

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217759Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217759
PDUFA Goal Date	March 29, 2023
OSE RCM #	2022-751
Reviewer Name(s)	Timothy Bernheimer, Pharm.D
Team Leader	Carolyn Tieu, Pharm.D, MPH
Division Director	Cynthia LaCivita, Pharm.D
Review Completion Date	March 21, 2023
Subject	Evaluation of Need for a REMS
Established Name	Leniolisib phosphate
Trade Name	Joenja
Name of Applicant	Pharming Technologies B.V.
Therapeutic Class	Kinase inhibitor
Formulation	Oral tablet
Dosing Regimen	70 mg administered orally twice daily approximately 12 hours apart with or without food

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Joenja (leniolisib phosphate) is necessary to ensure the benefits outweigh its risks. Pharming Technologies B.V. submitted a New Drug Application (NDA) 217759 for Joenja with the proposed indication for the treatment of activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adult and pediatric patients 12 years or age and older. The risks associated with Joenja include embryo-fetal toxicity and less effectiveness of live, attenuated vaccinations. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Joenja outweigh its risks. Joenja will likely be prescribed by pediatric rheumatologists and immunologists who have experience in monitoring, diagnosing, and managing the aforementioned risks. These risks will be communicated through labeling.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Joenja (leniolisib) is necessary to ensure the benefits outweigh its risks. Pharming Technologies B.V. submitted a New Drug Application (NDA) 217759 for Joenja with the proposed indication for the treatment of activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adult and pediatric patients 12 years or age and older. This application is under review in the Division of Pulmonology, Allergy, and Critical Care (DPACC). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Joenja (leniolisib phosphate), a new molecular entity,^a is a kinase inhibitor proposed for the treatment of activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adult and pediatric patients 12 years or age and older. The mechanism of action of Joenja is inhibition of p110 δ that inhibits the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). Joenja is proposed as 70 mg tablets by oral administration. Due to APDS being caused by dominant mutations that increase the activity of PI3K δ ,¹ treatment duration is likely to be lifelong.^b Joenja is likely to be prescribed by pediatric rheumatologists and immunologists and administered in the outpatient setting. Joenja has been granted orphan drug and rare pediatric disease designations. Joenja is not currently approved in any jurisdiction.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217759 relevant to this review:

- 01/30/2018: Orphan designation granted
- 08/26/2020: Rare Pediatric Disease designation granted
- 07/29/2022: NDA 217759 submission for the treatment of activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adult and pediatric patients 12 years or age and older received
- 10/18/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Joenja
- 12/15/2022: Joenja Rare Disease Council Meeting was convened to discuss if substantial evidence of effectiveness has been demonstrated and if the benefit/risk assessment is favorable for traditional approval of Joenja for the proposed indication.
- 01/30/2023: A Late-cycle meeting was held between the Agency and the Applicant via teleconference.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

APDS is an autosomal dominant primary immunodeficiency caused by gain-of-function mutations in either PIK3CD or PIK2R1 genes.² This disorder is a significant cause of primary antibody deficiency.³ APDS is an ultra-rare disease with an estimated prevalence ranging between one to two cases per million.^{1,c} Clinical manifestations of APDS include recurrent chest infections, viral warts, widespread lymphadenopathy, lymphoma and autoimmune inflammatory disease, such as arthritis and glomerulonephritis.⁴ In addition, patients often have chronic non-resolving infections with herpes group viruses which can cause mononucleosis and pneumonitis.⁵ Severe, recurrent or persistent infections with herpes group viruses may cause early death in some affected individuals.⁶ Neurodevelopmental abnormalities such as speech and global developmental delay have been reported in patients with APDS and patients commonly have growth retardation.⁵ Patients often experience digestive tract issues such as bowel inflammation or chronic diarrhea.⁷ APDS causes combined immunodeficiency with accumulation of transitional B cells and senescent T cells. Complications include bronchiectasis, hearing

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

loss, and malignancy which can be fatal.^d APDS typically progress from recurrent infections and lymphoproliferation in early childhood, to autoimmunity in mid-childhood, and malignancy in late childhood-adulthood.⁸

