Janssen-Cilag AG
Gubelstrasse 34
CH-6300 Zug
tel +41 58 231 34 34
fax +41 58 231 34 00

Summary of the Risk Management Plan (RMP) for Uptravi® (Selexipag)

Marketing Autorisation Holder (MAH): Janssen-Cilag AG

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Uptravi® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Uptravi® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Uptravi®.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for UPTRAVI® (selexipag)

This is a summary of the risk management plan (RMP) for UPTRAVI. The RMP details important risks of UPTRAVI, how these risks can be minimized, and how more information will be obtained about UPTRAVI's risks and uncertainties (missing information).

UPTRAVI's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how UPTRAVI should be used.

This summary of the RMP for UPTRAVI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of UPTRAVI's RMP.

I. The Medicine and What it is Used For

UPTRAVI is authorized for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. (see SmPC for the full indication).

It contains selexipag as the active substance and it is given by oral route of administration.

Further information about the evaluation of UPTRAVI's benefits can be found in UPTRAVI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/medicines/human/EPAR/UPTRAVI

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of UPTRAVI, together with measures to minimize such risks and the proposed studies for learning more about UPTRAVI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

1. Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
2. Important advice on the medicine's packaging;
3. The authorized pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
4. The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of UPTRAVI, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR)/Periodic Benefit-risk Evaluation Report (PBRER) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of UPTRAVI is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of UPTRAVI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of UPTRAVI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	• Hypotension • Anemia • Hyperthyroidism • Concomitant use with strong inhibitors of CYP2C8
Important potential risks	• Pulmonary edema associated with pulmonary veno-occlusive disease (PVOD) • Major adverse cardiovascular events • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Medication error
Missing information	• Use in pediatric patients • Use in elderly over 75 years old • Use during pregnancy and lactation • Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

II.B. Summary of Important Risks

Important Identified Risk: Hypotension	
Evidence for linking the risk to the medicine	Selexipag as well as other pulmonary vasodilators widens blood vessels, and there is a risk that patients could have a small drop in blood pressure. In the double-blind GRIPHON study, about 7 out of every 100 patients (7%) who took selexipag had low blood pressure compared to 4 out of every 100 patients (4%) who took placebo. The pattern and frequency of hypotension events in GRIPHON OL (AC-065A303) was consistent with what was reported for the double-blind studies. In GRIPHON OL, there was no indication of an increased risk of low blood pressure in selexipag-treated patients over long-term treatment. In the TRITON study, about 9 out of every 100 patients (9%) who took selexipag had low blood pressure compared to 7 out of every 100 patients (7%) who took placebo. No patients who took selexipag in the TRACE study had low blood pressure.

Important Identified Risk: Hypotension	
Risk factors and risk groups	General risk factors for hypotension are, eg, a history of systemic hypotension, vegetative dysfunction, concurrent infections or dehydration; and polytherapy with vasodilators and/or other hypotensive medications (eg, ERAs, riociguat, PDE-5 inhibitors, anti-hypertensives and/or diuretics). Hypotension is a main prognostic factor of poor outcome related to right heart failure (RHF) hospitalization. Four-fold increase of in-hospital mortality for patients with SBP <100 mmHg upon admission is observed among PAH patients hospitalized for RHF.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8 'Undesirable effects' in the adverse drug reaction (ADR) table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Anemia	
Evidence for linking the risk to the medicine	Selexipag may lower the amount of hemoglobin in the blood. In the double-blind GRIPHON study, a decrease in hemoglobin was reported in about 11 out of 100 patients (11%) who took selexipag and 9 out of 100 (9%) patients who took placebo. In this study, treatment-emergent decreases in hemoglobin from baseline to <10 g/dL were reported for 8.6% of patients who took selexipag and 5.0% of patients who took placebo. In GRIPHON OL, there was no indication of increased occurrence of anemia in selexipag-treated patients over long-term treatment. Anemia events were mostly reported as non-serious and were clinically manageable, with no participant discontinuing selexipag due to anemia. In the TRITON study, a decrease in hemoglobin was reported in about 27 out of 100 patients (27%) who took selexipag and 17 out of 100 (17%) patients who took placebo. In the TRITON study, treatment-emergent decreases from baseline to <8 g/dL in hemoglobin were reported for 6.8% of patients who took selexipag and 4.1% of patients who took placebo. In TRITON, mean changes in hemoglobin from baseline up to Month 18 ranged from −1.8 to −1.3 g/dL in the selexipag group and −1.6 to −1.3 g/dL in the placebo group. In the TRACE study, a decrease in hemoglobin was reported in about 4 out of 100 patients (4%) who took selexipag or placebo.
Risk factors and risk groups	General risk factors for anemia are, eg, iron deficiency, history of anemia, concomitant platelet inhibitors, anticoagulants, steroids, pre-existing or concurrent bleeding.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 ‘Undesirable effects’ in the ADR table as a common adverse reaction based on data from the GRIPHON study. Section 4.8 of the SmPC also includes a description that anemia was reported at a higher frequency in the TRITON study. PL section 4: ‘Possible side effects’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Hyperthyroidism	
Evidence for linking the risk to the medicine	In the double-blind GRIPHON study, signs of an overactive thyroid gland were seen in about 3 out of every 100 patients (3%) who took selexipag and 1 out of every 100 patients (1%) who took placebo. In GRIPHON OL, overall, the pattern and frequency of hyperthyroidism events was comparable to that seen in the double-blind studies. In the TRITON and TRACE studies, no patients who took selexipag had signs of an overactive thyroid gland.
Risk factors and risk groups	Patients susceptible to the stimulatory effect of an IP receptor at the thyroid gland may be at risk. In some studies, prostacyclin treatment has been reported concomitantly with thyroid disorder occurrence (Chu 2002). Prostacyclins stimulate intracellular thyroid processes and mimic the effects of TSH on the thyroidal metabolism and stimulate the synthesis and secretion of thyroid hormone (Virgolini 1988). A possible role of epoprostenol (Chadha 2009, Ferris 2001, Fojas 2016, Richter 2016, Srimatkandada 2014) and of treprostinil (Gu 2016) in triggering hyperthyroid disease was suspected in PAH patients.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Concomitant use with Strong Inhibitors of CYP2C8	
Evidence for linking the risk to the medicine	In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold, whereas exposure to the active metabolite increased approximately 11-fold (AC-065-113). Concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (eg, gemfibrozil) is therefore contraindicated.
Risk factors and risk groups	Patients treated with gemfibrozil and selexipag.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3: 'Contraindications'. SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None.

