adult and 12 pediatric patients. Additional safety data were collected in the open-label extension portion of the same study.

Table 2 lists the adverse reactions reported in ≥ 5% of patients treated with JOENJA in the randomised portion of Study 2201 (Part 2).

Table 2 – Adverse Reactions Reported by 2 or More Patients Receiving JOENJA in the Randomised Portion of the Pivotal 2201 Study

System Organ Class / Preferred Term	JOENJA (N = 21)	Placebo (N = 10)
	n (%)	n (%)
Gastrointestinal disorders		
Abdominal pain[1]	2 (10)	2 (20)
Diarrhea	2 (10)	0
General disorders and administration site conditions		
Fatigue	2 (10)	1 (10)
Pyrexia	2 (10)	0
Infections and infestations		
Sinusitis	4 (19)	0
Musculoskeletal and connective tissue disorders		
Back pain	2 (10)	0
Neck pain	2 (10)	0
Nervous system disorders		
Headache	5 (24)	2 (20)
Skin and subcutaneous tissue disorders		
Dermatitis atopic and eczema[2]	3 (10)	0
Alopecia	2 (10)	0

[1]Abdominal pain: including abdominal pain, abdominal discomfort, and abdominal pain upper.
[2]Treatment with topical corticosteroids (e.g., triamcinolone, betamethasone), non-sedating antihistamines, and systemic corticosteroids (e.g., prednisone <25 mg/day) was allowed for all patients and was based on severity and duration of skin rashes.

Thirty-seven eligible patients enrolled in the open-label long-term extension study (Study 2201E1). Of these, 26 patients had previous exposure to leniolisib in Study 2201 and 11 patients had no previous exposure (9 had received placebo in earlier portions of Study 2201 and 2 had previously used another PI3Kδ inhibitor). At the time of the data extract, 31 (84%) patients were ongoing in the study and six (16%) had discontinued treatment (2 due to adverse events). Thirty-seven patients continued treatment with JOENJA 70 mg twice daily for 60 weeks, and 81% were exposed for 96 weeks or longer, corresponding to approximately 120 patient-exposure years. The median duration of JOENJA treatment was approximately 3 years, and 5 patients had more than 5 years of JOENJA exposure.

The most common adverse events reported in Study 2201E1 (≥ 15%) were COVID-19 (29.7%), upper respiratory tract infection (27.0%), headache (18.9%), and pyrexia (18.9%). The most commonly reported adverse events considered to be related to leniolisib in the extension study (but not previously reported in the same patients in the pivotal portion of the study) were weight increased (8.1%), hyperglycemia, neutrophil count decreased, and arthralgia (2.7% each). The majority of the adverse events reported overall were mild-to-moderate, and no serious adverse events were considered to be related to leniolisib.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Thirteen adolescent patients aged 12 to 17 were treated with leniolisib in the clinical trials. Alopecia was reported only in pediatric patients (4/13; 31%) and investigator-reported weight gain was observed more commonly in the pediatric patients (3/13; 23%) than adults. Overall, the frequency, type, and

severity of adverse reactions in children are expected to be the same as in adults.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions, considered by the investigator to be related to leniolisib, were reported in > 2% of patients treated with JOENJA in Studies 2201 Part 2 (N=21) and 2201E1 (N=37):

Gastrointestinal disorders: Aphthous ulcer (Study 2201 Part 2 n=1, 4.8%); vomiting (Study 2201 Part 2 n=1, 4.8%)

Investigations: Weight increased (Study 2201 Part 2 n=1, 4.8%; Study 2201E1 n=3, 8.1%).

Metabolism and nutrition disorders: Hyperglycemia (Study 2201E1 n=1, 2.7%)

Musculoskeletal and connective tissue disorders: Arthralgia (Study 2201E1 n=1, 2.7%)

Nervous system disorders: Taste disorder (Study 2201 Part 2 n=1, 4.8%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Pivotal Study Findings (2201, Part 2)

Table 3 presents select hematological abnormalities that were considered to be clinically relevant to APDS. Other abnormalities were excluded.

