European Union Risk Management Plan
UPTRAVI (selexipag)

Details of this RMP Submission
RMP Version number: 12.1
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Rationale for Submitting an Updated RMP

Per the EXPOSURE/EXTRACT Type II variation outcome (EMEA/H/C/003774/II/0045), there was a request from the EMA to update the EU RMP by removing the now completed EXTRACT study from the additional pharmacovigilance activities.

Update of EXPOSURE PASS milestones to align with the current EXPOSURE protocol (Version 8, Amendment 7; EMA/PAM/0000256686).

Summary of Significant Changes in this RMP

Pharmacovigilance Plan

- Update of EXPOSURE PASS milestones:
    - Removed the 'Submission of combined final report of study results from EXPOSURE and EXTRACT for PRAC agreement' milestone for EXPOSURE.
    - Updated 'Final study report' milestone from '12 months after PRAC agreement' to '12 months after PRAC agreement that commitment is fulfilled.'
    - Added a footnote to the 'Annual updates' milestone to state that the PRAC Rapporteur agreed on 01 September 2025 that the next interim report will be provided once the full sample size is reached.
- Removal of the now completed EXTRACT study from additional pharmacovigilance activities throughout the RMP and moved to Annex II, Table 2, Completed Studies.

Other RMP Versions Under Evaluation

Version Number	Date Submitted	Procedure Number
Not Applicable		

Details of the Currently Approved RMP
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QPPV Details

QPPV Name: Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Oversight Declaration: The QPPV has reviewed and approved this RMP (electronic signature on file, as applicable).

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ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
CHD-PAH	pulmonary arterial hypertension associated with congenital heart disease
CTD-PAH	pulmonary arterial hypertension associated with connective tissue disorder
$AUC_{0-\infty}$	area under plasma concentration-time curve from zero to infinity
bid	twice daily
BCC	basal cell carcinoma
BMI	body mass index
CES	carboxylesterase
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use (of the European Union)
CI	confidence interval
CTD	connective tissue disorder
CYP	cytochrome P450
DDI	drug-drug interaction
DHPC	Dear healthcare professional communication
DLP	data lock point
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
ERA	endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
FC	functional class
FPAH	familial pulmonary arterial hypertension
GI	gastrointestinal
GRIPHON	Prostacyclin (PGI_2) Receptor agonist In Pulmonary HypertensiON
GVP	good pharmacovigilance practices
HCP	healthcare professional
HIV	human immunodeficiency virus
IV	intravenous
IBD	international birth date
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP receptor	prostacyclin receptor
IPAH	idiopathic pulmonary arterial hypertension
MACE	major adverse cardiovascular event
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MM	morbidity/mortality
NOEL	no-observed-effect-level
NYHA	New York Heart Association
OL	open-label
PAH	pulmonary arterial hypertension
PAS	Postauthorization study
PASS	Postauthorization safety study
PBRER	Periodic Benefit-risk Evaluation Report

PD	pharmacodynamic(s)
PDE-5	Phosphodiesterase type 5
PGI_2	prostacyclin
PH	pulmonary hypertension
PIP	Pediatric investigational plan
PK	pharmacokinetic(s)
PL	Package leaflet
PoPH	portopulmonary hypertension
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	preferred term
PVOD	pulmonary veno-occlusive disease
qd	once daily
QRD	Quality Review of Documents
RHF	right heart failure
RMP	Risk Management Plan
ROW	rest of the World
sGC	soluble guanylate cyclase
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SSc	systemic sclerosis
TSH	thyroid-stimulating hormone
UGT	uridine 5'-diphospho-glucuronosyltransferase
vWF	Von Willebrand factor
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Selexipag
Pharmacotherapeutic group(s) (ATC Code)	B01AC27
Marketing Authorization Holder	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	UPTRAVI® (selexipag)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Selexipag is a selective IP receptor agonist distinct from prostacyclin and its analogs. Selexipag is hydrolyzed by carboxylesterases to yield its active metabolite, which is approximately 37-fold more potent than selexipag. Selexipag and the active metabolite are high affinity IP receptor agonists with a high selectivity for the IP receptor versus other prostanoid receptors (EP_1-EP_4, DP, FP, and TP). **Summary of mode of action:** Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. **Important information about its composition:** The selexipag active substance, 2-{4-[(5,6-diphenylpyrazin-2-yl) (isopropyl) amino] butoxy}-N-(methylsulfonyl) acetamide, is of chemical origin.
Reference to the Product Information	UPTRAVI Annexes I–III submitted in Module 1.3.1.
Indication(s) in the EEA	**Current:** UPTRAVI is indicated for the long-term treatment of PAH in adult patients with WHO FC II–III, either as combination therapy in patients insufficiently controlled with an ERA and/or a 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 CTD, and PAH associated with corrected simple CHD.
Dosage(s) in the EEA	**Current:** *Individualized dose titration* Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 µg bid to 1600 µg bid (individualized maintenance dose).

Pharmaceutical form(s) and strength(s)	**Current:** Film-coated tablet for oral use 100, 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg	
Is/will the product be subject to additional monitoring in the EU?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: PAH

Incidence and Prevalence

In the US, approximately 500 to 1000 new cases of PAH are diagnosed each year (NORD 2012). Based on the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), the incidence of all adult patients with Group 1 PAH is estimated at 2.3 cases per million in the US (Frost 2011).

A recent critical appraisal of the literature reported epidemiology estimates of approximately 5.8 adult patients per million for PAH incidence and 47.6 to 54.7 per million for PAH prevalence (Leber 2021) using recent (<5 years) national systematic registry data from centralized healthcare systems (NHS Digital 2021, Kjellström 2020).

The Orphanet 2021 report estimates the overall prevalence of PAH in Europe to be about 20 cases per million. PAH can be further classified into subtypes according to etiology. These are IPAH, heritable PAH, PAH induced by exposure to drugs and toxins, or PAH associated with other conditions, such as connective tissue disease (CTD-PAH) and congenital heart disease (CHD-PAH). For the most common PAH subtypes, incidences and prevalences per million population are reported in systematic national registries: for IPAH 2.6 to 7.6 and 9.0 to 18.3; CTD-PAH 2.8 and 10.0 to 13.0; and CHD-PAH 2.2 and 7.0 to 19.0, respectively (Peacock 2007, Skride 2018, NHS Digital 2021).

The Orphanet 2021 report describes prevalence for IPAH of 11 cases per million and heritable PAH of 0.8 cases per million (Orphanet 2021). The prevalence of CTD-PAH and CHD-PAH are reported as 2.5 and 5.7 cases per million, respectively.

From the REVEAL registry, a lower estimate for adult prevalence for Group 1 PAH is calculated at 12.4 cases per million in the US (Frost 2011). Both the incidence and prevalence of PAH confirm the rarity of the condition.

The US IPAH incidence estimate from the REVEAL registry is 0.9 patients per million, which is lower compared with European data (McGoon 2013) (Table SI.1).

Table SI.1: Annual Incidence and Prevalence of PAH Identified from National Systematic and Multicenter Registries in Adults

Publication	Country	Time period	Annual incidence (patients per million)	Prevalence (patients per million)
Peacock 2007 (SPVU)	UK (Scotland)	2005	IPAH: 2.6 CTD-PAH: 2.8 CHD-PAH: 2.2	IPAH: 9.0 CTD-PAH: 10.0 CHD-PAH: 7.0
Skride 2018	Latvia	2007-2016	IPAH: 7.6	IPAH: 18.3
NHS Digital 2021	UK	2019-2020	-	IPAH: 16.8* CTD-PAH: 13.0* CHD-PAH: 19.0*
McGoon 2013 (REVEAL)	USA	2006-2009	IPAH: 0.9	-

Note: *Numerator: number of active PAH patients on March 2020 (IPAH n = 1128; CTD-PAH n = 873; CHD-PAH n = 1273); denominator: Great Britain population 2020 mid-year (N = 87,081,000).

Demographics of the Population with PAH and Risk Factors for the Disease

Demographics of Patients With PAH

A median or mean age of 50 to 64 years at diagnosis is commonly reported from PAH registries across European countries, with a higher proportion of females (66% to 80%) (Escribano-Subias 2012, Kopeć 2020, Hoeper 2016b, Ling 2012, Hurdman 2012). In the REVEAL registry, patients had a mean age of 50 years at diagnosis and were more likely to be females (80%) (Badesch 2010). The same observation was reported from a pulmonary hypertension expert center in Southeast Asia, where the mean age was 51 years and 77% were female (Lim 2019).