Important Potential Risk: Pulmonary Edema Associated with Pulmonary Veno-occlusive Disease	
Evidence for linking the risk to the medicine	Experience with other pulmonary vasodilators, ie, ERAs, PDE-5 inhibitors, riociguat, prostacyclin and its analogue. Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with previously undiagnosed pulmonary veno-occlusive disease. Close monitoring for such events continues for emerging data from clinical studies as well as in post-approval use. In the double-blind GRIPHON study, about 1 out of every 100 patients (1%) who took selexipag or placebo had pulmonary edema associated with pulmonary veno-occlusive disease. In GRIPHON OL, overall, the pattern and frequency of pulmonary veno-occlusive disease associated with pulmonary edema AESIs was consistent with that seen in the double-blind studies. In the TRITON study, about 2 out of every 100 patients (2%) who took selexipag and 1 out of every 100 patients (1%) who took placebo had pulmonary edema associated with pulmonary veno-occlusive disease. No patients who took selexipag or placebo in the TRACE study had pulmonary edema associated with pulmonary veno-occlusive disease.
Risk factors and risk groups	Patients with undiagnosed PVOD and on concurrent medications leading to pulmonary vasodilatation.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4: 'Special warnings and precautions for use'. Additional risk minimization measures: None

Important Potential Risk: Pulmonary Edema Associated with Pulmonary Veno-occlusive Disease	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Major Adverse Cardiovascular Events	
Evidence for linking the risk to the medicine	Results of adjudication performed by the external cardiologist and the Critical Event Committee in study AC-065A302 (GRIPHON) [D-15.136]. In the pivotal double-blind Phase 3 AC-065A302/GRIPHON study, MACE was observed in 4.4% of selexipag-treated patients versus 4.0% of placebo-treated patients. The long-term safety data for MACE showed a decreasing trend in average annualized event rates. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies. In the TRITON study, about 3 out of every 100 patients (3%) who took selexipag had MACE compared to 6 out of every 100 patients (6%) who took placebo. No patients who took selexipag or placebo in the TRACE study had MACE.
Risk factors and risk groups	As in the general population, patients with high cardiovascular risk due to intercurrent atherosclerotic disease requiring antihypertensive and/or lipid-lowering and/or antidiabetic treatment are identified as groups at risk. Systematic multidisciplinary approach, which addresses lifestyle and cardiovascular risk factor management, is part of general medical management of each patient.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3: ‘Contraindications’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None