Table 3 – Treatment-Emergent Hematological Laboratory Abnormalities After Exclusion of Baseline and Non-Treatment-Related Findings (Safety Population)

	JOENJA N=21		Placebo N=10	
Laboratory abnormality[a]	**All Grades n (%)**	**Grade 3 n (%)**	**All Grades n(%)**	**Grade 3 n(%)**
Hematologic parameters				
Hemoglobin decreased	10 (48)	0 (0)	3 (30)	0 (0)
Lymphocyte decreased	7 (33)	2 (10)	1 (10)	0 (0)
Neutrophil decreased	15 (71)	4 (19)	1 (10)	0 (0)
Platelet decreased	2 (10)	0 (0)	1 (10)	0 (0)
Eosinophils increased[b]	13 (61.9)	N/A	2 (20.0)	N/A
Monocytes decreased[b]	14 (66.7)	N/A	1 (10.0)	N/A
Monocytes increased[b]	3 (14.3)	N/A	0	N/A

The analysis was conducted using the safety population (N=31). For each abnormality, captured according to CTCAE grade, *n* reflects the total number of patients with an abnormality reported at any subsequent visit after Day 1.

[a] Participants entering the study with hematologic laboratory abnormalities and normal values thereafter were not counted as findings in this analysis.

[b] Cell counts were reported as abnormally high or low, and not according to CTCAE grade.

Table 4 presents clinical chemistry laboratory abnormalities that were associated with laboratory-related adverse events and considered to be clinically relevant. Other abnormalities were excluded.

Table 4 – Clinically-Relevant Treatment-Emergent Clinical Chemistry Abnormalities (Safety Population)

Clinical Chemistry parameters	Study 2201 Part 2 leniolisib N=21	Study 2201 Part 2 placebo (N=10)
(Preferred terms)	**n (%)**	**n (%)**
Amylase increased	1 (4.8)	0 (0)
Aspartate aminotransferase increased	1 (4.8)	0 (0)
Lipase increased	1 (4.8)	0 (0)
Pancreatic enzymes increased	1 (4.8)	0 (0)
Protein urine present	1 (4.8)	0 (0)

Parameters were identified using MedDRA-coded laboratory-related adverse events and corresponding clinical chemistry laboratory values.

Neutrophil count decreased

Seven (33%) patients receiving leniolisib in Study 2201 developed a transient and asymptomatic absolute neutrophil count (ANC) between 500 and 1500 cells/µL. No patients developed an ANC < 500 cells/µL, there were no reports of infection associated with neutropenia, and no intervention was required. The nadir was reached at day 15, after which the neutrophil counts recovered.

Open-label Extension (2201E1) Findings

During the long-term open-label extension (Study 2201E1), 11/37 (30%) patients experienced clinically-relevant Grade 3 or Grade 4 cytopenia-related hematologic laboratory abnormalities. These abnormalities, associated with laboratory-related adverse events, were observed predominantly in the lymphocyte, neutrophil, and hemoglobin parameters. Hemoglobin decreases were the most common finding, and 6/37 (16%) patients reached Grade 3 severity. One patient (3%) experienced recurrent Grade 4 lymphocyte decreases at two time points. Grade 3 neutrophil and lymphocyte decreases were each reported in 3/37 (8%) patients. Other hematologic laboratory abnormalities were excluded from this analysis.

Clinically-relevant treatment-emergent clinical chemistry abnormalities associated with laboratory-related adverse events were generally infrequent. Alanine aminotransferase increased was the most frequently reported clinical chemistry abnormality, occurring in 3/37 (8.1%) patients. Aspartate aminotransferase increased was reported in 2/37 (5.4%) patients. All other clinical chemistry abnormalities were each reported in 1/37 (2.7%) patients. No clinical chemistry abnormality associated with a laboratory-related adverse event occurred in more than 3/37 (8.1%) patients. Other clinical chemistry laboratory abnormalities were excluded from the analysis.

9 Drug Interactions

9.3 Drug-Behavioural Interactions

Leniolisib is metabolized by CYP1A1 and CYP1A2. Tobacco smoke is a moderate inducer of CYP1A2. Patients taking JOENJA are advised to reduce or completely refrain from smoking.

9.4 Drug-Drug Interactions

The drugs listed in Table 5 are based on either drug interaction studies or potential interactions due to expected magnitude and seriousness of the interaction.

