New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Joenja® (leniolisib) [Pharming Healthcare, Inc.]** (len"-i-oh-lis'-ib)
Dosage Formulations:	70 mg tablets supplied in 60 count bottles; to be stored and dispensed in the original container
FDA Approval Date: **FDB File Date:**	FDA: March 24, 2023 FDB: April 2, 2023
Indication:	Treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and pediatric patients 12 years of age and older weighing at least 45 kg
Mechanism of Action:	Joenja is an immune modulator that targets the root cause of APDS by modulating the overactive PI3Kδ pathway to reduce lymphoproliferation and improve cellular immunodysregulation. • Variants in the gene encoding the p110δ catalytic subunit or in the gene encoding the p85α regulatory subunit each lead to hyperactivity of PI3Kδ. • PI3Kδ phosphorylates PIP_2 (phosphatidylinositol-4,5-bisphosphate) to produce PIP_3 (phosphatidylinositol-3,4,5-trisphosphate). • PIP_3 production leads to activation of the downstream mTOR/AKT pathway and increases transcription factors which are involved in the regulation of the cell cycle. • Joenja blocks the active binding site of PI3Kδ, inhibiting the signaling pathways that lead to increased production of PIP_3, hyperactivity of the downstream mTOR/AKT pathway, and to the dysregulation of B and T cells.
Dose/ Administration:	• Verify patients of reproductive potential are not pregnant prior to beginning therapy. • Take 1 tablet by mouth twice daily approximately 12 hours apart. • If dose is missed by more than 6 hours, wait and take the next dose at the next scheduled time. • If vomiting occurs within 1 hour of administration, take another dose as soon as possible. If vomiting occurs more than 1 hour after administration, wait and take the next dose at the next scheduled time.

Disease State Clinical Highlights:	• Activated PI3Kδ syndrome (APDS) is a primary immunodeficiency that results from pathogenic variants in genes that encode PI3Kδ. APDS has also been named "p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency" (PASLI disease). The disease was first described in 2013.
	• The PI3Ks belong to family of kinases that have an important role in intracellular signaling. There are 3 class IA PI3Ks in mammalian cells: PI3Kα, PI3Kβ, and PI3Kδ. Each class of PI3K consists of 3 catalytic subunits and 5 regulatory subunits. The regulatory subunit stabilizes the catalytic subunit to prevent its proteasomal degradation, inhibits activity of the catalytic subunit, and recruits it to the plasma membrane. PI3Kδ consists of catalytic subunits p110α, p110β and p110δ and regulatory subunits p85α, p55α, p50α, p85β, p55γ.
	• The regulatory subunit p85α and catalytic subunit p110δ included in PI3Kδ play an important role in the development, differentiation, and functions of different stages of T and B lymphocytes. Dysregulation of this pathway is seen in patients with APDS, leading to PI3Kδ hyperactivity causing immune deficiency and immune dysregulation.
	  ○ APSD1 is caused by a pathogenic variant in the *PIK3CD* gene that encodes for the p110δ catalytic subunit of PI3Kδ.
	  ○ APSD2 (or PASLI-R1) is caused by a pathogenic variant in the *PIK3R1* gene that encodes for the p85α regulatory subunit of PI3Kδ.
	  ○ Both APSD1 and APSD2 are known together as APSD.
	• APSD affects an estimated 1,500 patients worldwide, with a prevalence of 1 to 2 patients per 1 million. A genetic test is now available to provide a definitive diagnosis. Currently Pharming has identified over 500 of these patients.
	• Disease severity in APSD may range from severe infections and lymphoproliferation at an early age to an asymptomatic adult patient.