Ethnicity distribution in patients with PAH is reported to be similar to the general population. REVEAL data reflect the contemporaneous US census data with 73% of the included patients being White non-Hispanic, 12% Black, 9% Hispanic, 3% Asian, and 3% other categories (Medrek 2018, Frost 2011). Similarly, racial distribution in Southeast Asian patients with PAH was consistent with the Southeast Asia population census (Lim 2019).

Risk Factors for the Disease

Any factor or condition that is suspected to play a predisposing or facilitating role in the development of the disease is defined as a risk factor. A number of risk factors for the development of PAH have been identified that include family history, drugs and chemicals, diseases, age, and sex (Simonneau 2019).

IPAH and heritable PAH

IPAH corresponds to sporadic disease in which there is neither a family history of PAH nor an identified risk factor, and represents the most frequent form of PAH. When PAH occurs in a familial context, germ-line mutations in the bone morphogenetic protein receptor type 2 gene, a member of the transforming growth factor beta signaling family, can be detected in approximately

70% to 80% of cases. Mutations of this gene can also be detected in 10% to 20% of apparently sporadic cases, thus representing the major genetic predisposing factor for PAH (Morrell 2019).

Drug- and toxin-induced PAH

There are several well-known toxin and drug risk factors for PAH including aminorex, fenfluramine derivatives, methamphetamines, dasatinib, and toxic rapeseed oil. Possible associations are suspected for cocaine, phenylpropanolamine, L-tryptophan, St John's wort, amphetamines, interferon α and β, alkylating agents, bosutinib, direct-acting antiviral agents against hepatitis C virus, leflunomide, and indirubin (Simonneau 2019).

PAH associated with underlying conditions/diseases

PAH may also occur in association with other diseases. Associated conditions include CTD, CHD, PoPH, HIV infection, and schistosomiasis (Galiè 2015a). Frequent causes of PAH in countries where these diseases are endemic are schistosomiasis, HIV infection, post-streptococcal rheumatic heart disease, and sickle cell disease (Hoeper 2016a).

CTD-PAH represents about 15% to 25% of adult patients with PAH. Several CTDs are associated with PAH, such as mixed CTD and systemic lupus erythematosus but is most commonly seen with SSc (Mukerjee 2003, Hachulla 2005, Humbert 2006, Escribano-Subias 2012, Hoeper 2016a).

A significant proportion of adult patients with CHD, in particular those with relevant systemic-to-pulmonary shunts, will develop PAH if left untreated (Simonneau 2013). Eisenmenger syndrome represents the most advanced form of CHD-PAH (Simonneau 2013). CHD-PAH represents about 7% to 15% of cases in the adult PAH population (Humbert 2006, Escribano-Subias 2012, Hoeper 2016a).

PoPH is a form of PAH associated with portal hypertension with or without underlying chronic liver disease. In the French Pulmonary Hypertension Network registry, PoPH represented 18% of all PAH patients, the majority of whom had alcohol-related cirrhosis (58%) (Savale 2020).

PAH associated with PoPH accounted for 4.9% of PAH patients in the REVEAL Registry (Krowka 2012).

PAH is a rare complication of HIV infection (Simonneau 2013). In France, the prevalence of this condition was estimated at 0.5% of the PAH population in 2005 (Sitbon 2008).

Main Existing Treatment Options

Supportive therapy

A range of conventional therapies have been shown to provide some degree of symptomatic benefit to PAH patients. However, they have a limited effect on the disease process or its prognosis.

Among those conventional treatments are oxygen for patients with dyspnea associated with PAH, anticoagulants to decrease the risk for intrapulmonary thrombosis and thromboembolism, diuretics

for patients with decompensated RHF associated with PAH, and calcium channel blockers, which may be of benefit in PAH patients with a positive vasoreactive response during right heart catheterization (Simonneau 2019, Fuso 2011).

Advanced therapy (also termed PAH-specific therapy)

PAH-specific therapies target one of four major pathways known to be involved in the development of PAH: the prostacyclin and nitric oxide pathways, which are underexpressed in patients with PAH, and the endothelin and activin/transforming growth factor beta pathways, which are overexpressed. Route of administration varies between the drugs (IV, subcutaneous, oral, or inhaled). These PAH-specific therapies are either prescribed alone or in combination, which can be either provided as initial or sequential therapies (Humbert 2022, Humbert 2023).

- PDE-5 inhibitors: these oral agents act on the nitric oxide pathway to induce vasodilation. They also have antiproliferative effects on vascular smooth muscle cells. A systematic review and meta-analyses of clinical trials reported that treatment with PDE-5 inhibitors has a beneficial effect on exercise capacity, hemodynamic parameters, WHO FC, and survival in patients with PAH (Barnes 2019).
- ERAs: endothelin is implicated in the pathogenesis of PAH through its actions on the pulmonary vasculature. Endothelin is elevated in patients with PAH and levels are directly related to disease severity and prognosis. ERAs are oral treatments that act by blocking the binding of endothelin to either one (single antagonist) or both (dual antagonist) of its receptors. Clinical trials have shown that treatment with ERAs has a beneficial effect on exercise capacity, WHO FC, hemodynamics and time to clinical worsening in patients with PAH (Mehta 2017, Pulido 2013). Currently marketed ERA therapies are bosentan (dual antagonist), macitentan (dual antagonist), and ambrisentan (single antagonist).
- Drugs targeting the prostacyclin pathway: synthetic prostacyclins (eg, epoprostenol), prostacyclin analogs (eg, treprostinil, beraprost, iloprost), and IP receptor agonists (eg, selexipag) act by correcting the deficiency of endogenous prostacyclin seen in patients with PAH. The clinical use of IV administered prostacyclins in patients with PAH has been extended by the synthesis of more stable analogs that can be given by subcutaneous infusion, by inhalation, or by oral administration. Clinical trials with prostacyclin and prostacyclin analogs have shown improvement in PAH symptoms (eg, epoprostenol, iloprost, treprostinil), exercise capacity (eg, beraprost, epoprostenol, iloprost, treprostinil), hemodynamics (eg, epoprostenol, iloprost, treprostinil, selexipag), and survival (eg, epoprostenol, selexipag) (Sitbon 2015, Galiè 2015b).
- sGC stimulator (riociguat) acts in synergy with endogenous nitric oxide and directly stimulates sGC to produce intracellular cyclic guanosine monophosphate, which influences vascular tone, proliferation, fibrosis, and inflammation. Short-term clinical trials (12 weeks) have demonstrated a statistically significant improvement in exercise capacity, WHO FC, and delay in clinical worsening with riociguat (Galiè 2015c).
- The human fusion protein, sotatercept, acts as a ligand trap that scavenges excess activin A as well as other growth differentiation factors to inhibit activin signaling (Humbert 2023, WINREVAIR SmPC 2025). This inhibition of activin signaling modulates vascular cell proliferation, decreasing pulmonary vascular resistance and improving hemodynamics. Clinical trials with sotatercept have shown improvements in exercise capacity.

Natural History of PAH in the Untreated Population, Including Mortality and Morbidity

PAH is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodeling. These vascular changes result in a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. There is currently no cure for PAH. Common symptoms of PAH are shortness of breath, fatigue, non-productive cough, angina pectoris, fainting or syncope, peripheral edema, rarely hemoptysis, and other signs and symptoms of cardiovascular decompensation. With disease progression, exercise tolerance is markedly decreased, and life expectancy is reduced (Galiè 2015a).

Survival estimates in adult patients with PAH

In the French, UK, Russian and US registries, published survival rates at 1 year were 85% to 99%; after 2 years were 76% to 81%; after 3 years were 67% to 94%; and after 5 years were 57% to 86% (Humbert 2010, Hurdman 2012, Benza 2012, Chazova 2019; Table SI.2). Survival rates for PAH are worse in males (Thenappan 2018).

Table SI.2: Survival Estimates in Adult Patients with PAH

Study Name, Region, Reference	Analysis period	Population characteristics	Survival (years), %			
			1	2	3	5
REVEAL, USA (Benza 2012)	2006-2009	n = 2,635, ≥3 months	85	-	68	57
Russian National Registry (Chazova 2019)	2012-2017	n = 470, >18 years	99	-	94	86
French PAH Registry, France (Humbert 2010)	2002-2003	n = 674, ≥18 years	87*	76*	67*	-
ASPIRE, UK (Hurdman 2012)	2001-2010	n = 598, adults	88[1]	81*[1]	68[1]	57*[1]

Note: *Extracted from graph; [1]Transplant-free survival.