Table 5 – Established or Potential Drug-Drug Interactions

Drug Class	Source of Evidence	Effect	Clinical Comment
Agents that may increase leniolisib plasma concentrations			
Strong CYP3A4 inhibitors	CT	Leniolisib is a CYP3A4 substrate. In a study of healthy adults, co-administration of leniolisib and itraconazole, a strong CYP3A inhibitor, resulted in a 2-fold increase in leniolisib exposure.	Avoid concomitant use of leniolisib with strong CYP3A4 inhibitors (e.g., cobicistat, danoprevir, dasabuvir, elvitegravir, indinavir, ketoconazole, lopinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telithromycin, tipranavir, troleandomycin, voriconazole).
Agents that may decrease leniolisib plasma concentrations			
Strong and moderate CYP3A4 inducers	T	No interaction studies have been conducted with leniolisib and strong and moderate CYP3A4 inducers. Concomitant use may result in reduced leniolisib exposure and efficacy.	Avoid concomitant use of leniolisib with strong and moderate CYP3A4 inducers (e.g., avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, thioridazine, tipravavir).
Locally acting antacids	T	Leniolisib exhibits pH-dependent solubility, with lower solubility at higher pH-values. Co-administration with locally acting antacids may result in reduced leniolisib exposure and efficacy.	Magnesium-, aluminum-, and calcium-based locally acting antacids and sodium bicarbonate should be taken 2 hours before or 2 hours after leniolisib administration.

Drug Class	Source of Evidence	Effect	Clinical Comment
Agents that may have their plasma concentrations altered by leniolisib			
CYP1A2 substrates with a narrow therapeutic index	In vitro	Time-dependent (irreversible) inhibition of CYP1A2 was observed in the presence of leniolisib in vitro. Leniolisib may potentially increase the systemic exposure of co-administered medicinal products primarily cleared by CYP1A2.	Avoid concomitant use with medicinal products that are primarily cleared by CYP1A2 and have a narrow therapeutic index (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine).
OATP1B1, OATP1B3, and BCRP substrates	In vitro	In vitro, leniolisib is an inhibitor of the hepatic uptake and efflux transporters OATP1B1, OATP1B3, and BCRP. Leniolisib may potentially increase the systemic exposure of co-administered medicinal products that are mainly substrates of these transporters.	Avoid concomitant use with medicinal products that are OATP1B1, OATP1B3 and BCRP substrates (e.g., rosuvastatin, pitavastatin, letermovir).
MATE1, MATE2K, and OCT2 substrates	In vitro	In vitro, leniolisib is an inhibitor of the renal transporters MATE1, MATE2K, and OCT2.	Avoid concomitant use with medicinal products that are primarily MATE1, MATE2K, and OCT2 substrates (e.g., metformin).

Legend: CT = Clinical Trial; T = Theoretical

Proton pump inhibitors: Pharmacokinetic results from APDS patients did not indicate that acid reducing agents (e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole) have a clinically relevant effect on leniolisib systemic exposure.

CYP2D6 and P-gp inhibitors: Co-administration with quinidine (strong P-gp and CYP2D inhibitor) did not affect leniolisib exposure (AUC and C_{max}). Leniolisib is not a sensitive substrate of P-gp and CYP2D6.

Oral 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 not expected to reduce the effectiveness of a combined oral contraceptive composed of ethinylestradiol and levonorgestrel.

Vaccines: No vaccine interaction studies have been performed using leniolisib. Vaccinations may be less effective if administered during leniolisib treatment.

9.5 Drug-Food Interactions

Avoid concomitant use with grapefruit juice and grapefruit, as they contain inhibitors of CYP34A and may increase leniolisib exposure.

JOENJA can be taken with or without food (see 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Avoid concomitant use of St. John's Wort, as this herb is a strong inducer of CYP3A4 and may decrease leniolisib exposure.

Interactions with other herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Leniolisib inhibits PI3K-delta by blocking the active binding site of PI3K-delta. 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.

10.2 Pharmacodynamics

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%.

Cardiac Electrophysiology

In a modeling and simulation study in healthy participants receiving leniolisib (N=118) at single doses ranging from 10 to 400 mg or multiple doses of 20 to 140 mg twice daily, no QTc prolongation with increasing leniolisib-concentration was identified. Over the range of concentrations in this study, no large mean increase in the QTc interval (>20 msec) was observed.

10.3 Pharmacokinetics

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.