	○ Recurrent respiratory tract infections are the most common clinical manifestation; recurrent respiratory tract infections often lead to bronchiectasis in more than half of patients. ○ Approximately half of patients have chronic non-resolving infections with herpes viruses [e.g., Epstein Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV)]. ○ Chronic non-malignant lymphoproliferation (generalized lymphadenopathy and hepatosplenomegaly) is seen in approximately 75% of patients. ○ Autoimmune manifestations (predominantly cytopenias and glomerulonephritis) are seen in approximately one third of patients. ○ APDS patients have an increased risk of lymphoma, with an incidence reported as high as 13%. ○ Neurodevelopmental abnormalities such as speech delay and global developmental delay have been reported in patients with APDS. Pervasive developmental disorders are more common in patients with APDS2. ○ Growth retardation is seen in 45% of APSD2 patients but is typically not present in APSD1. • Because the symptoms of APDS may be associated with a variety of other disorders, patients are frequently misdiagnosed, with a median diagnostic delay of 7 years. Many patients are misdiagnosed with other primary immunodeficiency disorders including hyper IgM syndrome due to the elevated levels of IgM seen in APDS. • A definitive diagnosis can only be made through genetic testing.
Drug Clinical Highlights:	• Joenja is the first FDA-approved therapy specifically for the treatment of APDS. It received an orphan drug designation, rare pediatric disease designation, and priority review from the FDA. • Contraindications: none • Warnings: ○ Embryo-Fetal Toxicity ▪ May cause fetal harm when administered to a pregnant woman. ▪ Verify the pregnancy status of patients of reproductive potential prior to beginning therapy. ▪ Females of reproductive potential should use highly effective methods of contraception during treatment and for 1 week after the last dose. ○ Vaccinations: live, attenuated vaccines may be less effective if administered during therapy with Joenja. • Adverse Reactions > 10%: headache, sinusitis, and atopic dermatitis • Drug Interactions: ○ Joenja is a substrate of CYP3A4 ▪ Concomitant use with strong CYP3A4 inhibitors should be avoided ▪ Concomitant use with strong and moderate CYP3A4 inducers should be avoided ○ Joenja inhibits CYP1A2 – avoid concomitant use with drugs that are primarily metabolized by CYP1A2 and have a narrow therapeutic index ○ Joenja inhibits BCRP, OATP1B1, and OATP1B3 – avoid concomitant use with drugs that are BCRP, OATP1B1, and OATP1B3 substrates • Use in Specific Populations: ○ Pregnancy: Joenja can cause fetal harm based on findings from animal studies and should not be given to pregnant patients. ○ Lactation: Advise women not to breastfeed while taking Joenja and for 1 week after the last dose. ○ Safety and efficacy of Joenja therapy in patients < 12 or ≥ 65 years of age or patients weighing < 45 kg has not been established. ○ Joenja is extensively metabolized by the liver and is not recommended for use in patients with moderate to severe hepatic impairment. **Clinical Studies** • Study 2201 (NCT02435173)

- Part 1: Phase 2, non-randomized, open-label, within-patient up-titration dose-finding study in 6 patients
  - Assessed 3 different doses: 10 mg, 30 mg, and 70 mg twice a day for 4 weeks at each dose
  - Based on immune findings, clinical findings, safety, and tolerability, the 70 mg twice a day dose was chosen for Part 2
- Part 2: Phase 3, blinded, randomized, placebo-controlled study
  - Included adult and pediatric patients ≥ 12 years of age and weighing ≥ 45 kg with confirmed APDS and all the following:
    - documented variants in either *PIK3CD* or *PIK3R1*
    - clinical findings consistent with APDS (e.g., history of repeated oto-sino-pulmonary infections, organ dysfunction)
    - ≥ 1 measurable lymph node on computed tomography or MRI scan
  - Patients were randomized 2:1 to receive either Joenja 70 mg or placebo twice a day for 12 weeks.

Baseline Demographics and Clinical Characteristics, n (%)	**Joenja (n = 21)**	**Placebo (n = 10)**
Age, years Median (range) Age < 18 years	 20.0 (12 – 54) 8 (38.1%)	 19.5 (15 – 48) 4 (40%)
APDS1 (*PIK3CD* variant) APSD2 *(PIK3R1* variant)	16 (76%) 5 (24%)	9 (90%) 1 (10%)
Baseline glucocorticoids[a]	12 (57%)	6 (60%)
Baseline IRT[b]	14 (67%)	7 (70%)
Baseline antibiotic prophylaxis	9 (42.9%)	4 (40%)
Previous sirolimus use[c]	4 (19%)	3 (30%)
Lymphoproliferation[d]	15 (71.4%)	7 (70.0%)
Chronic infections	18 (85.7%)	7 (70.0%)
Pulmonary disease	14 (66.7%)	8 (80.0%)
Bronchiectasis	8 (38.1%)	8 (80.0%)
Asthma	7 (33.3%)	4 (40.0%)
Cytopenias	13 (61.9%)	5 (50.0%)
Gastrointestinal disease	10 (47.6%)	7 (70.0%)

