

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

Marketing Authorisation 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](http://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®.

**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);

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**List of Important Risks and Missing Information**

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Important identified risks	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Anemia</li> <li>• Hyperthyroidism</li> <li>• Concomitant use with strong inhibitors of CYP2C8</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Pulmonary edema associated with PVOD</li> <li>• MACE</li> <li>• Renal function impairment / acute renal failure</li> <li>• Bleeding events</li> <li>• Light-dependent non-melanoma skin malignancies</li> <li>• Ophthalmological effects associated with retinal vascular system</li> <li>• GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)</li> <li>• Medication error</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use in pediatric patients</li> <li>• Use in elderly over 75 years old</li> <li>• Use during pregnancy and lactation</li> <li>• Concomitant use with strong inhibitors of UGT1A3 and UGT2B7</li> </ul>

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**II.B. Summary of Important Risks**

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**Important Identified Risk: Hypotension**

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Evidence for linking the risk to the medicine	<p>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.</p> <p>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.</p> <p>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.</p>
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**Important Identified Risk: Hypotension**

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Risk factors and risk groups	<p>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).</p> <p>Hypotension is a main prognostic factor of poor outcome related to RHF hospitalization. Four-fold increase of in-hospital mortality for patients with systolic blood pressure &lt;100 mmHg upon admission is observed among PAH patients hospitalized for RHF.</p>
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Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC section 4.4: ‘Special warnings and precautions for use’.</p> <p>SmPC section 4.8 ‘Undesirable effects’ in the ADR table as a common adverse reaction.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>PL section 4: ‘Possible side effects’.</p> <p>Additional risk minimization measures: None</p>
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Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>AC-065A401 EXPOSURE</p> <p>67896049PAH0002 EXTRACT</p> <p>Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024</p> <p>Final study report for EXPOSURE: 12 months after PRAC agreement</p> <p>See Section II.C. of this summary for an overview of the postauthorization development plan.</p>
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**Important Identified Risk: Anemia**

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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.

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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.

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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

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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

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**Important Identified Risk: Hyperthyroidism**

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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.

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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.

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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

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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  
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**Important Identified Risk: Concomitant use with Strong Inhibitors of CYP2C8**

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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.
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Risk factors and risk groups	Patients treated with gemfibrozil and selexipag.
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Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC section 4.3: ‘Contraindications’.</p> <p>SmPC section 4.5: ‘Interaction with other medicinal products and other forms of interaction’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None.</p>
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**Important Potential Risk: Pulmonary Edema Associated with PVOD**

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

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

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Evidence for linking the risk to the medicine	<p>Results of adjudication performed by the external cardiologist and the Critical Event Committee in Study AC-065A302 (GRIPHON) [D-15.136].</p> <p>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.</p> <p>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.</p>
Risk factors and risk groups	<p>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.</p>
Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC section 4.3: ‘Contraindications’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None</p>

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**Important Potential Risk: MACE**

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

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Evidence for linking the risk to the medicine	<p>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.</p> <p>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.</p> <p>In the TRITON and GRIPHON studies, no numerical imbalance in estimated glomerular filtration rate &lt;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.</p> <p>Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.</p>
Risk factors and risk groups	<p>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.</p>
Risk minimization measures	<p>Risk minimization measures:</p> <p>SmPC section 4.2: ‘Posology and method of administration’.</p> <p>SmPC section 4.4: ‘Special warnings and precautions for use’.</p> <p>SmPC section 5.2: ‘Pharmacokinetic properties’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None</p>

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**Important Potential Risk: Renal Function Impairment / Acute Renal Failure**

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

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Evidence for linking the risk to the medicine	<p>Known effects of other prostacyclins.</p> <p>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.</p> <p>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.</p> <p>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.</p>
Risk factors and risk groups	<p>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.</p>
Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC section 4.5: ‘Interaction with other medicinal products and other forms of interaction’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None</p>

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**Important Potential Risk: Bleeding Events**

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Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>AC-065A401 EXPOSURE</p> <p>67896049PAH0002 EXTRACT</p> <p>Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024</p> <p>Final study report for EXPOSURE: 12 months after PRAC agreement</p> <p>See Section II.C. of this summary for an overview of the postauthorization development plan.</p>
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**Important Potential Risk: Light-dependent Non-melanoma Skin Malignancies**