Table 6 – Summary of JOENJA 70 mg Twice Daily Pharmacokinetic Parameters in Healthy Participants Under Fasted Condition

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{tau, ss}$ (ng*h/mL)	CL_{ss}/F (L/h)	Vd
Steady state	3790 (1010)	1.00 (0.50, 2.00)	10.3 (5.24)	20400 (7540)	4.03 (1.85)	45 L

C_{max}=maximum concentration; T_{max}=time to maximum concentration; $t_{1/2}$=elimination half-life associated with the terminal slope; $AUC_{tau,ss}$=area under concentration-time curve from time zero to tau (dosing interval) hours at steady-state; CL_{ss}/F=total body clearance at steady-state; Vd=volume of distribution.
Values are arithmetic mean (SD) except for T_{max} which is median (range).

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 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 (AUC). The effect of food on leniolisib exposure is not expected to be clinically meaningful. Patients may therefore take leniolisib irrespective of food.

Distribution
The systemic decay in leniolisib plasma concentration over time is biexponential, indicating a distribution delay towards peripheral tissues. 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. Leniolisib was highly (94.5%) bound to human plasma proteins in vitro.

Metabolism
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 feces and urine, respectively) 168 hours postdose. Unchanged leniolisib (7.8%) was the predominant drug-related material recovered in urine.

Special Populations and Conditions

- **Pediatrics:** Following a single 70 mg oral dose of leniolisib in APDS patients, leniolisib systemic exposures were comparable between pediatric 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 pediatric 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 Insufficiency:** 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.
- **Renal Insufficiency:** No studies have been conducted to investigate the pharmacokinetics of leniolisib in renally impaired patients since renal clearance is a minor elimination pathway.

11 Storage, Stability, and Disposal

Store at room temperature (15°C to 30°C). Do not refrigerate. Keep out of the sight and reach of children.

JOENJA should not be disposed of via wastewater or household waste.

Healthcare professionals should advise their patients to return all unused or expired medications to pharmacy for proper disposal according to local requirements.

Part 2: Scientific Information

13 Pharmaceutical Information

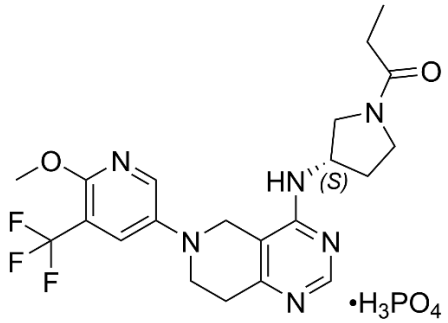
Drug Substance

Non-proprietary name of the drug substance: leniolisib phosphate

Chemical name: 1-[(3*S*)-3-[[5,6,7,8-Tetrahydro-6-[6-methoxy-5-(trifluoromethyl)-3-pyridinyl] pyrido [4,3-*d*] pyrimidin-4-yl]amino]-1-pyrrolidinyl]-1-propanone phosphate (1:1)

Molecular formula and molecular mass: $C_{21}H_{25}F_3N_6O_2 \bullet H_3PO_4$, 450.47 g/mol for the free base, 548.46 g/mol for the phosphate salt

Structural formula:



Physicochemical properties: Leniolisib phosphate is a white to yellowish to yellowish-greenish powder. The aqueous solubility of leniolisib phosphate is pH dependent with decreasing solubility observed with increasing pH: water, 29.7 mg/mL; hydrochloric acid, 8.88±0.95 mg/mL; citrate buffer (pH 4.2), 0.70±0.03; citrate buffer (pH 5.2), 0.09±0.01; phosphate buffer (pH 6.2), 0.04±0 mg/mL; phosphate buffer (pH 6.8), 0.04±0 mg/mL.

14 Clinical Trials

14.1 Clinical Trials by Indication

The clinical efficacy of JOENJA was evaluated in a randomised, triple-blinded, placebo-controlled study (Study 2201, Part 2) in patients with a confirmed APDS-associated genetic PI3Kδ mutation with a documented variant in either *PIK3CD* (APDS1) or *PIK3R1* (APDS2). A summary of the pivotal study design is provided in Table 7.

Table 7 – Summary of Patient Demographics for Clinical Trials in APDS

Study #	Study design	Dosage, route of administration, and duration	Study subjects (n)	Age (Range)	Sex
2201, Part 2	Randomised, triple-blinded, placebo-controlled	JOENJA 70 mg BID or placebo, orally, for 12 weeks	JOENJA: 21 Placebo: 10	Mean: 23.7 years (12-75)	M: 15 (48.4%) F: 16 (51.6%)

Male and female patients aged 12 years to 75 years and weighing at least 45 kg were permitted to enroll in Europe and North America.