Important Potential Risk: Major Adverse Cardiovascular Events	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Renal Function Impairment / Acute Renal Failure	
Evidence for linking the risk to the medicine	In the double-blind GRIPHON study, a numerically small imbalance in AEs of renal failure between selexipag and the placebo group was observed. These events were transient and reversible in nature, and the majority of renal events resolved while treatment with selexipag was maintained. The long-term safety data for renal function impairment / acute renal failure showed a decreasing trend in average annualized event rates. In the TRITON study, about 10 out of every 100 patients (10%) who took selexipag had events of renal failure compared to 4 out of every 100 patients (4%) who took placebo. In the TRACE study, no patients who took selexipag had events of renal failure compared to about 2 out of every 100 patients (2%) who took placebo. In the TRITON and GRIPHON studies, no numerical imbalance in estimated glomerular filtration rate < 60 mL/min and overall mean increases in creatinine clearance from baseline to regular visits were observed in the selexipag or placebo groups, suggesting no overall detrimental effect of selexipag on renal function. Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.
Risk factors and risk groups	General risk factors include hemodynamic decompensation in the context of PAH worsening, RHF, or other concurrent illnesses (eg, sepsis, hypovolemic shock) or as a complication in patients with pre-existing renal impairment.
Risk minimization measures	Risk minimization measures: SmPC section 4.2: ‘Posology and method of administration’. SmPC section 4.4: ‘Special warnings and precautions for use’. SmPC section 5.2: ‘Pharmacokinetic properties’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None

Important Potential Risk: Renal Function Impairment / Acute Renal Failure	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Bleeding Events	
Evidence for linking the risk to the medicine	Known effects of other prostacyclins. In the double-blind GRIPHON study, the overall proportions of patients with bleeding events in the selexipag and placebo groups were similar (approximately 17 out of 100 patients [17%]). The long-term safety data for bleeding events showed a decreasing trend in average annualized event rates. There was no indication of an increased bleeding risk upon long-term treatment with selexipag. In the TRITON study, about 22 out of every 100 patients (22%) who took selexipag or placebo had bleeding events. In the TRACE study, about 13 out of every 100 patients (13%) who took selexipag or placebo had bleeding events. As shown in in-vitro experiments, selexipag is a weak platelet aggregation inhibitor and close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.
Risk factors and risk groups	Available data do not support any overall increased risk of bleeding with selexipag or any synergically increased risk of bleeding if selexipag is co-administered with anticoagulants or other antithrombotics. No specific risk factor has been identified to predict the occurrence of bleeding events in selexipag-treated patients.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.5: ‘Interaction with other medicinal products and other forms of interaction’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None

Important Potential Risk: Bleeding Events	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Light-dependent Non-melanoma Skin Malignancies	
Evidence for linking the risk to the medicine	During the double-blind GRIPHON study, 4 patients aged >68 years in the selexipag group were diagnosed with BCC compared to none in the placebo group. Confounding factors were present in all cases (eg, immunosuppressant use, history of malignancy, or short duration of exposure). In GRIPHON OL, there was no indication of an increased risk of light-dependent non-melanoma skin malignancies associated with long-term selexipag treatment. In the TRITON study, less than 1 out of every 100 patients (<1%) who took selexipag had skin malignancies compared to 2 out of every 100 patients (2%) who took placebo. In the TRACE study, no patients who took selexipag or placebo had skin malignancies. Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.
Risk factors and risk groups	PAH is known to be associated with autoimmune disease as the underlying cause of PAH or associated co-morbidity. Therefore clinical management of these conditions frequently requires administration of medications with immunosuppressant effect. In general, sunlight exposure is considered as a relevant susceptibility factor.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the

Important Potential Risk: Light-dependent Non-melanoma Skin Malignancies	
	postauthorization development plan.