Important Comorbidities

The co-occurrence of PAH and comorbidities increases the complexity of disease management for patients who may require multiple pharmacological interventions to treat both PAH and the comorbidity. In PAH, approximately three quarters of patients have at least one comorbidity, with patients aged 65 years and older having a greater number of comorbidities. Current research suggests that the presence of comorbid conditions in patients with PAH negatively affects outcomes (Lang 2019).

A variety of comorbid conditions, not representing the principal cause of the development of PAH, have been identified in patients with PAH. The REVEAL Registry (2006 to 2007) reported the following comorbidities in more than 10% of all IPAH patients: systemic hypertension, obesity, sleep apnea, clinical depression, obstructive airway disease, thyroid disease, diabetes mellitus, and ischemic cardiovascular events (Lang 2019). In the US Pulmonary Hypertension Scientific Registry conducted almost 10 years later (2015 to 2018), obesity, diabetes, hypertension, hypothyroidism, and clinical depression were found to be among the most common comorbid conditions (Badlam 2021).

Additional comorbidities associated with PAH include anemia, chronic kidney disease, chronic liver disease, chronic pain, chronic muscle disease, frailty, peripheral vascular disease, cancer, dementia, cirrhosis, renal insufficiency, and atrial fibrillation (Lang 2019). The main causes of death reported in PAH patients are cardiovascular events, including heart failure and sudden death, which account for 44% to 89% of deaths in PAH patients (Tonelli 2013, Ruiz-Cano 2009).

Patients with PAH may develop various severe liver complications (due to severe congestive hepatopathy induced by RHF and/or due to autoimmune disease/CTD) (Wells 2018, Nickel 2021).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety assessment was focused on the active metabolite (ACT-333679) because it is the main contributor to efficacy and potential safety-relevant effects.

The results from the non-clinical toxicology, carcinogenicity, reproductive toxicity, and DDI studies are adequately reflected in the SmPC for UPTRAVI.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Toxicity	
Selexipag has undergone a complete program of toxicity studies in rodents, rabbits, and dogs.	
Single & repeat-dose toxicity	
Clinical observations (flaccidity, decreased activity) in rats at 39-fold the human exposure at 1600 µg bid were due to strong blood pressure decrease at high doses. Effects on food consumption and body weight development were secondary to the blood pressure decrease and reversible during the treatment period.	This effect is considered to reflect exaggerated PD in rat toxicity studies and is not expected to occur similarly in humans at therapeutic doses.
In dogs less than 1 year of age, intestinal intussusception occurred in both sexes and generally developed during the first 4 weeks of treatment in acute to chronic toxicity studies and in the 39 week juvenile toxicity study. Mortality or early necropsy of animals in these studies was directly related to this finding. Clinical signs included decreased food consumption, bloody stool, and anus protrusion. Macroscopically, intussusception was characterized by the invagination of proximal bowel segments (jejunum and/or ileum) into a distal segment (eg, colon). Histopathologically, intussusception led to necrosis, hemorrhage, and congestion of the intestinal mucosa of the affected bowel segments. Intestinal intussusception (invagination) in individual dogs below 1 year of age is considered to be a result of exaggerated PD, related to the IP receptor-mediated disturbance of gastric motility. The effect occurred at 5-fold the human exposure (ie, corrected for potency; 415-fold based on total exposure). Safety margins based on no-observed-adverse-effect levels for the active metabolite, corrected for difference in receptor potency between human and dog, were 2-fold in relation to human exposure at a dose of 1600 µg of selexipag bid. Intussusception was not observed in mice or rats.	Due to the known susceptibility of young dogs to develop intussusception and the safety margin of 2-fold (ie, corrected for potency; at 180-fold based on total exposure) for the active metabolite, the finding is considered as not relevant for adult humans. However, in infants and young children, intussusception is the most common cause of intestinal obstruction. Available epidemiological data show that 75–90% 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, Hutchison 1980, Pollack 1991). The high background incidence of and susceptibility to intussusception in young children may pose a risk in this patient population when treated with selexipag. Considering the toxicological and epidemiological data, a waiver on safety grounds for pediatric development in children from birth to less than 2 years of age was justified. The particular pattern of bone or bone marrow findings after treatment of dogs with selexipag is explained by an off-target activation of EP_4 receptors in dogs. As human EP_4 receptors are not activated by selexipag and its active metabolite, the finding is dog specific and not relevant for humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Treatment of juvenile or adult dogs with selexipag induces a particular pattern of bone and bone marrow findings after 2 to 39 weeks of treatment. These findings consisted of increased ossification, bands of fibroblasts and collagen fibers and variable appearance of hematopoietic tissue. These findings are considered to be related to activation of EP_4 receptor in dogs, which is activated with similar potency as the IP receptor in this species. Increased ossification and the occurrence of fibrocytes with collagen fibers in bone in dog studies are considered to be related to the activation of EP_4 receptors by selexipag.	
Minimal decrease in platelet counts in rat studies were reversible and were not accompanied by effects on blood coagulation. Decreased platelet counts in dog studies were due to low individual values in animals in very poor general condition because of intussusception.	This finding is not considered to be relevant for the clinical use of selexipag because of the minimal severity and reversibility in rats, and the fact that it was seen as an effect secondary to individual poor condition in dogs. The thrombocytopenia AE data and the platelet count data recorded in the clinical studies confirm the conclusion that selexipag has no effect on platelets in patients with PAH.
Tortuosity and dilation of retinal vessels were observed at ophthalmological examination in Week 104 at 95-fold the human exposure. The NOEL was 10 mg/kg/day, corresponding to 35-fold the human exposure.	Retinal tortuosity is considered to reflect exaggerated PD resulting in continuous blood vessel dilation for the whole lifespan. Because of high safety margins, it is not considered relevant for the clinical use of selexipag. The potential relevance to humans was evaluated in the Phase 2 and Phase 3 clinical studies. Based on clinical data, the non-clinical finding is not relevant to humans.
Reproductive toxicity	
Reproductive toxicity of selexipag was assessed in fertility and embryofetal studies and pre-/post-natal development studies. These studies were complemented by a dog juvenile toxicity study, including exposure assessment. Selexipag was not teratogenic in rats and rabbits, and had no effect on fertility of male and female rats. In the rat pre- and post-natal development study, selexipag induced no effects on maternal and pup reproductive function. In rats, selexipag or its metabolites are excreted in milk.	Nonclinical data do not indicate a safety concern for humans. UPTRAVI is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether selexipag or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. UPTRAVI should not be used during breast-feeding.
Developmental toxicity	
Toxicity of selexipag was determined in pre-/post-natal development studies. There were no effects on maternal and pup reproductive function.	Nonclinical data do not indicate a safety concern for humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Genotoxicity	
Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.	Nonclinical data do not indicate a safety concern for humans.
Carcinogenicity	
In the mouse carcinogenicity study, the incidence of thyroid adenomas was increased at 250 mg/kg/day corresponding to 113-fold the human exposure.	The finding in mice is considered secondary to hepatic enzyme induction, which leads to degradation of thyroid hormones, up-regulation of TSH release, and continuous stimulation of the thyroid. This mechanism is rodent specific, and the findings were observed at exposures more than 25-fold above human exposure and are, therefore, not relevant for humans. Hyperthyroidism was identified as an important risk in clinical studies based on a different mechanism of action.
In the rat carcinogenicity study, the incidence of Leydig cell adenomas and hyperplasia was marginally increased at the high dose of 100 mg/kg/day, corresponding to 458-fold the human exposure. A NOEL for adenoma development was 30 mg/kg/day, corresponding to 95-fold the human exposure.	As rats are known to be particularly susceptible to develop Leydig cell adenomas and because of the high effect and safety margins more than 25-fold above human exposure, this finding is not relevant for humans.
<u>Other toxicity-related information or data</u>	
Selexipag was phototoxic in vitro.	The relevance to humans was investigated in a dedicated Phase 1 clinical study that did not show phototoxic potential.