Patient demographics and baseline characteristics are shown in Table 7. A total of 31 patients were randomised 2:1 to receive either JOENJA 70 mg (N = 21) or placebo (N = 10) twice daily for 12 weeks. Eligible patients were able to continue in a long-term safety extension study (Study 2201E1).

Overall, the median age was 20.0 years, 51.6% were female, 80.6% were Caucasian, 80.6% had APDS1 (*PIK3CD* mutation), and 58.1% and 19.4% were using glucocorticoids and intravenous IgG, respectively, at baseline. The study included 12 adolescent patients 12 to < 18 years of age (N=8 in the JOENJA arm and N=4 in the placebo arm). A summary of patient demographics and disease characteristics is reported in Table 8.

Table 8 – Summary of Patient Demographics and Baseline Disease Characteristics for Study 2201

Demographics and Disease Characteristics	JOENJA (N=21)	Placebo (N=10)
Demographics		
Mean Age[1] (years) (SD)	22.2 (10.0)	26.7 (13.4)
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)

Demographics and Disease Characteristics	JOENJA (N=21)	Placebo (N=10)
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 identified by the Cheson methodology on computed tomography (CT) or magnetic resonance imaging (MRI) as well as clinical findings and manifestations compatible with APDS (e.g., history of repeated oto-sino-pulmonary infections, lung and/or 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 using or who had previously used 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. Use of immunoglobulin replacement therapy, antibiotics, and limited topical or oral steroid use was permitted during the study.

The co-primary efficacy endpoints were (1) improvement in lymphoproliferation as measured by the change from baseline in the log10-transformed sum of product diameters (SPD) of the index lesions (up to six of the largest lymph nodes) as per the Cheson methodology and (2) the normalization of immunophenotype as measured by the percentage of naïve B cells out of total B cells in patients with a baseline percentage of naïve B cells that was < 48% of total B cells. There was no inclusion criterion for participants to have a naïve B cell percentage < 48%. Some participants were, therefore, excluded, thus the analysis set used to assess the second co-primary endpoint included fewer patients (Table 9).

Treatment with JOENJA resulted in statistically significant improvement in both of the co-primary efficacy endpoints in Study 2201 (Table 9).

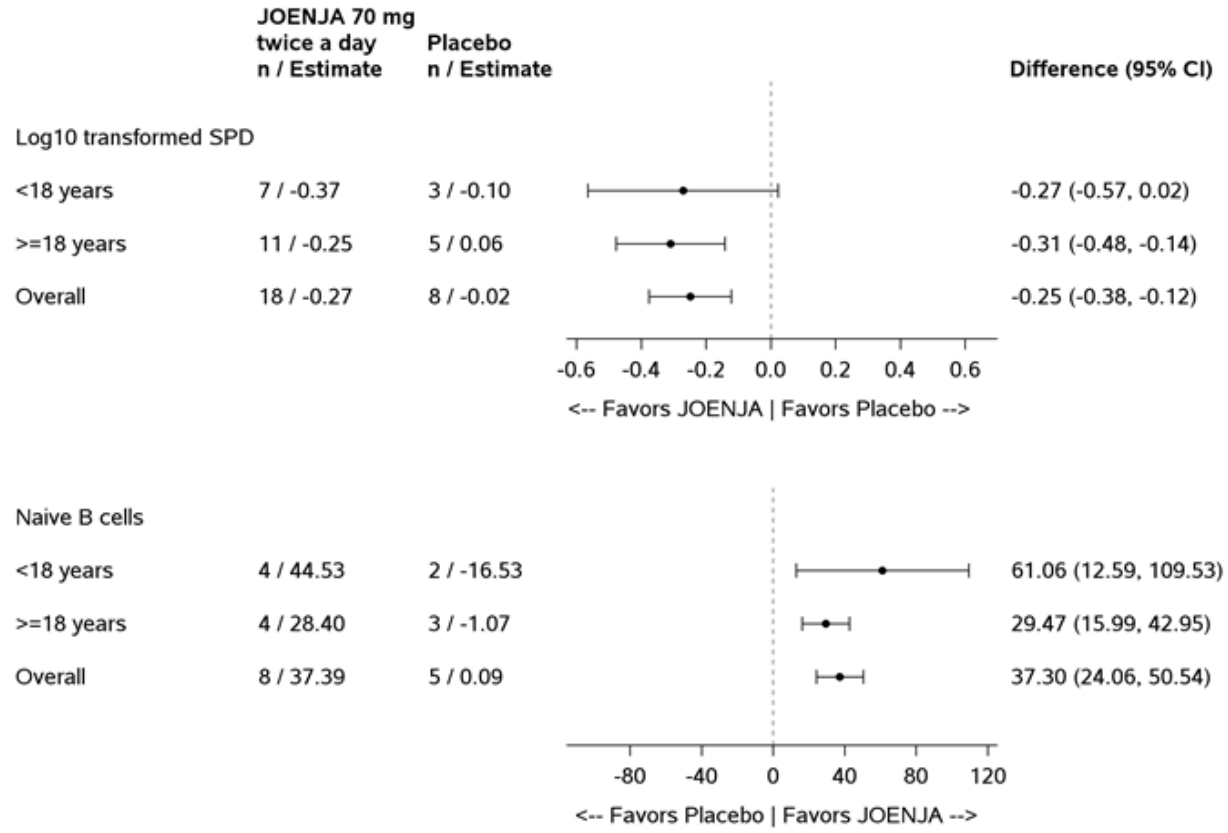
Table 9 – Results of Co-Primary Endpoints in the Placebo-Controlled Portion of Study 2201 in APDS at Week 12 (Pharmacodynamic Analysis Set*)