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Evidence for linking the risk to the medicine	<p>During the double-blind GRIPHON study, 4 patients aged &gt;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.</p> <p>In the TRITON study, less than 1 out of every 100 patients (&lt;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.</p> <p>Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.</p>
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Risk factors and risk groups	<p>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.</p> <p>In general, sunlight exposure is considered as a relevant susceptibility factor.</p>
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Risk minimization measures	No risk minimization measures
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Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>AC-065A401 EXPOSURE</p> <p>67896049PAH0002 EXTRACT</p> <p>Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024</p> <p>Final study report for EXPOSURE: 12 months after PRAC agreement</p> <p>See Section II.C. of this summary for an overview of the postauthorization development plan.</p>
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<b>Important Potential Risk: Ophthalmological Effects Associated with Retinal Vascular System</b>	
Evidence for linking the risk to the medicine	<p>Nonclinical findings of tortuosity and dilatation of retinal blood vessels in rats at the end of a 2-year carcinogenicity study (D-14.104).</p> <p>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 funduscopy findings or worsening of pre-existing retinal arterial tortuosity were reported in the selexipag group (D-14.407).</p> <p>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.</p> <p>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.</p>
Risk factors and risk groups	<p>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.</p>
Risk minimization measures	<p>Routine risk minimization measures: SmPC section 5.3: 'Preclinical safety data'.</p> <p>Additional risk minimization measures: None</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT</p> <p>Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024</p> <p>Final study report for EXPOSURE: 12 months after PRAC agreement</p> <p>See Section II.C. of this summary for an overview of the postauthorization development plan.</p>

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**Important Potential Risk: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)**

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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.
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In the double-blind GRIPHON study, less than 1 out of every 100 patients (<1%) who took selexipag or placebo had GI disturbances denoting intestinal intussusception. The long-term safety data for GI 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 GI disturbances denoting intestinal intussusception compared to no patients who took placebo. In the TRACE study, no patients who took selexipag or placebo had GI 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.
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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	<p>Routine risk minimization measures:</p> <p>SmPC section 4.2: ‘Posology and method of administration’.</p> <p>SmPC section 5.3: ‘Preclinical safety data’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None</p>
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Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>AC-065A401 EXPOSURE</p> <p>67896049PAH0002 EXTRACT</p> <p>Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024</p> <p>Final study report for EXPOSURE: 12 months after PRAC agreement</p> <p>See Section II.C. of this summary for an overview of the postauthorization development plan.</p>
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**Important Potential Risk: Medication Error**

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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 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg 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	<p>Routine risk minimization measures:</p> <p>SmPC section 4.2: ‘Posology and method of administration’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>PL section 3: ‘How to take UPTRAVI’.</p> <p>Additional risk minimization measures:</p> <p>Controlled Access System</p> <p>Educational material in a Prescriber Kit containing:</p> <ul style="list-style-type: none"> <li>• Cover Letter to the HCP and pharmacist</li> <li>• A4 laminated card HCP titration guide (specific for starting doses of 100 µg or 200 µg)</li> <li>• SmPC</li> <li>• Package leaflet and patient titration guide</li> </ul> <p>Specific patient titration guides are included in the titration packs of the 100 µg and 200 µg tablets.</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <p>AC-065A403 EDUCATE</p> <p>Collection of targeted number (60) of HCP surveys completed: 16 June 2023</p> <p>Second interim report submission: Once 100 patients’ questionnaires are completed</p> <p>Final study report: 12 months after PRAC agreement</p> <p>See Section I.I.C. of this summary for an overview of the postauthorization development plan.</p>

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**Missing Information: Use in Pediatric Patients**

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Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC section 4.2: ‘Posology and method of administration’.</p> <p>SmPC section 5.1: ‘Pharmacodynamic properties’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None</p>
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**Missing Information: Use in Elderly Over 75 Years Old**

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

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Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC 4.4: ‘Special warnings and precautions for use’.</p> <p>SmPC 4.6 ‘Fertility, pregnancy and lactation’.</p> <p>SmPC section 5.3: ‘Preclinical safety data’.</p> <p>PL section 2: ‘What you need to know before you take UPTRAVI’.</p> <p>Additional risk minimization measures: None</p>
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**Missing Information: Concomitant Use with Strong Inhibitors of UGT1A3 and UGT2B7**

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Risk minimization measures	<p>Routine risk minimization measures:</p> <p>SmPC section 4.5 ‘Interactions with other medicinal products and other forms of interaction’.</p> <p>SmPC section 5.2: ‘Pharmacokinetic properties’.</p>
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**Missing Information: Concomitant Use with Strong Inhibitors of UGT1A3 and UGT2B7**

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Additional risk minimization measures: None

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