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Overview of Clinical Trials in the RMP

Data from the following clinical trials are included in this RMP:

PAH

- **AC-065A302 (GRIPHON)**: Randomized, placebo-controlled, double-blind, parallel groups (completed study, 2 October 2014) and Treatment Extension Period (completed 27 February 2015).
- **AC-065A303 (GRIPHON OL)**: Uncontrolled extension of AC-065A302, completed (data cut-off date was 20 December 2020).
- **NS-304/-02:** Uncontrolled single dose of selexipag including 2 treatment periods: an acute hemodynamic period and a randomized, placebo-controlled, double-blind, parallel-group period, which were handled as if they were 2 studies (completed study, 20 January 2010).
- **NS-304/-03:** Uncontrolled, open-label extension of NS-304/-02 (completed study, 16 October 2018).
- **AC-065A201:** Uncontrolled, open-label study to assess the efficacy, safety and PK of selexipag in patients with PAH (completed study, 14 February 2018).
- **AC-065A304 (TRANSIT):** Open-label, single-group study to assess the tolerability and safety of the transition from inhaled treprostinil to oral selexipag in adult patients (completed study, 1 December 2017).
- **AC-065A308 (TRITON):** Double-blind, placebo-controlled, Phase 3b study to assess the efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed PAH (completed study, 9 December 2020).
- **AC-065A404 (TRACE):** Double-blind, placebo-controlled, Phase 4 study in patients with PAH to assess the effect of selexipag on daily life, physical activity and patient's self-reported symptoms and their impacts (completed study, 15 December 2020).

SIII.2. Clinical Trial Exposure

Clinical trial exposure to selexipag is presented in the following tables by duration of exposure, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, ethnic origin, by concomitant PAH-specific medication at baseline).

Exposure in Randomized Clinical Trials

The tables below present selexipag exposure from the following randomized clinical trials in adults:

- AC-065A302 (GRIPHON)
- NS-304/-02
- AC-065A308 (TRITON)
- AC-065A404 (TRACE)

Table SIII.1: Exposure in Randomized Clinical Trials by Duration of Exposure

	Selexipag N=779	
Total Population	**Persons**	**Person Time (year)**
PAH		
Duration of exposure		
<1 m	40	1.8
1 to <3 m	47	7.5
3 to <6 m	131	53.7
6 to <12 m	73	52.7
12 to <24 m	235	354.5
24 to <36 m	163	407.8
36 to <48 m	88	291.9
48 to <60 m	2	8.7
≥60 m	0	0.0
Total	**779**	**1178.7**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.2: Exposure in Randomized Clinical Trials by Age Group and Sex

	Selexipag N=779			
Total Population	**Persons Male**	**Person Time (year) Male**	**Persons Female**	**Person Time (year) Female**
PAH				
Age group				
<18 years	0	0.0	0	0.0
18 to 64 years	141	206.1	492	780.7
65 to 74 years	26	31.8	108	138.8
75 to 84 years	3	6.6	9	14.7
≥85 years	0	0.0	0	0.0
Total	**170**	**244.5**	**609**	**934.2**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.3: Exposure in Randomized Clinical Trials by Dose

	Selexipag N=779	
Total Population	**Persons**	**Person time (year)**
PAH		
Dose of exposure		
<200 µg bid	11	0.6
200 to 600 µg bid	251	320.5
>600 to <1600 µg bid	304	467.6
≥1600 µg bid	213	389.9
Total	**779**	**1178.7**

Individual maximum tolerated dose (µg bid) in the titration period.
Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.4: Exposure in Randomized Clinical Trials by Race/Ethnicity

	Selexipag N=779	
Total Population	**Persons**	**Person time (year)**
PAH		
Race/ethnicity		
Caucasian / Hispanic	601	904.3
Asian	138	213.8
Black	20	31.2
Other	12	17.2
Unknown	3	1.4
Missing	5	10.7
Total	**779**	**1178.7**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.5: Exposure in Randomized Clinical Trials by Concomitant PAH-specific Medication at Baseline

	Selexipag N=779	
Total Population	**Persons**	**Person time (year)**
PAH		
Concomitant PAH-specific medication at baseline		
No PAH medication	112	204.1
ERA alone	108	150.3
PDE5-i/sGC stimulator alone	198	317.7
≥2 PAH medications	361	506.6
Total	**779**	**1178.7**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Exposure in All Clinical Trials

The tables below present selexipag exposure from all 8 clinical trials in adults:

- **AC-065A302 (GRIPHON)**
- **AC-065A303 (GRIPHON OL)**
- **NS-304/-02**
- **NS-304/-03**
- **AC-065A201**
- **AC-065A304 (TRANSIT)**
- **AC-065A308 (TRITON)**
- **AC-065A404 (TRACE)**

Table SIII.6: Exposure in All Clinical Trials by Duration of Exposure

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
PAH		
Duration of exposure		
<1 m	58	2.4
1 to <3 m	75	11.8
3 to <6 m	137	54.4
6 to <12 m	114	83.9
12 to <24 m	210	323.3
24 to <36 m	149	370.2
36 to <48 m	92	312.9
48 to <60 m	92	413.9
≥60 m	310	2288.1
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.7: Exposure in All Clinical Trials by Age Group and Sex

			Selexipag N=1237	
Total Population	**Persons Male**	**Person Time (year) Male**	**Persons Female**	**Person Time (year) Female**
PAH				
Age group				
<18 years	0	0.0	0	0.0
18 to 64 years	210	591.5	811	2754.6
65 to 74 years	37	60.3	150	378.0
75 to 84 years	7	22.5	22	54.1
≥85 years	0	0.0	0	0.0
Total	**254**	**674.3**	**983**	**3186.6**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.8: Exposure in All Clinical Trials by Dose

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
PAH		
Dose of exposure		
<200 µg bid	20	9.6
200 to 600 µg bid	420	1256.6
>600 to <1600 µg bid	477	1448.3
≥1600 µg bid	320	1146.4
Total	**1237**	**3860.9**

Individual maximum tolerated dose (µg bid) in the titration period.
Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.9: Exposure in All Clinical Trials by Race/Ethnicity

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
PAH		
Race/ethnicity		
Caucasian / Hispanic	914	2681.0
Asian	269	1064.8
Black	29	56.0
Other	17	47.0
Unknown	3	1.4
Missing	5	10.7
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.10: Exposure in All Clinical Trials by Concomitant PAH-specific Medication at Baseline

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
PAH		
Concomitant PAH-specific medication at baseline		
No PAH medication	185	864.1
ERA alone	163	508.4
PDE5-i/sGC stimulator alone	339	1317.3
≥2 PAH medications	550	1171.1
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.11: Exposure in All Clinical Trials by Study

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
PAH		
Study		
AC-065A302 + AC-065A303	953	3315.4
NS-304/-02 + NS-304/-03	41	190.4
AC-065A201	37	111.8
AC-065A304	34	14.1
AC-065A308	119	207.1
AC-065A404	53	22.2
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Patients with moderate or severe hepatic impairment (ie, Child-Pugh class B and C)**
Reason for being an exclusion criterion	PAH patients with moderate or severe hepatic impairment were excluded from the clinical studies as a precautionary measure due to the limited amount of data on the PK of selexipag in patients with severe hepatic impairment at the time of the start of the study.
Included as missing information?	No
Rationale if not included as missing information	As stated in the SmPC, selexipag should not be used in patients with severe liver impairment (Child-Pugh class C). The exposure to selexipag and its active metabolite is increased in participants with moderate hepatic impairment (Child-Pugh class B; SmPC section 5.2). For patients with moderate hepatic impairment, the starting dose of treatment should be 100 µg bid or 200 µg qd and increased at weekly intervals by increments of 100 µg bid or 200 µg qd until adverse reactions reflecting the mode of action of selexipag that cannot be tolerated or medically managed are experienced (SmPC section 4.2). No additional pharmacovigilance activities are planned to further characterize the use in patients with moderate to severe hepatic impairment.
Criterion 2	**Patients with severe renal insufficiency (estimated creatinine clearance <30 mL/min, or serum creatinine >2.5 mg/dL)**
Reason for being an exclusion criterion	PAH patients with severe renal impairment were excluded from the clinical studies as a precautionary measure due to the limited amount of data on the PK of selexipag in patients with renal impairment at the time of the start of the study.
Included as missing information?	No
Rationale if not included as missing information	As stated in the SmPC, no adjustment to the dose regimen is needed in patients with mild or moderate renal impairment. No change in starting dose is required in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), dose titration should be done with caution in these patients (SmPC sections 4.2 and 4.4). There is no experience with selexipag in patients undergoing dialysis (SmPC section 5.2), therefore selexipag should not be used in these patients. Dialysis is however unlikely to affect plasma concentrations of the drug because selexipag and its active metabolite are highly protein bound (SmPC section 4.9). No additional pharmacovigilance activities are planned to further characterize the use in patients with severe renal