	JOENJA (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)	-0.27 (0.04)	-0.02 (0.06)
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 (5.35)	0.09 (6.66)
Difference vs. Placebo (95% CI)		37.30 (24.06, 50.54)
p-value		0.0002

*All patients who received any study drug and experienced no protocol deviations with relevant impact on pharmacodynamic data.
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 depicts 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



The open-label extension study (Study 2201E1) enrolled 37 patients (26 patients with previous leniolisib exposure and 11 patients with previous exposure to placebo [N=9] or a PI3Kδ inhibitor other

than leniolisib [N=2]). All patients were exposed to leniolisib 70 mg twice daily for ≥ 60 weeks and 81% were exposed for ≥ 96 weeks. The median duration of leniolisib treatment was approximately 3 years, and five patients had more than 5 years of leniolisib exposure.

There was a continued reduction of lymphoproliferation within the first 9 months, as measured by mean reductions from baseline of 66% for SPD of index lesions, 37% for spleen volume, and 21% for spleen bi-dimensional size. Immunophenotype also continued to improve within the first 9 months, with an increase from baseline of 65% in naïve to total B cells (naïve B-cell functionality was not assessed), a reduction of 55% in transitional B cells, a reduction of 81% in senescent CD57+ CD4+ T cells, and a reduction of 38% in exhausted PD-1+ CD4+ T cells. Additionally, there were clinically meaningful reductions in infection rates.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General Toxicology

The repeat dose toxicity studies identified the haemolymphopoietic system (immunosuppression), male reproductive organs (see Reproductive and Developmental Toxicology section below), and the gastrointestinal tract as target organ systems in mice, rats, and/or monkeys. Specifically, 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 ($AUC_{0\text{-}24h,tot}$) was half the human exposure at the therapeutic dose.

Genotoxicity

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).

Carcinogenicity

No long-term animal studies have been performed to evaluate carcinogenic potential of leniolisib. In a 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic mice, there was no evidence of carcinogenicity at leniolisib doses up to 80 mg/kg/day. The combined male/female plasma exposure ($AUC_{024h,tot}$) was similar to the human steady state exposure at the therapeutic dose.

Reproductive and Developmental Toxicology

Embryonic and fetal 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 rats, the maternal exposure at the NOAEL of 30 mg/kg/day was 1.6 times the human exposure based on steady state $AUC_{0\text{-}24h,tot}$ at the recommended dose of 70 mg twice a day.

In lactating rats, 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, corresponding to an exposure ($AUC_{0\text{-}24h,tot}$) of 0.3 to 1.6-fold of the human steady state exposure at the therapeutic dose.