3.2. Description of Current Treatment Options

Currently, there are no FDA-approved pharmacological treatment options for APDS. Available therapies are symptomatic treatments such as intravenous immunoglobulin replacement therapy, anti-inflammatory drugs such as corticosteroids, and immunosuppressive drugs.² The immunosuppressive drug Rapamune (sirolimus), which is not approved for APDS, has been shown to lessen the severity of benign lymphoproliferative manifestations and improve immunologic markers in APDS.² Rapamune has a box warning for immunosuppression and use is not recommended in liver or lung transplant patients.⁹

Hematopoietic stem cell transplantation (HSCT) is a non-pharmacological treatment option for APDS that carries the risks of complications such as acute or chronic graft versus host disease (GVHD) and carries a mortality risk of 10 to 20%. This indicates that HSCT should likely be restricted to those APDS patients with severe disease with no or insufficient response to current therapies.² As a result, there is an unmet need for safe and effective APDS treatment options.

4. Benefit Assessment

The efficacy of Joenja was evaluated from one pivotal study CCDZ173X2201 (referred to as Study 2201), which had two parts (Part 1 and Part 2). Study 2201 Part 1 consisted of a non-randomized, open-label, non-placebo controlled 12-week treatment period where the pharmacokinetics (PK) of Joenja was assessed, and dosing was determined. Study 2201 Part 2 consisted of a single, 12-week multicenter, randomized, double blind, placebo-controlled study.

Study 2201 Part 1 was a phase 2/3 dose-finding study evaluating safety, tolerability, and PK of Joenja 10 mg, 30 mg, and 70 mg delivered orally twice daily in subjects over 12 years of age diagnosed with APDS. The primary endpoints for Part 1 included safety parameters including number of adverse events, single and multiple dose concentrations of Joenja, and pAkt inhibition in unstimulated and stimulated whole blood in order to determine the appropriate dose for Part 2. The secondary endpoints of Part 1 consisted of changes from baseline in 36-Item Short Form Survey (SF-36) and Work Productivity Activity Impairment Classroom Impairment Questionnaire (WPAI-CIQ), and of visual analogue scale scores for the Physician's Global Assessment Questionnaire (PGA) and Patient Global Assessment (PtGA) at week 12. Part 1 also provided summary data for the change from baseline in the log₁₀ transformed sum of product diameters (SPD) of index lesions, spleen, and liver as well B cell and T cell immunophenotype, serum immunoglobulins, soluble biomarkers, high sensitivity C-reactive protein (hsCRP), and lactate dehydrogenase (LDH) also at week 12.

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

In Study 2201 Part 2, 15 male and 16 female subjects (n=31) over the age of 12 who had a documented APDS genetic PI3K delta mutation were randomized 2:1 to Joenja 70 mg or placebo taken orally twice daily for twelve weeks. Subjects in Part 1 were not enrolled in Part 2. Subjects were excluded if there was administration of live vaccines starting from 6 weeks before study entry, during the study, and up to 7 days after the last dose. Pregnant or nursing women, and women of child-bearing potential were also excluded from the study.

The co-primary efficacy endpoints for Study 2201 Part 2 were change from baseline in the log₁₀ transformed SPD in the index lesions selected as per the Cheson methodology from MRI/CT imaging at day 85 and change from baseline in percentage of naïve B cells out of total B cells at day 85. Secondary endpoints included change in baseline in 3D volume of index and measurable non-index lesions selected as per the Cheson methodology, and 3D volume and bi-dimensional size of the spleen at day 85, single dose PK parameters, change in baseline in SF-36 and WPAI-CIQ at day 85, visual analogue scales for physician global assessment and patient global assessment change from baseline at day 85, change in baseline in C-reactive protein (CRP), LDH, Beta2 microglobulin, ferritin, fibrinogen, and erythrocyte sedimentation rate (ESR) at day 85, and individual subject narratives. All 31 patients completed the study but only 27 patients met the inclusion criteria and were included in the primary analysis.