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
	insufficiency.
Criterion 3	**Patients with moderate or severe obstructive lung disease**
Reason for being an exclusion criterion	Patients with moderate or severe obstructive lung disease were excluded to ensure that patients with PH group 3 were not enrolled in the study.
Included as missing information?	No
Rationale if not included as missing information	Selexipag is not indicated for treatment of patients with PH due to lung diseases and/or hypoxia (Group 3).
Criterion 4	**Patients with moderate or severe restrictive lung disease**
Reason for being an exclusion criterion	Patients with moderate or severe restrictive lung disease were excluded to ensure that patients with PH group 3 were excluded from the study, in order to prevent co-morbidities interfering with the diagnosis of PAH.
Included as missing information?	No
Rationale if not included as missing information	Selexipag is not indicated for treatment of patients with PH due to lung diseases and/or hypoxia (Group 3).
Criterion 5	**Patients with documented left ventricular dysfunction**
Reason for being an exclusion criterion	Left heart disease represents the most frequent cause of PH and belongs to PH group 2. Patients with documented left ventricular dysfunction were excluded to ensure that patients with PH group 2 were excluded from the study, in order to prevent co morbidities interfering with the diagnosis of PAH.
Included as missing information?	No
Rationale if not included as missing information	Selexipag is not indicated for treatment of patients with PH due to left heart disease (Group 2).
Criterion 6	**Patients with BMI <18.5 kg/m^2**
Reason for being an exclusion criterion	Patients with BMI <18.5 kg/m^2 were excluded in order to limit variability of drug exposure and facilitate interpretation of study results.
Included as missing information?	No
Rationale if not included as missing information	No implications are expected for the treatment of PAH patients. Individualized dosing based on tolerability.
Criterion 7	**Psychotic, addictive, or any other disorder**
Reason for being an exclusion criterion	The exclusion of patients with this condition from the clinical trial was based on practicality of conducting the clinical trial, as psychotic, addictive or any other disorder would limit the ability to provide informed consent or to comply with study requirements.
Included as missing information?	No
Rationale if not included as missing information	No implications are expected for the treatment of PAH patients.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 8	**Lactating or pregnant (positive pre-randomization serum pregnancy test) women or those who planned to become pregnant during the study**
Reason for being an exclusion criterion	Pregnancy: a) There were no data on the use of selexipag in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity. b) Current treatment guidelines recommend avoiding pregnancy in PAH patients, as this is associated with high risk of mortality for the mother. Pregnant women or those who planned to become pregnant were excluded as the condition could interfere with the assessment of the efficacy of selexipag in a mortality/morbidity event-driven clinical trial. Lactating: It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, selexipag and its metabolites are excreted in milk.
Included as missing information?	Yes
Rationale if not included as missing information	Not applicable.
Criterion 9	**Known hypersensitivity to any of the excipients of the drug formulations**
Reason for being an exclusion criterion	These individuals were excluded from clinical trials to avoid potentially severe and life-threatening allergic/hypersensitivity reactions
Included as missing information?	No
Rationale if not included as missing information	Required by QRD template of the SmPC, these criteria will remain as a contraindication in section 4.3 of the SmPC.

SIV.2. Limitations to Detecting Adverse Reactions in the Clinical Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3. Limitations With Respect to Populations Typically Under-represented in Clinical Development Programs

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Cumulatively, since the IBD (21 December 2015) and up to the data cut-off date of 20 December 2020, 46 confirmed pregnancies in selexipag-treated patients have been reported, including 11 from interventional clinical trials, 17 from noninterventional solicited clinical studies, and 18 from spontaneous sources (1 spontaneous case was from a literature source). Drug exposure was during the first trimester in 22 cases; selexipag was started 6 weeks prior to birth in 1 case; time of exposure was unknown in 19 cases; and pregnancy was

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
	confirmed after selexipag discontinuation in 4 cases.
Breastfeeding women	To date, no reports of selexipag use during lactation have been received.
Population of relevant different ethnic origin	In the All Clinical Trials Population included in this RMP, of the 1237 patients treated with selexipag, 73.9% of the participants were Caucasian / Hispanic; 21.7% were Asian; and 2.3% were Black (Table SIII.9). Pharmacokinetics The results from study NS304/P1/01, which mainly included Japanese participants, suggested higher plasma concentrations of both selexipag and its active metabolite when compared to study QGUY/2006/NS304/-01, which mainly included Caucasian participants. Upon review, the differences in PK were explained by differences in body weight. In study AC-065A302, race/ethnicity was not identified as a significant covariate towards the PK of selexipag and its active metabolite (D-14.470). In this study, the majority of patients were Caucasian (ie, White/Hispanic; 74.7%) or Asian (21.3%). There were some demographic/baseline characteristic differences between Asian and non-Asian populations, with Asian patients generally being younger and exhibiting less severe PAH disease as assessed by NYHA / WHO FC. There were no important differences between Asian and non-Asian populations regarding duration of exposure to study drug, selexipag dose achieved, or exposure to selexipag in population PK analysis. Safety In the Phase 3 study, the safety findings were similar across geographical regions / ethnicities. Efficacy In contrast to findings in other subgroups, the observed treatment effect in the primary endpoint was small in the Asian population / Asia geographic subgroup. As fewer patients in the placebo group in Asia had a MM event compared to the rest of the world (probably linked to the higher proportion of less severe disease status at baseline), it was more challenging to demonstrate an effect in the active treatment arm. While no single factor was identified that could explain lower efficacy of selexipag in Asian patients compared to non-Asian patients, it was concluded that the results are likely to represent random variation; however, an influence of unidentified racial/ethnic factors cannot be excluded. The analysis requested by CHMP, using the definition of a composite MM endpoint in accordance with the EMEA/CHMP/EWP/356954/2008 guideline, shows that the treatment effect in the Asian geographical region is consistent with the overall observed treatment effect (hazard ratio selexipag versus placebo of

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
	0.76 [99% CI: 0.46, 1.25] and of 0.73 [99% CI: 0.6, 0.91], respectively). This could be due to the difference in the definition of an MM component: the CHMP guideline, allowing an isolated deterioration in either WHO FC, or 6-minute walk distance, or signs and symptoms of RHF to qualify as PAH-related deterioration.
Subpopulations carrying relevant genetic polymorphisms	In study AC-065-117 investigating the effect of a moderate inhibitor of CYP2C8 on selexipag in healthy male participants, the following CYP2C8 genotypes were present in the study: *1/*1 (wild-type) (n = 13) *1/*3 (n = 6) and *1/*4 (n= 2). Investigations according to genetic polymorphisms have not been included in the remaining clinical development program. Enzymatic hydrolysis of selexipag by carboxylesterase 1 and 2 yields ACT-333679, the active metabolite of selexipag (D-14.482, Selexipag IB, Imai 2018). In vitro functional studies indicated that certain CES gene mutations could lead to dysfunctional CES activity in humans. However, there are no known CES genetic variants that can be utilised as biomarkers to predict the activity of CES in clinical practice (Zhu 2008, Zhu 2013, Merali 2014). The most important polymorphisms in CYP enzymes are those for CYP2C9, CYP2C19, and CYP2D6 (McGraw 2012, Zhou 2009), which can result in reduced therapeutic efficacy or increased incidence of adverse reactions. These enzymes are not involved in the metabolism of selexipag and ACT-333679. For CYP2C8, which is an important enzyme in elimination of ACT-333679, there are several alleles. Three alleles, known as *CYP2C8*2*, *CYP2C8*3*, and *CYP2C8*4*, account for the majority of polymorphic variants of the *CYP2C8* gene in humans. Other alleles, such as *CYP2C8*5, CYP2C8*7,* or *CYP2C8*8*, are very rare variants (Daily 2009, Backman 2016). Some of these variants might affect the activity of the CYP2C8 enzyme, but, for example, *CYP2C8*4* does not seem to have a significant effect on enzyme activity (Bahadur 2002). The frequency of these variants differs significantly between ethnic groups. For example, *CYP2C8*2* has been detected in the Black population (Dai 2001), but was not found in Caucasians. *CYP2C8*3* is commonly found in Caucasians (10% to 23%) but it is rare in African and Asian populations (Totah 2005, Daily 2009, Bahadur 2002). *CYP2C8*5* has been found in the Japanese population. There are also reports about the presence of this variant in the Black population (Brown 2016, Ishikawa 2004, Nakajima 2003). During the development of selexipag, and in the population PK analysis performed in study AC-065A302 (GRIPHON) with patients with PAH, as well as additional exploratory subgroup PK analyses, there was some variability but no clear correlation between ethnicity and PK of selexipag. In the DDI study between selexipag and gemfibrozil (AC-065-113) a large inter-individual variability was observed in the magnitude of the gemfibrozil effect on the PK of