[a] *Glucocorticoid doses equivalent to ≤ 25 mg per day of prednisone were allowed within 2 weeks before the first Joenja dose and throughout the study.*
[b] *IRT = immunoglobulin replacement therapy*
[c] *Patients taking immunosuppressive agents, including sirolimus, underwent washout periods before entry.*
[d] *Although all patients were required to have lymphadenopathy for trial inclusion, documented clinical history of lymphoproliferation (e.g., lymphadenopathy, splenomegaly, hepatomegaly) varied.*

  - Primary Efficacy Endpoints:
    - Improvement in lymphoproliferation as measured by a change from baseline in lymphadenopathy measured by the $\log_{10}$-transformed sum of product diameters of the index lymph nodes
    - Normalization of immunophenotype as measured by the percentage of naïve B cells out of total B cells (naïve B cells are B cells that can respond to infections and antigens)

Co-Primary Endpoints at Week 12 (Day 85)	**Joenja (n = 21)**	**Placebo (n = 10)**
Log_{10}-Transformed Sum of Product Diameters of Index Lymph Nodes		
n[a]	18	8
Baseline Mean (SD)	3.03 (0.42)	3.05 (0.39)
Change from Baseline, LS Mean (SE)	-0.27 (0.04)	-0.02 (0.05)
Difference vs. Placebo (95% CI)	-0.25 (-0.38, -0.12)	
p-value	0.0006	
Percentage of Naïve B Cells out of Total B Cells		
n[b]	8	5
Baseline Mean (SD)	27.16 (13.16)	30.51 (7.97)
Change from Baseline, LS Mean (SE)	37.39 (5.34)	0.09 (6.66)
Difference vs. Placebo (95% CI)	37.30 (24.06, 50.54)	
p-value	0.0002	

[a] *The analysis excluded 2 patients from each treatment group due to protocol deviations and 1 Joenja patient because the baseline index node fully resolved by Day 85.*

[b] *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.*

- Results:
  - Both Primary Endpoints were met
    - Joenja significantly reduced lymphadenopathy (improved immune dysregulation)
    - Joenja increased the percentage of naïve B cells (improved immune deficiency)
  - Secondary Endpoints:
    - Other key disease outcome measures, including spleen size, lymphocyte subsets, and cytopenias improved.
    - Joenja markedly reduced serum IgM, and CD8+, senescent CD57+ T cells and PD-1+ T cells, which are often elevated in patients with APDS.
    - Joenja patients had a reduced number of infections experienced.
    - 37% of Joenja patients who were receiving baseline IRT reduced or discontinued their dose.

- Part 3: Open Label Extension Study (NCT02859727)
  - 35 patients from Parts 1 and 2 plus 2 patients with APDS previously treated with other investigational PI3Kδ inhibitors
  - Estimated completion date: January 2027
  - Primary Endpoint: Evaluation of the long term safety and tolerability of Joenja in APDS patients
  - Secondary Endpoints:
    - Evaluation of impact to health-related quality of life (HRQOL)
    - Evaluation of efficacy in reducing systemic inflammatory components of APDS
    - Characterization of the pharmacokinetics of Joenja in APDS patients
- Adverse Events:
  - Part 2 (Phase 3 trial)
    - Adverse reactions reported by ≥ 2 patients treated with Joenja and more frequently than placebo

Adverse Events, n (%)	Joenja (n = 21)	Placebo (n = 10)
Headache	5 (24%)	2 (20%)
Sinusitis	4 (19%)	0
Atopic Dermatitis	3 (14%)	0
Tachycardia	2 (10%)	0
Diarrhea	2 (10%)	0
Fatigue	2 (10%)	1 (10%)
Pyrexia	2 (10%)	0
Back Pain	2 (10%)	0
Neck Pain	2 (10%)	0
Alopecia	2 (10%)	0

    - No adverse events led to discontinuation of study treatment
  - Part 3 (Open-Label Extension Study as of 12/13/2021)
    - 32 out of 37 patients reported ≥ 1 adverse event
    - 78.4% of adverse events were grade 1, 48.6% grade 2, 27% grade 3, and none were grade 4

Most Common Adverse Events	Joenja (n = 37)
Upper Respiratory Tract Infection	8
Headache	6
Pyrexia	6
Otitis externa	5
Weight increase	5
COVID-19 positive/negative	5/14