The clinical reviewer concludes that Joenja met statistical significance for both co-primary endpoints, demonstrating an improvement over placebo in change from baseline in the log₁₀ transformed SPD in the index lesions and percentage of naïve B cells out of total B cells at Day 85.^{10,e} The least squares (LS) mean difference estimate was -0.24 [95% CI: -0.37, -0.11; p-value <0.01] in change from baseline in the log₁₀ transformed SPD in the index lesions at Day 85 and 40.13 [95% CI: 28.51, 51.75; p-value <0.01] in change from baseline at Day 85 in naïve B cells.

Given that the co-primary endpoints are not direct reflections of how patients feel, function, or survive, and the lack of regulatory precedence for this condition, the review team assessed other outcomes in the trial to determine if the Joenja treatment effect is clinically meaningful.

In Study 2201 Part 2, the secondary endpoint analysis of the SF-36 examined change from baseline to Day 85 on the 8 subscales and the Physical Component Scale and Mental Component Scale. There was no significant change from baseline in overall SF-36 score observed in the Joenja versus placebo group, but there were improvement trends in the physical functioning scale, general health scale, and physical component summary scores as well as the PtGA and PGA changes.

Although not pre-specified endpoints, the review team evaluated antibiotic use, intravenous immunoglobulin use, and infection rates over the course of Trial 2201, Part 1 and 2 to assess if improvements in the co-primary endpoints of percentage of naïve B cells translated into clinical benefit related to infections. The review team concluded that overall, trends were favorable for treatment with Joenja.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

In Study 2201 Part 2, in addition to the imaging data collected to evaluate the co-primary endpoint of change from baseline in the log₁₀ transformed SPD in the index lesions, additional measurements were collected from index lymph nodes, non-index lymph nodes, liver, and spleen. In general, lesion measurements appeared to decrease in most subjects in the Joenja treatment group and increase or remain the same in the placebo treatment group. Although there are relatively few data, there were patients with thrombocytopenia (n=3) or anemia not found to be caused by iron deficiency (n=6) enrolled in the trial. Patients with thrombocytopenia (n=1) or anemia not found to be caused by iron deficiency (n=4) those treated with Joenja appeared to show an improvement, whereas those who received placebo showed no improvement.

Additionally, confirmatory evidence in the form of mechanistic data was also evaluated in Trial 2201 Part 1 and 2. The characteristic laboratory and flow cytometric findings in APDS are: reversed CD4/CD8 ratio, decreased naïve CD4+ and CD8+ cells, reduced follicular T helper cells, decreased CD19+ B Cell, increased transitional B cells and plasmablasts, decreased class switched memory B cells, normal or elevated concentrations of immunoglobulin M (IgM) and low to normal concentrations of immunoglobulin G (IgG) and immunoglobulin A (IgA). According to the clinical reviewer, most subjects in Trial 2201, Part 2 demonstrated a decrease in the change from baseline of transitional B cells and all subjects experienced a decrease in the change from baseline of plasmablasts, suggesting a normalization in immunophenotype. Individual changes in IgM levels appeared to have decreased from baseline in more subjects treated with Joenja than placebo, although there were no apparent differences in change in IgG and IgA.

The clinical reviewer concludes that, overall, the Applicant has demonstrated substantial evidence of effectiveness for Joenja for the treatment of APDS in adults and adolescents aged 12 or older based on the statistically and clinically persuasive results for the co-primary endpoints and favorable trends in clinically meaningful secondary and exploratory endpoints from one adequate and well-controlled pivotal trial in combination with confirmatory evidence in the form of mechanistic data.

Refer to the Multi-disciplinary Review and Evaluation: NDA 217759 Joenja (leniolisib phosphate) for more information.¹⁰

5. Risk Assessment & Safe-Use Conditions

Study 2201 Parts 1 and 2, and study CCDEZ173X2201E1 (referred to as Study 2201E1) of the Joenja development program were evaluated for safety. Study 2201E1 was an open label extension study to Study 2201 Part 2 where safety was further assessed. The safety database included 196 healthy volunteers, 20 subjects with Sjorgren's syndrome, and 38 subjects with APDS that received at least one dose of Joenja. Study 2201 Part 2 provided the only blinded, controlled safety data and therefore is the focus of the safety review.