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
	selexipag and ACT-333679, with increases in ACT-33679 exposure ranging from 4-fold to 20-fold (out of 20 enrolled participants, 18 were Caucasian and 2 Asian). In the absence of a genetic analysis in this study, it is not known if there is any correlation between *CYP2C8*3* carriers and the observed variability in gemfibrozil effect. Based on the non-clinical findings and data from a dedicated clinical DDI study, concomitant administration of selexipag with strong inhibitors of CYP2C8 (eg, gemfibrozil) is contraindicated. Concomitant administration of selexipag with clopidogrel (300 mg as a loading dose or maintenance doses of 75 mg qd), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite by approximately 2.2-fold and 2.7-fold following loading dose and maintenance dose, respectively (AC-065-117). In the presence of clopidogrel (both loading and maintenance doses), comparable increased exposure to ACT-333679 was observed in all identified CYP2C8 genotypes present in the study (genotypes *1/*1, *1/*3, and *1/*4). When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide), the total daily dose of selexipag should be reduced by half. This can be achieved by either administering half the dose of selexipag bid or reducing the dosing frequency of selexipag to qd. When co-administration of a moderate CYP2C8 inhibitor is stopped, the total daily dose of selexipag should be increased by either increasing each dose or reverting to bid dosing, as applicable. The maximum dose of 1600 µg bid should not be exceeded (SmPC section 4.2). In the presence of rifampicin, an inducer of CYP2C8 (and UGT enzymes), the exposure to selexipag did not change, whereas exposure to the active metabolite was reduced by half. Dose adjustment of Uptravi may be required with concomitant administration of inducers of CYP2C8 (eg, rifampicin, carbamazepine, phenytoin).

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Children	As of 20 December 2020, 50 pediatric patients received selexipag during the currently ongoing AC-065A203 study. Selexipag starting dose is based on their body weight: 100 µg for participants from ≥9 to <25 kg, 150 µg for participants from ≥25 to <50 kg, and 200 µg for participants ≥50 kg. Since initiation of the study, the planned first and the second interim PK analyses for age Cohort 1 (≥12 to <18 years of age) and Cohort 2 (≥6 to <12 years of age) were completed. Selexipag starting doses and up-titration increments according to patient's weight category (≥9 to <25 kg; ≥25 to 50 kg; and ≥50 kg) were confirmed for patients aged ≥6 to <18 years of age. Enrollment to Cohort 3 (≥2 to <6 years of age) has been initiated and is still ongoing. Based on data from Cohorts 1 and 2, no significant safety findings were identified from the clinical trial that had an impact on the benefit-risk balance of selexipag. The safety and efficacy of selexipag in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of selexipag in the pediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown (SmPC section 4.2). In the current PIP, a waiver was granted for children from birth to less than 2 years (EMEA-000997-PIP01-10-M07).
Elderly	Data for patients aged between 65 (according to the definition of 'elderly' used by the ICH guideline E7) and 80 years are available. Experience in the elderly is substantial, based on 99 patients treated with selexipag and 107 with placebo in the Phase 3 study AC-065A302. Of the 99 patients on selexipag, 91 were aged between 65 and 74 years, and 8 patients were ≥75 years old (range: 75-80 years). In the placebo group, 102 patients were 65-74 years old, and 5 patients were ≥75 years old. No patients >80 years old were exposed in the clinical program of selexipag. In the EXPOSURE PASS, as of 30 November 2021, 151 selexipag-treated patients were aged between 65 and 75 years and 67 selexipag-treated patients were >75 years old. There is no clinically relevant effect of age on the PK of selexipag and its active metabolite in healthy participants or PAH patients. Therefore, no adjustment to the dosing regimen is needed in elderly patients. No important differences for efficacy or safety were observed between elderly and non-elderly patients. However, the experience in patients >75 years old is limited. The recommendations regarding the use of selexipag in the elderly are described in the SmPC in sections 4.2 and 4.4.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Patients with relevant comorbidities:	
Patients with hepatic impairment	PAH patients with moderate and severe hepatic impairment were excluded from the clinical studies as a precautionary measure due to the absence of data on the PK of selexipag in patients with hepatic impairment before the start of Phase 2 or 3 clinical trials. The PK, safety, and tolerability of a single dose of selexipag (400 µg) were assessed in participants with different degrees of liver impairment (Child-Pugh class A or B) in a single-center, OL, Phase 1 study (AC-065-104). Results showed a 2-fold increase of exposure to selexipag ($AUC_{0-\infty}$) in participants with mild liver impairment (Child-Pugh class A) compared to healthy participants, while exposure to the active metabolite remained unchanged. In participants with moderate liver impairment (Child-Pugh class B), $AUC_{0-\infty}$ of selexipag and its active metabolite increased approximately 4-fold and 2-fold, respectively. Only 2 participants with severe hepatic impairment (Child-Pugh class C) were dosed with selexipag. Exposure to selexipag and its active metabolite in these 2 participants was similar to that in participants with moderate hepatic impairment (Child-Pugh class B). Based on modeling and simulation data from this study, the exposure to selexipag at steady state in participants with moderate hepatic impairment (Child-Pugh class B) after a qd regimen is predicted to be approximately 2-fold higher than that in healthy participants during a bid regimen. The exposure to the active metabolite at steady state in these participants during a qd regimen is predicted to be similar to that in healthy participants during a bid regimen. Participants with severe hepatic impairment (Child-Pugh class C) showed similar predicted exposure at steady state as participants with moderate hepatic impairment during a qd regimen. In patients with moderate hepatic impairment, the total daily dose of selexipag should be reduced (SmPC section 4.4). See SmPC section 4.2 'Posology and method of administration' under 'hepatic impairment', section 4.4 'Special warnings and precautions for use' under 'hepatic impairment', and section 5.2 'Pharmacokinetic properties'.
Patients with renal impairment	Patients with severe renal insufficiency (estimated creatinine clearance <30 mL/min, or serum creatinine >2.5 mg/dL) were excluded from the clinical studies in the pre-authorization phase as the data on the specific dedicated Phase 1 study in patients with renal impairment were lacking at the time of planning of the Phase 3 trials. The PK, safety, and tolerability of a single oral dose of selexipag (400 µg) in participants with renal function impairment were investigated in a single-centre, OL study (AC-065-105). Results showed that a 1.4- to 1.7-fold increase in exposure to selexipag and its active metabolite was observed in participants with severe renal function impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2). The increase in exposure was not associated with any unexpected AEs in participants with severe renal function impairment and was not

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
	considered large enough to require investigation in participants with moderate renal function impairment. Selexipag is not expected to be dialysable as selexipag, and its active metabolite are highly bound to plasma proteins (approximately 99% in total and to the same extent to albumin and alpha1-acid glycoprotein). Laboratory data in the Phase 3 study indicated no detrimental effect of selexipag on renal function. See SmPC section 4.2 'Posology and method of administration' under 'renal impairment', section 4.4 'Special warnings and precautions for use' under 'renal impairment', and section 5.2 'Pharmacokinetic properties'.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

The number of patients exposed to selexipag during the post-marketing period is estimated via controlled distribution systems or from the number of packages sold. The cut-off date used for the postauthorization exposure for the purpose of this document is 30 November 2020.

SV.1.2. Exposure

Cumulatively, since IBD (21 December 2015) and up to the data cut-off point of 30 November 2020, an estimated 21,142 patients (corresponding to 31,267 patient years) were exposed to commercial selexipag worldwide, including 4,815 patients in the EEA (22.8%), 10,830 patients in the US (51.2%), 3,005 patients in Japan (14.2%), and 2,492 patients in the ROW (11.8%). Selexipag is currently approved in PAH (WHO group 1), and the vast majority of patients for whom an indication was provided had PAH.

