**News Release**

**Media contact:**
Natalia Salomao
Mobile: +1 732-325-8306
nsaloma7@its.jnj.com

**Investor contact:**
Jen McIntyre
Office: +1 732-524-3922
JMcInty3@its.jnj.com

# Janssen Submits New Drug Application (NDA) to U.S. FDA for UPTRAVI® (selexipag) Injection for Intravenous Use to Treat Pulmonary Arterial Hypertension (PAH)

**SOUTH SAN FRANCISCO, CA – September 30, 2020 –** The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for UPTRAVI® (selexipag) as an injection for intravenous (IV) use for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adults with WHO functional class (FC) II–III, who are currently prescribed oral UPTRAVI but are temporarily unable to take oral therapy. In patients with PAH, interruptions in treatment should be avoided due to the progressive nature of the disease.[1]

UPTRAVI is a selective, prostacyclin IP receptor agonist. Oral UPTRAVI was approved by the FDA in 2015 for the treatment of PAH to delay disease progression and reduce the risk of hospitalization.[2]

"Even relatively short-term PAH treatment interruptions due to a temporary inability to take oral medication, like during surgery, can have a significant negative impact on a person's health," said Neil Davie, Ph.D., Global Therapeutic Area Head,

Pulmonary Hypertension, Janssen Research & Development, LLC. "We have demonstrated that continued treatment with UPTRAVI can significantly improve patients' long-term outcomes. Preventing an interruption of treatment with an IV formulation is an important therapeutic option and we are pleased to be one step closer to bringing this important treatment to the PAH community."

The NDA is based on the prospective, multi-center Phase 3 study designed to evaluate the safety and tolerability of patients with PAH temporarily switching from oral UPTRAVI to UPTRAVI IV, and then transitioning back to the initial oral dose. Results showed that UPTRAVI IV is suitable to maintain continuous dosing for short periods of time when oral administration of UPTRAVI is not feasible.[1]

**About the UPTRAVI IV Study[1]**

The UPTRAVI IV study (NCT03187678) was a prospective, multi-center, open-label single-sequence cross–over, Phase 3 study designed to assess the safety, tolerability and pharmacokinetics of temporarily switching between oral UPTRAVI and UPTRAVI IV. The study examined a stable dose of UPTRAVI tablets to a corresponding dose of UPTRAVI for injection and switching back to UPTRAVI tablets. The treatment and observation phase was divided into 3 periods. In Period 1, patients received their stable oral dose of UPTRAVI twice daily (morning and evening of Day 1). In Period 2, patients received three infusions of corresponding UPTRAVI IV doses (morning and evening of Day 2, and morning of Day 3). In Period 3, patients resumed their stable oral UPTRAVI dose twice daily in the evening of Day 3 for 9 days, which was continued through the safety follow-up. Patients were hospitalized during Periods 1 and 2.

All 20 enrolled patients completed the study as planned and received all UPTRAVI doses (oral or IV). The switch between oral UPTRAVI and UPTRAVI IV was well tolerated, and there were no unexpected safety findings. Adverse reactions that resulted from UPTRAVI for injection were similar to those associated with UPTRAVI tablets, with the exception of infusion site reaction. Prostacyclin-associated adverse events included headache, diarrhea, nausea, vomiting, pain in jaw, myalgia, pain in extremity, flushing and arthralgia.[1]

## IMPORTANT SAFETY INFORMATION[2]

## INDICATION

UPTRAVI® (selexipag) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

## CONTRAINDICATIONS

Concomitant use of strong inhibitors of CYP2C8 (eg, gemfibrozil) with UPTRAVI is contraindicated.

## WARNINGS AND PRECAUTIONS

### Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

## ADVERSE REACTIONS

Adverse reactions more frequent compared to placebo (≥3%) are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

## DRUG INTERACTIONS

### CYP2C8 Inhibitors

Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant use of UPTRAVI with strong inhibitors of CYP2C8 is contraindicated.

Concomitant administration of UPTRAVI with clopidogrel, a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.7–fold. Reduce the dosing of UPTRAVI to once daily in patients on a moderate CYP2C8 inhibitor.

### CYP2C8 Inducers

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase UPTRAVI dose, up to twice, when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped.

## DOSAGE AND ADMINISTRATION

### Recommended Dosage

Recommended starting dose is 200 mcg twice daily. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

### Patients With Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

**Co-administration With Moderate CYP2C8 Inhibitors**

When co-administered with moderate CYP2C8 inhibitors (eg, clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI to once daily. Revert back to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped.

**Dosage Strengths**

UPTRAVI tablet strengths:

200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

Please see full Prescribing Information.

**About Pulmonary Arterial Hypertension (PAH)**

PAH is a specific form of PH that causes the walls of the pulmonary arteries (blood vessels leading from the right side of the heart to the lungs) to become thick and stiff, narrowing the space for blood to flow, and causing an increased blood pressure to develop within the lungs. PAH is a serious, progressive disease with a variety of etiologies and has a major impact on patients' functioning as well as their physical, psychological and social wellbeing. There is currently no cure for PH and it is often fatal.[3,4,5] However, the last decade has seen significant advances in the understanding of the pathophysiology of PAH, transforming the prognosis for PAH patients from symptomatic improvements in exercise tolerance 10 years ago, to delayed disease progression today.

## About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

*Cautions Concerning Forward-looking Statements*

*This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding UPTRAVI® (selexipag) and product development of UPTRAVI IV. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC or any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost*

*containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2019, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors", and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.*

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**References**


1. Data on file.
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