In Study 2201 Part 2, most patients were exposed to treatment for the full 12 weeks in both Joenja and placebo arms and mean and median exposure times were similar between the two treatment arms. Study 2201 Part 1 and Study 2201E1 provided supportive information regarding dose response (Part 1) and long-term safety (2201E1).

There were no serious adverse events (SAEs) leading to discontinuation of Joenja in Study 2201 Part 2.

There were two deaths reported in the Joenja clinical program. One death (pulmonary hypertension) occurred in a placebo-treated subject during the follow-up period of Study 2201 Part 2 and one death (cardiac arrest) occurred in a Joenja treated subject in Study 2201E1. The patient death that occurred in Study 2201E1 is thought to be due to direct sequelae of a worsening chronic disseminated mycoplasma oral infection and underlying cardiomyopathy.

There were no apparent drug-related SAEs. The frequency of nonfatal SAEs was similar between treatment groups in Trial 2201 Part 2 with 3 (14%) of patients experiencing an SAE in the Joenja group versus 2 (20%) in the placebo group. One patient in the treatment group experienced an episode of Grade 2 mastoiditis and was hospitalized for treatment. One patient in the treatment group suffered from Grade 4 alcohol intoxication resulting in coma on Day 4 of Study 2201 Part 2, however, she subsequently recovered and completed the study after which she entered Study 2201E. One patient experienced Grade 3 elevated liver enzymes and failure to thrive resulting in discontinuation of Joenja and hospitalization on day 877 of Study 2201E.

Significant adverse events were defined as those of grade 3 or higher. In addition to the Grade 4 and Grade 3 nonfatal SAEs mentioned in the previous paragraph, one subject experienced a significant adverse event of grade 3 syncope from which he recovered and that was not thought to be related to Joenja.

The *Warnings and Precautions* section of the labeling include risks of embryo-fetal toxicity and potential reduced effectiveness of live attenuated vaccinations (described below).^f

5.1. Embryo-Fetal Toxicity

Based on findings in animals, Joenja may cause fetal harm when administered to a pregnant woman. This label advises healthcare providers to advise pregnant women of the potential risk to a fetus and to advise females of reproductive potential to use highly effective methods of contraception during treatment and for one week after the last dose.

5.2. Vaccinations

The label advises healthcare providers that live, attenuated vaccinations may be less effective if administered during Joenja treatment.

The clinical reviewer states the safety review did not identify any risks that would outweigh the potential benefit for APDS patients who have no alternative therapies and concludes that there is a favorable benefit-risk assessment to support approval.

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6. Expected Postmarket Use

Joenja will be used in the outpatient setting and prescribed by pediatric rheumatologists and immunologists. In addition to being a very rare disease, APDS may mimic more common conditions. The onset of APDS may be somewhat variable over time, both in terms of age at presentation and in terms of clinical and immunological complications. As a result, patients are often referred to various specialists such as hematologists, rheumatologists, gastroenterologists, and others, before an immunological evaluation is performed.¹¹

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Joenja beyond routine pharmacovigilance and labeling.

7.1. Other Proposed Risk Management Activities

At the time of this review, the review team has determined that the following post marketing requirements (PMRs) and post marketing commitments (PMCs) are necessary for the Applicant to complete:

- PMR-1 to conduct a 6-month carcinogenicity study in transgenic (rasH2) mice.
- PMR-2 to conduct a 2-year carcinogenicity study in rats
- PMR-3 to conduct a pre- and post- natal development study in rats
- PMC-1 to submit the final clinical study report (SCR) from the ongoing open-label extension study CCDZ733201E1.

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to Division of Epidemiology for review and input.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Joenja for the treatment of APDS in adult and pediatric patients 12 years of age and older based on the efficacy and safety information currently available.

APDS is a rare serious disease with significant morbidity and mortality, manifested by immunodeficiency, recurrent infections, benign and malignant lymphoproliferation, and autoimmunity. Currently, there are no FDA-approved pharmacological treatment options for APDS and as a result there is an unmet need for treatment.