The estimated cumulative exposure to commercial selexipag by region is presented in Table SV.1.

Table SV.1: Cumulative Exposure to Selexipag by Region (Launch to 30 November 2020)

Region	Patient-Years	Number of Patients Exposed
EEA	5,378	4,815
US	15,031	10,830
Japan	8,075	3,005
ROW	2,783	2,492
Total	**31,267**	**21,142**

The estimated cumulative exposure to commercial selexipag in the EEA, by country, is presented in Table SV.2.

Table SV.2: Estimated Cumulative Post-marketing Exposure in the EEA (Launch to 30 November 2020)

Country	Number of Patients Exposed
Austria	84
Belgium	156
Croatia	1
Cyprus	15
Czech Republic	51
Denmark	38
Estonia	3
Finland	41
France	650
Germany	1,263
Greece	178
Hungary	42
Iceland	7

Table SV.2: Estimated Cumulative Post-marketing Exposure in the EEA (Launch to 30 November 2020)

Country	Number of Patients Exposed
Ireland	32
Italy	483
Lithuania	6
Luxembourg	3
Malta	1
Netherlands	472
Norway	64
Poland	3
Portugal	95
Slovakia	39
Spain	536
Sweden	205
United Kingdom	347
Total	**4,815**

The split into gender and age groups was estimated based on data collected in the US in the context of controlled distribution; due to local data privacy regulations, such information cannot consistently be collected outside the US.

According to cumulative exposure data available from the US, 72.0% of the exposed patients were females and 28.0% were males (this matches the gender distribution for the indication of PAH); 41% of the exposed patients were elderly (including 16.1% ≥75 years), 57.0% were adults, 1.0% were aged between 12 and 18 years, and 1.0% were younger than 12 years (Table SV.3)

Table SV.3: Estimated Cumulative Post-marketing Exposure in the US – Number of Patients by Age Group and Gender

	Age	Number of Patients Exposed					
		Females		Males		Total	
Pediatric Patients	**<12 y**	48	0.4%	62	0.6%	110	**1.0%**
	≥12 to 18 y	69	0.6%	42	0.4%	111	**1.0%**
Adult Patients	**≥18 to <65 y**	4,476	41.3%	1,697	15.7%	6,173	**57.0%**
Elderly Patients	**≥65 to <75 y**	1,953	18.1%	739	6.8%	2,692	**24.9%**
	≥75 to <85 y	1,084	10.0%	439	4.1%	1,523	**14.1%**
	≥85 y	172	1.6%	49	0.4%	221	**2.0%**
Total		**7,802**	**72.0%**	**3,028**	**28.0%**	**10,830**	**100.0%**

Note: Estimated cumulative post-marketing exposure in the US: number of patients by age group and sex (21 December 2015 to 30 November 2020). The methodology regarding patient age calculation is based on patient age at the time of first product shipment. Percentages were obtained based on the proportion of the US patients in the concerned category and are displayed in this table as values rounded up or down to 1 decimal point.

The estimated cumulative exposure in the US corresponds to 15,033 patient-years (Table SV.4).

Table SV.4: Estimated Cumulative Post-marketing Exposure in the US – Patient-Years by Age Group and Gender

	Age	Number of Patient-years		
		Females	**Males**	**Total**
Pediatric Patients	**≥2y to <12 y**	85	82	168
	≥12 to 18 y	87	66	153
Adult Patients	**≥18 to <65 y**	6,932	2,437	9,369
Elderly Patients	**≥65 to <75 y**	2,543	922	3,465
	≥75 to <85 y	1,242	448	1,690
	≥85 y	145	43	188
Total		**11,034**	**3,998**	**15,033**

Note: Estimated cumulative post-marketing exposure in the US: number of patient-years, by age group and sex (21 December 2015 to 30 November 2020). The methodology regarding patient age calculation is based on patient age at the time of first product shipment.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Based on the pharmacology and mechanism of action of selexipag, it is considered highly unlikely that selexipag has the potential for abuse. No systematic examination of the abuse potential of selexipag has been performed in nonclinical and clinical studies; however, there have been no reports of misuse for illegal use or dependence during the clinical development or post-approval use of selexipag. There are no data suggesting that selexipag has the potential for illicit use, abuse, or dependency.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks and Missing Information

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns

Not applicable.

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns

Not applicable.

SVII.1.2. Important Risks and Missing Information for Inclusion in the List of Safety Concerns

Not applicable.

SVII.2. New, Reclassified, and Removed Safety Concerns with Submission of an Updated RMP

None.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important Identified Risks

1. Hypotension
2. Anemia, decrease in hemoglobin concentration
3. Hyperthyroidism
4. Concomitant use of strong inhibitors of CYP2C8

Important Potential Risks

1. Pulmonary edema associated with PVOD
2. MACE
3. Renal function impairment / acute renal failure
4. Bleeding events
5. Light-dependent non-melanoma skin malignancies
6. Ophthalmological effects associated with retinal vascular system
7. GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
8. Medication error

Missing Information:

1. Use in pediatric patients
2. Use in elderly patients over 75 years old
3. Use during pregnancy and lactation
4. Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Hypotension

Potential Mechanisms

As with other pulmonary vasodilators (ie, ERAs, PDE-5 inhibitors, and other prostanoids), treatment with selexipag may be associated with a reduction in blood pressure due to its vasodilatory effects.

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.1: Important Identified Risk: Treatment-emergent Adverse Events of Hypotension in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	38 / 574 (6.6%)	22 / 578 (3.8%)	1.739 (1.042 - 2.903)	0.0481 [936.4]	0.0274 [875.9]
PAH	NS-304/-02	2 / 33 (6.1%)	0 / 10 (0)	NA	0.1534 [13.0]	0 [3.7]
PAH	AC-065A308	11 / 119 (9.2%)	8 /120 (6.7%)	1.387 (0.578 - 3.325)	0.0531 [207.1]	0.0482 [186.9]
PAH	AC-065A404	0 / 53 (0%)	1 /55 (1.8%)	NA	0 [22.2]	0.0390 [25.7]

All selexipag studies

Table SVII.2: Important Identified Risk: Treatment-emergent Adverse Events of Hypotension in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	82 / 953 (8.6%)	0.0308 [3315.4]
PAH	NS-304/-02 + NS-304/-03	7 / 41 (17.1%)	0.0368 [190.4]
PAH	AC-065A201	8 / 37 (21.6%)	0.1073 [111.8]
PAH	AC-065A304	2 / 34 (5.9%)	0.1421 [14.1]
PAH	AC-065A308	11 / 119 (9.2%)	0.0531 [207.1]
PAH	AC-065A404	0 / 53 (0%)	0 [22.2]

Table SVII.3: Important Identified Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Hypotension

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Hypotension										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	51 (6.5%)	31 (4.1%)	38 (6.6%)	22 (3.8%)	2 (6.1%)	0	11 (9.2%)	8 (6.7%)	0	1 (1.8%)
Serious	7 (0.9%)	5 (0.7%)	5 (0.9%)	4 (0.7%)	0	0	2 (1.7%)	1 (0.8%)	0	0
Leading to discontinuation	0	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0
Fatal outcome	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Relative Risk	1.611	-	1.739	-	NA	-	1.387	-	NA	-
95% CI	(1.043 - 2.490)		(1.042 - 2.903)				(0.578 - 3.325)			
Number of recurrent AESI	58	34	45	24	2	0	11	9	0	1
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0492	0.0311	0.0481	0.0274	0.1534	0	0.0531	0.0482	0	0.0390
Severity (worst)*										
Mild	17 (2.2%)	10 (1.3%)	12 (2.1%)	6 (1.0%)	1 (3.0%)	0	4 (3.4%)	3 (2.5%)	0	1 (1.8%)
Moderate	27 (3.5%)	19 (2.5%)	19 (3.3%)	14 (2.4%)	1 (3.0%)	0	7 (5.9%)	5 (4.2%)	0	0
Severe	7 (0.9%)	2 (0.3%)	7 (1.2%)	2 (0.3%)	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.4: Important Identified Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Hypotension

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Hypotension						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	102 (8.5%)	82 (8.6%)	7 (17.1%)	2 (5.9%)	11 (9.2%)	0
Serious	15 (1.3%)	13 (1.4%)	0	0	2 (1.7%)	0
Leading to discontinuation	1 (0.1%)	1 (0.1%)	0	0	0	0
Fatal outcome	1 (0.1%)	1 (0.1%)	0	0	0	0
Number of recurrent AESI	122	102	7	2	11	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0325	0.0308	0.0368	0.1421	0.0531	0
Severity (worst)*						
Mild	38 (3.2%)	30 (3.1%)	3 (7.3%)	1 (2.9%)	4 (3.4%)	0
Moderate	53 (4.4%)	41 (4.3%)	4 (9.8%)	1 (2.9%)	7 (5.9%)	0
Severe	11 (0.9%)	11 (1.2%)	0	0	0	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.