  - Across all trials 38 patients had a median exposure of ~ 2 years and 4 patients had > 5 years of exposure to Joenja

Price Per Unit (WAC):	• $750 per capsule • $1,500 per day (1 capsule twice daily) • $45,000 per 30 days • $547,500 per year
Therapeutic Alternatives:	• Joenja is the first FDA approved treatment for APDS and targets the root cause of the disease by modulating the overactive PI3Kδ pathway. • Previous treatment for APDS has been based on treatment of symptoms and not the actual cause of the disease. Because disease severity can vary wildly, therapeutic options vary from simple observation to hematopoietic stem cell transplantation (HSCT). • Antimicrobial agents are used for prophylaxis of respiratory tract infections, similar to other antibody deficiencies. The most commonly used agents are azithromycin and trimethoprim/sulfamethoxazole. • IRT may also be utilized due to the defects in antibody production and function with APDS. It is beneficial in decreasing recurrent respiratory infections; however, it is not effective in preventing herpes infections, autoimmunity, and lymphoproliferation. • Immunosuppressive therapies, including rituximab (anti-CD20 monoclonal antibody), have been used to treat the autoimmunity and lymphoproliferation frequently seen in APDS. • Sirolimus (mTOR inhibitor) has been used to decrease hepatosplenomegaly and lymphadenopathy, restore T cell proliferation, and treat lymphoproliferation. • HSCT has been used to treat lymphomas and life threatening infections in APDS patients. Pharming estimates that fewer than 10% of APDS patients have received HSCT.
Prior Authorization Approval Criteria:	**Must meet the following criteria:** <u>Initial Therapy:</u> • Prescribed by or in consultation with a specialist in the treated disease state **AND** • Participant aged ≥ 12 years **AND** • Documented diagnosis of APDS (ICD10 D81.82) **AND** • Documentation of genetic testing results confirming APDS diagnosis **AND** • Documentation of clinical findings consistent with APDS (e.g., lymphoproliferation, history of repeated oto-sino-pulmonary infections, organ dysfunction) **AND** • Participant lacks concurrent use of immunosuppressant therapy (e.g., rituximab, sirolimus) **AND** • Participant is not currently pregnant or lactating **AND** • Participant lacks moderate to severe hepatic impairment • Initial approval is for 3 months <u>Continuation of Therapy:</u> • Documentation of clinical benefit of therapy (e.g., reduced signs and symptoms of disease state from baseline) • Continuation of approval is for 1 year **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Ensure any live, attenuated vaccines needed are given before beginning Joenja therapy • Females of reproductive potential should be advised to use highly effective methods of contraception during therapy and for 1 week after the last dose.
Implication to State Medicaid Program:	• LOE: TBD • A new diagnosis code for APDS (D81.82 - Activated Phosphoinositide 3-kinase Delta Syndrome [APDS]) was just recently added to the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) by the U.S. Centers for Disease Control and Prevention (CDC), effective October 1, 2022. • Pharming is partnering with PantherX Specialty Pharmacy for exclusive distribution of Joenja.

- Pharming has stated that it plans to collaborate with providers to further identify patients and get them tested for APDS and has partnered with Invitae to offer no-charge genetic testing and counseling for individuals who are suspected to have APDS through the navigateAPDS testing program. The company also plans to employ APDS clinical educators to assist with family mapping to help identify additional patients who may be eligible for treatment with Joenja.
- Pharming also stated that it will provide a bridge program for instances of continuation of therapy in insured patients during prior authorization and a 30-day starter supply program for Joenja.
- The All about APDS website by Pharming lists two providers in Missouri with experience diagnosing and managing APDS: one at Washington University/St Louis Children's Hospital in St Louis, MO and one at Children's Mercy in Kansas City, MO.
- Pharming has plans to seek future label expansion to patients aged ≥ 1 year. The ongoing LE 3301 pediatric study (NCT05438407) in children aged 4 to 11 years enrolled its first patient in February 2023. This is a two-part, prospective, open-label, single-arm, multicenter study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of Joenja in at least 15 pediatric patients with APDS. Joenja tablets at 10 mg and 30 mg strengths will be administered orally, twice a day, based on body weight for 12 weeks for Part I and for one year for Part II of the study.

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