The risks of embryo-fetal toxicity and reduced efficacy of live, attenuated vaccinations will be communicated through the *Warnings and Precautions* section of labeling. The risk of embryo-fetal toxicity is further communicated in the *Use in Specific Populations* section of labeling. Although not

approved for APDS, Rapamune (approved in 1999) has been shown to improve some markers of APDS and as a result have been used by pediatric rheumatologists and immunologists (the likely prescribers of Joenja) as a treatment for APDS. Rapamune also shares the risks of embryo-fetal toxicity and avoidance of live vaccine immunizations, which are communicated through the *Warnings and Precautions* section of labeling. As a result, likely prescribers of Joenja are likely to be familiar with Rapamune and their shared risks and should be knowledgeable of the monitoring for and management of these risks. Currently, treatment of APDS is symptomatic and involves corticosteroids and immunosuppressants. Pediatric rheumatologists and immunologists often use immunosuppressants to treat a variety of conditions that involve inflammation and immune system dysfunction.¹² For example, methotrexate sodium (approved in 1953)¹³ is approved for the treatment of adults with rheumatoid arthritis and is approved for the treatment of pediatric patients with polyarticular juvenile idiopathic arthritis. Methotrexate is also used by pediatric rheumatologist off-label to treat other pediatric rheumatic diseases^{14,15} and immunologists also use the drug for many other autoimmune disorders.^{12,16} Methotrexate has a box warning for embryo-fetal toxicity and the risk of reduced vaccination effectiveness with live vaccines is communicated in the *Warnings and Precautions* section of labeling. Methotrexate shares these risks with Joenja and is a drug that the likely prescribers of Joenja have experience with prescribing and monitoring. As a result, likely prescribers of Joenja should have experience in monitoring, diagnosing, and managing the aforementioned risks.

Of note, Joenja is in the same class of drugs as Aliqopa¹⁷ (approved in 2017), and alpelisib marketed under Piqray¹⁸ (approved in 2019) and Vijoice¹⁹ (approved in 2019) and none of these products were approved with a REMS. However, it is important to note that these drugs are approved for various oncologic indications, and target PI3K isoforms that differ from Joenja which results in distinct mechanisms of action and safety profiles. All of these drugs communicate the risk of embryo-fetal toxicity in the *Warning and Precautions* section of their labeling.^{17,18,19}

Zydelig (approved in 2014) is a PI3K δ inhibitor for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.²⁰ The Zydelig REMS was approved to mitigate the risks of fatal and/or serious hepatotoxicity; fatal and/or serious and severe diarrhea or colitis; fatal and/or serious pneumonitis; fatal and/or serious infections, and fatal and serious intestinal perforation associated with Zydelig. These risks were not identified during Joenja's clinical development program. Adverse events of diarrhea and infections were reported with Joenja but none were not fatal or serious. Risk mitigation of embryo-fetal toxicity was not a goal of the Zydelig REMS and this risk is communicated in the *Warning and Precautions* section of the Zydelig labeling.²⁰ The REMS for Zydelig was released in July 2022 because the most recent REMS assessment demonstrated that healthcare providers demonstrate acceptable understanding of the risks and therefore FDA determined that the REMS is no longer necessary to ensure the benefits of Zydelig outweigh its risks.

Copiktra (approved in 2018) is a PI3K inhibitor with dual activity against PI3K δ and PI3K γ for the treatment of adult patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) after at least two prior therapies.²¹ Copiktra REMS was approved to mitigate the risks of fatal and/or serious toxicities associated with use of Copiktra, including infections, diarrhea or colitis, cutaneous reactions

and pneumonitis. As mentioned above, these risks were not identified during Joenja's clinical developmental program and the adverse events of diarrhea and infections reported with Joenja were not fatal or serious. The risk of embryo-fetal toxicity is communicated in the *Warnings and Precautions* section of Copiktra's labeling.²¹

This reviewer has determined that a REMS is not necessary to ensure the benefits outweigh the risks. The *Warnings and Precautions* section of the label will communicate the risks of embryo-fetal toxicity and reduced efficacy of live, attenuated vaccinations. Joenja will likely be prescribed by pediatric rheumatologists and immunologists who have experience in monitoring, diagnosing, and managing the aforementioned risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Joenja to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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