Fertility

Effects on the male reproductive organs (prostate, testes, and epididymis) were observed in rats. In the 26-week repeat dose rat study, lower prostate weights correlated with a decreased glandular eosinophilic 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. The minimal histological findings occurred only in occasional males at 90 and 120 mg/kg/day (approximately 2 and 4 times the human exposure, respectively, based on steady state $AUC_{0\text{-}24h,tot}$ at the recommended human dose of 70 mg twice a day) with no effects on mating, fertility indices, or pregnancy rates. In the 26-week study, these effects were observed in the high dose group with similar incidence and severity with no progression by increasing the treatment duration. The described histological changes were reversible and limited to studies in rats. These effects were not observed in studies in monkeys with up to 39 weeks of exposure. The clinical relevance of these findings is unknown.

Juvenile Toxicity

In the 10-week juvenile study, rats were dosed from 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, 8.8-times the human steady state exposure at the therapeutic dose on an AUC0-24h,tot basis 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 0.8-times the human steady state exposure at the therapeutic dose on an AUC0-24h,tot basis. A no effect dose level was identified at an exposure approximately 0.2 times the human steady state exposure at the therapeutic dose on an AUC0-24h,tot basis. Similarly, during the preweaning period of the pre- and postnatal development (PPND) study in rats, a 9% reduction in the lactation index (percentage of pups born that survived 21 days post-partum) at the high dose of 90 mg/kg/day (i.e., 2.9-times the human steady state exposure at the therapeutic dose on an AUC0-24h,tot) was observed.

Special Toxicology

Phototoxicity

Leniolisib is not considered phototoxic.

Ocular

In a topical ocular tolerability study in rabbits, leniolisib was well tolerated. Only minimal and transient conjunctival hyperemia occurred at 2% and 5% leniolisib.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]JOENJA®

leniolisib tablets

This Patient Medication Information is written for the person who will be taking **JOENJA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **JOENJA**, talk to a healthcare professional.

What JOENJA is used for:

JOENJA is used to treat adults and children (12 years of age or older and weigh 45 kg or more) with activated phosphoinositide 3-kinase delta syndrome (APDS). APDS is an inherited condition that causes your immune system to not work properly.

How JOENJA works:

In patients with APDS, an enzyme called phosphoinositide 3-kinase is overactive. This interferes with the normal development of B and T cells (white blood cells that help the body fight infections).

JOENJA contains the active substance leniolisib, which belongs to a group of medicines called immunostimulants. It works by blocking the action of the enzyme phosphoinositide 3-kinase. This allows B and T cells to develop normally, reducing the symptoms of this disease.

The ingredients in JOENJA are:

Medicinal ingredients: leniolisib (as leniolisib phosphate)

Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate (Type A), talc, titanium dioxide

JOENJA comes in the following dosage form:

Tablets: 70 mg

JOENJA is available in bottles containing 60 tablets.

Do not use JOENJA if:

- you are allergic to leniolisib or to any ingredient in the formulation, or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JOENJA. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- are planning to receive any vaccines. JOENJA may affect how well a vaccine works.

Other warnings you should know about:

- **Female patients**
  Pregnancy and birth control
  - Tell your healthcare professional if you are pregnant, think you might be pregnant, or are planning to become pregnant. There are specific risks you should discuss with your healthcare professional.
  - You should NOT take JOENJA if you are pregnant. This is because it is possible that JOENJA can harm your unborn baby.
  - If you are able to become pregnant:
    - Your healthcare professional will verify your pregnancy status before starting treatment with JOENJA.
    - You should use highly effective methods of birth control while taking JOENJA and for at least 1 week after the last JOENJA dose. Talk to your healthcare professional about birth control options that may be right for you.
  - If you become pregnant during treatment with JOENJA, tell your healthcare professional right away.

  Breast-feeding
  - Do NOT breast-feed while taking JOENJA. It is not known if JOENJA passes through breast milk.
  - Talk to your healthcare professional about the best way to feed your baby during treatment with JOENJA.

- **Male patients – fertility**
  It is unclear if JOENJA will affect your ability to father children in the future. Talk to your healthcare professional if this is a concern for you.