Important Potential Risk: Ophthalmological Effects Associated with Retinal Vascular System	
Evidence for linking the risk to the medicine	Nonclinical findings of tortuosity and dilatation of retinal blood vessels in rats at the end of a 2-year carcinogenicity study (D-14.104). During the double-blind GRIPHON study, there was no evidence of an increase in relevant adverse ocular effects in selexipag-treated patients compared to placebo-treated patients. In the AC-065A302/GRIPHON ophthalmology sub-study, no new post-baseline fundoscopy findings or worsening of pre-existing retinal arterial tortuosity were reported in the selexipag group (D-14.407). The long-term safety data for ophthalmological events and events associated with the retinal vascular system showed a decreasing trend in average annualized event rates. The pattern and frequency of ophthalmological events and events associated with the retinal vascular system remained similar for long-term selexipag treatment as had been reported for the double-blind studies. There was no indication of any adverse effect of selexipag on retinal vasculature upon long-term treatment, and the non-clinical findings of retinal arteriolar tortuosity continue to be considered of limited clinical relevance. In the TRITON study, about 5 out of every 100 patients (5%) who took selexipag had relevant adverse ocular effects compared to 7 out of every 100 patients (7%) who took placebo. In the TRACE study, no patients who took selexipag had relevant adverse ocular effects.
Risk factors and risk groups	The findings of tortuosity and dilation of retinal arterioles in rats were considered by the independent experts in ophthalmology to be animal species-specific and of limited clinical relevance. Therefore no particular risk group can be determined.
Risk minimization measures	Routine risk minimization measures: SmPC section 5.3: ‘Preclinical safety data’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Gastrointestinal Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)	
Evidence for linking the risk to the medicine	In pre-clinical studies, intestinal intussusception upon selexipag treatment was identified in young dogs, but not in rodents. Because of the species-specific sensitivity of dogs to develop intussusception and the safety margin, this finding is considered not relevant for adult humans. In the double-blind GRIPHON study, less than 1 out of every 100 patients (<1%) who took selexipag or placebo had gastrointestinal disturbances denoting intestinal intussusception. The long-term safety data for gastrointestinal disturbances denoting intestinal intussusception showed a decreasing trend in average annualized event rates. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies.In the TRITON study, less than 1 out of every 100 patients (<1%) who took selexipag had gastrointestinal disturbances denoting intestinal intussusception compared to no patients who took placebo. In the TRACE study, no patients who took selexipag or placebo had gastrointestinal disturbances denoting intestinal intussusception.
Risk factors and risk groups	Patients with PAH associated with systemic scleroderma represent patients at particular risk of GI motility disorder in the adult patient population. In infants and young children, intussusception is the most common cause of intestinal obstruction. Available epidemiological data show that 75% to 90% of cases arise before 2 years of age (Waseem 2008, Stringer 1992). The peak incidence is between 5 and 9 months of age and then starts to decline (Newman 1987).
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: ‘Posology and method of administration’. SmPC section 5.3: ‘Preclinical safety data’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Medication Error	
Evidence for linking the risk to the medicine	As compared to controlled clinical trials, where only selexipag 200 µg tablets were administered, a total of 8 dosage strengths (200, 400, 600, 800, 1000, 1200, 1400, and 1600 microgram film-coated tablets) are available on the market. Data regarding instructions on recommended daily dosing, titration and transition to maintenance dose are given in the respective national UPTRAVI product labelling documents and further educational materials provided to patients and healthcare professionals (HCPs). Information regarding medication errors with tablets during selexipag initial titration and transition to maintenance dose is therefore only collected from post-approval use.
Risk factors and risk groups	Patients during initial selexipag up-titration phase.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: 'Posology and method of administration'. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 3: 'How to take UPTRAVI'. Additional risk minimization measures: Controlled Access System Educational material in a Prescribing Kit containing: • Cover Letter to the HCP and pharmacist • A4 laminated card HCP titration guide • SmPC • Package leaflet and patient titration guide Patient titration guide included in the titration pack.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A403 EDUCATE Final study report 2024 See Section II.C. of this summary for an overview of the postauthorization development plan.

Missing Information: Use in Pediatric Patients	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.1: 'Pharmacodynamic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None

Missing Information: Use in Elderly Over 75 Years Old	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: 'Posology and method of administration'. SmPC Section 4.4: 'Special warnings and precautions for use'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Missing Information: Use During Pregnancy and Lactation	
Risk minimization measures	Routine risk minimization measures: SmPC 4.4: 'Special warnings and precautions for use'. SmPC 4.6 'Fertility, pregnancy and lactation'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None

Missing Information: Concomitant Use with Strong Inhibitors of UGT1A3 and UGT2B7	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.5 'Interactions with other medicinal products and other forms of interaction'. SmPC section 5.2: 'Pharmacokinetic properties'. Additional risk minimization measures: None

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of UPTRAVI.

II.C.2. Other Studies in Postauthorization Development Plan

AC-065A401 EXPOSURE

Postauthorization safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice.

Purpose of the study:

To further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to compare mortality and major adverse cardiovascular events (MACE) rates with PAH patients not treated with UPTRAVI.

67896049PAH0002 EXTRACT

Postauthorization safety study (PASS): retrospective medical chart review of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy.

Purpose of the study:

In order to avoid significant delay in completing EXPOSURE and assessing the study objectives, EXTRACT will be used to complement EXPOSURE with retrospectively identified patients with PAH who have been newly treated with UPTRAVI (as monotherapy or in combination with other PAH-specific therapy) before EXPOSURE was initiated, in order to achieve the desired overall sample size. A comparator group consisting of patients with PAH newly treated with other PAH-specific therapy will serve as an internal comparator cohort in EXTRACT and allow for pooling of the cohorts of EXPOSURE and EXTRACT in comparative analyses. The Other PAH-specific therapy cohort for EXTRACT will only include disease prevalent patients (ie, ≥6 months from first PAH diagnosis) who initiated a PAH-specific therapy other than UPTRAVI for the first time as part of a combination therapy.

The purpose of this PASS is to complement EXPOSURE to further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to describe mortality and MACE rates with PAH patients not treated with UPTRAVI.

AC-065A403 EDUCATE

Postauthorization safety study (PASS) to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice.

Purpose of the study:

The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimization materials and to record the

occurrence of patient-reported “wrong dose” medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration.

The safety concern addressed is the occurrence of medication errors during the UPTRAVI titration phase.