- **Children (under 12 years of age):** JOENJA should not be used in children under 12 years of age and/or who weigh less than 45 kg. This is because JOENJA has not been studied in this age group.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with JOENJA:

- avasimibe – a medicine used to treat build-up of cholesterol plaque in the arteries
- bosentan – a medicine used to treat pulmonary artery hypertension (PAH)
- carbamazepine, phenobarbital, phenytoin – medicines used to treat seizures (epilepsy)
- cobicistat, efavirenz, elvitegravir, etravirine, indinavir, lopinavir, ritonavir, saquinavir, tipranavir – medicines used to treat human immunodeficiency virus (HIV) infection
- danoprevir, dasabuvir, ombitasvir, paritaprevir – medicines used to treat hepatitis C (HCV)
- genistein, a hormone-like substance thought mimic estrogen – medicine used for conditions related to estrogen levels in the body
- itraconazole, ketoconazole, posaconazole, voriconazole – medicines used to treat fungal infections

- magnesium-, aluminum-, calcium-based antacids, sodium bicarbonate – fast acting antacids used to treat heartburn or indigestion. Take antacids 2 hours before or 2 hours after taking JOENJA.
- mitotane – a medicine used to treat cancer
- modafinil – medicine used for the treatment of excessive daytime sleepiness (narcolepsy)
- nafcillin, rifabutin, rifampin, telithromycin, troleandomycin – medicines used for bacterial infections
- St. John's Wort (Hypericum perforatum) – a herbal medicine for depression and sleep problems
- thioridazine – a medicine used in the treatment of schizophrenia
- alosetron – a medicine used to treat irritable bowel syndrome (IBS) in women
- caffeine – a stimulant found in some beverages and foods
- duloxetine – a medicine used to treat depression
- letermovir – a medicine to prevent cytomegalovirus (CMV) infection
- melatonin, ramelteon, tasimelteon – medicines used for insomnia
- metformin – a medicine used for high blood sugar levels caused by diabetes
- rosuvastatin, pitavastatin – medicines used for lowering cholesterol
- tizanidine – a medicine used for muscle relaxation
- certain type of vaccines

Do NOT eat or drink products or juices containing grapefruit while taking JOENJA.

Reduce or completely stop smoking while taking JOENJA.

How to take JOENJA:

- Take JOENJA exactly as your healthcare professional has told you to. Check with your healthcare professional if you're not sure.
- Take JOENJA at the same time every day.
- You can take JOENJA with or without food.

Usual dose:

Adults and children (12 years or older **and** weigh 45 kg or more):

- The usual dose is 70 mg (1 tablet) by mouth twice a day, approximately 12 hours apart.
- 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.

Overdose:

If you think you, or a person you are caring for, have taken too much JOENJA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take JOENJA by:

- **less than** 6 hours, take it as soon as you remember. Take the next dose at your usual scheduled time.
- **more than** 6 hours, do NOT take another tablet. Skip the missed dose and take your next dose at your usual scheduled time.

Possible side effects from using JOENJA:

These are not all the possible side effects you may have when taking JOENJA. If you experience any side effects not listed here, tell your healthcare professional.

- Headache
- Sinusitis
- Skin inflammation with rash
- Fever
- Abdominal pain or discomfort
- Diarrhea
- Hair loss
- Back pain
- Tiredness
- Neck pain
- Increased weight
- Canker sores
- Vomiting
- Taste disorder
- Pain in a joint

JOENJA may cause abnormal urine and blood test results, such as:

- High level of liver enzymes
- High level of pancreas enzymes
- Protein in the urine

Your healthcare professional will tell you if your blood or urine test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Anemia (low levels of red blood cells): tiredness, weakness, fatigue, pale skin		X	
Lymphopenia (low levels of white blood cells: lymphocytes): fever,		X	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
cough, runny nose, enlarged lymph nodes, painful joints; rash; night sweats, weight loss			
Neutropenia (low levels of white blood cells: neutrophils): fever, enlarged lymph nodes, gum inflammation, rash		X	
Thrombocytopenia (low platelet count): spontaneous bleeding or bruising		X	
Eosinophilia (high levels of white blood cells: eosinophils): abdominal pain, rash, weight loss, wheezing		X	
Changes in monocyte levels (increase or decrease in a type of white blood cells): fever, chills, sore throat, cough and fatigue		X	
Common			
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		X	
Liver problems: yellowing of the skin or eyes, dark urine, nausea, vomiting, loss of appetite, or pain in the upper right side of the abdomen		X	
Pancreas problems: severe abdominal pain, nausea, and vomiting		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail, or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C to 30°C). Do NOT refrigerate.
- Keep out of reach and sight 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.
- 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.

If you want more information about JOENJA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website [https://www.pharming.com/products], or by calling 1-800-930-5221.

This leaflet was prepared by Pharming Technologies BV.

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