* The event experienced by the patient with the worst severity is used.

AEs are coded using MedDRA Version 22.0

Table SVII.5: AESIs: Hypotension

	NS-304 N = 37 n (%)
Patients with at least one AESI	8 (21.6%)
Patients with at least one AESI leading to discontinuation	1 (2.7%)
Patients with at least one serious AESI	1 (2.7%)
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	12
Patient-years of observation	111.81
Average annualized event rate	0.1073
Severity (worst) (b)	
Asymptomatic	0
Mild	4 (10.8%)
Moderate	3 (8.1%)
Severe	1 (2.7%)
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Hypotension.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 1,644 cases containing events of hypotension or blood pressure decrease have been received from post-marketing data sources. Taking into account the estimated exposure of 21,142 patients, the estimated cumulative reporting rate is 7.8%.

Data from post-marketing data sources were consistent with data observed in the clinical studies. Altogether, in the majority of cases, the events of hypotension occurred in a context of severe medical conditions or other comorbidities that can lead to decrease in blood pressure, eg, PAH worsening, cardiac failure, syncope, infection/sepsis, chronic kidney disease, acute renal failure, hypovolemia or dehydration, or was associated with a bleeding event; and in patients treated with multiple concomitant medications with hypotensive effects (eg, ERAs, riociguat, PDE-5 inhibitors, anti-hypertensives [beta-blocking agents, anti-adrenergic agents, angiotensin converting enzyme inhibitors, angiotensin II antagonists], and/or diuretics).

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 RHF hospitalization. Four-fold increase of in-hospital mortality for patients with systolic blood pressure <100 mmHg upon admission is observed among PAH patients hospitalized for RHF.

Preventability

In the case of clinically significant blood-pressure reduction, appropriate measures should be taken as per usual clinical practice.

The following information is included in the SmPC:

Section 4.4 'Special warnings and precautions for use'

"Hypotension

Selexipag has vasodilatory properties that may result in lowering of blood pressure. Before prescribing UPTRAVI, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects (eg, patients on antihypertensive therapy or with resting hypotension, hypovolemia, severe left ventricular outflow obstruction or autonomic dysfunction)."

In section 4.8 'Undesirable effects', hypotension is listed as a commonly reported adverse reaction.

Impact on the Risk-Benefit Balance of the Product

Blood pressure is measurable, monitorable, and can typically be managed, eg, by adjusting administered medications. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Hypotension may require blood pressure monitoring and, in severe cases, may lead to hospitalization.

Important Identified Risk: Anemia, decrease in hemoglobin concentration

Potential Mechanisms

Selexipag therapy is associated with a modest decrease in mean hemoglobin concentration. The mechanism has not been elucidated. There is no evidence of hemolysis, occult or overt bleeding or bone-marrow depression associated with selexipag treatment.

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.6: Important Identified Risk: Treatment-emergent Adverse Events of Anemia in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	64 / 574 (11.1%)	49 / 578 (8.5%)	1.315 (0.923 - 1.873)	0.0854 [936.4]	0.0719 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	31 / 119 (26.1%)	20 / 120 (16.7%)	1.563 (0.946 - 2.581)	0.2077 [207.1]	0.1391 [186.9]
PAH	AC-065A404	2 /53 (3.8%)	2 / 55 (3.6%)	1.038 (0.152 - 7.102)	0.0903 [22.2]	0.0779 [25.7]

All selexipag studies

Table SVII.7: Important Identified Risk: Treatment-emergent Adverse Events of Anemia in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	153 / 953 (16.1%)	0.0615 [3315.4]
PAH	NS-304/-02 + NS-304/-03	8 / 41 (19.5%)	0.0683 [190.4]
PAH	AC-065A201	10 / 37 (27.0%)	0.1163 [111.8]
PAH	AC-065A304	1 / 34 (2.9%)	0.0711 [14.1]
PAH	AC-065A308	31 / 119 (26.1%)	0.2077 [207.1]
PAH	AC-065A404	2 /53 (3.8%)	0.0903 [22.2]

Table SVII.8: Important Identified Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Anemia

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Anemia										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	97 (12.5%)	71 (9.3%)	64 (11.1%)	49 (8.5%)	0	0	31 (26.1%)	20 (16.7%)	2 (3.8%)	2 (3.6%)
Serious	14 (1.8%)	7 (0.9%)	7 (1.2%)	5 (0.9%)	0	0	7 (5.9%)	2 (1.7%)	0	0
Leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.338	-	1.315	-	NA	-	1.563	-	1.038	-
95% CI	(1.002 - 1.787)		(0.923 - 1.873)				(0.946 - 2.581)		(0.152 - 7.102)	
Number of recurrent AESI	125	91	80	63	0	0	43	26	2	2
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.1060	0.0833	0.0854	0.0719	0	0	0.2077	0.1391	0.0903	0.0779
Severity (worst)*										
Mild	53 (6.8%)	29 (3.8%)	38 (6.6%)	21 (3.6%)	0	0	15 (12.6%)	7 (5.8%)	0	1 (1.8%)
Moderate	30 (3.9%)	34 (4.5%)	18 (3.1%)	22 (3.8%)	0	0	10 (8.4%)	11 (9.2%)	2 (3.8%)	1 (1.8%)
Severe	13 (1.7%)	8 (1.0%)	7 (1.2%)	6 (1.0%)	0	0	6 (5.0%)	2 (1.7%)	0	0
Missing	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.9: Important Identified Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Anemia

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Anemia						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	195 (16.3%)	153 (16.1%)	8 (19.5%)	1 (2.9%)	31 (26.1%)	2 (3.8%)
Serious	28 (2.3%)	19 (2.0%)	2 (4.9%)	0	7 (5.9%)	0
Leading to discontinuation	1 (0.1%)	1 (0.1%)	0	0	0	0
Fatal outcome	1 (0.1%)	1 (0.1%)	0	0	0	0
Number of recurrent AESI	263	204	13	1	43	2
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0702	0.0615	0.0683	0.0711	0.2077	0.0903
Severity (worst)*						
Mild	96 (8.0%)	80 (8.4%)	1 (2.4%)	0	15 (12.6%)	0
Moderate	69 (5.8%)	52 (5.5%)	4 (9.8%)	1 (2.9%)	10 (8.4%)	2 (3.8%)
Severe	27 (2.3%)	18 (1.9%)	3 (7.3%)	0	6 (5.0%)	0
Missing	3 (0.3%)	3 (0.3%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.10 : AESIs: Anemia

	NS-304 N = 37 n (%)
Patients with at least one AESI	10 (27.0%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	13
Patient-years of observation	111.81
Average annualized event rate	0.1163
Severity (worst) (b)	
Asymptomatic	0
Mild	5 (13.5%)
Moderate	5 (13.5%)
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Anemia, decrease in hemoglobin concentration.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 921 post-marketing cases with events of anemia and/or decreased hemoglobin have been received. The estimated reporting rate was 4.4% (921 cases/21,142 exposed patients). Transfusion was documented in 214 of the 921 cases of anemia.

Data from post-marketing data sources were consistent with data observed in Study AC-065A302 (GRIPHON). In the TRITON study, a higher incidence of AEs denoting anemia was observed in both the triple (selexipag) and double (placebo) combination therapy groups. More patients in the triple (selexipag) as compared to the double therapy (placebo) group experienced an anemia event; however, there was no difference in the magnitude of hemoglobin decrease as well as the proportion of patients with hemoglobin decrease between the treatment groups (measured from baseline until end-of-study).

In the majority of cases received from all sources, the events of anemia, including those treated by transfusion, occurred in a context of severe medical conditions or other comorbidities that can lead to progressive anemia, such as cardiac failure, renal failure, CTD, or bleeding, or in patients concomitantly treated with medications such as anti-thrombotics, platelet aggregation inhibitors, or other medications including ERA with known effects on blood hemoglobin levels.

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.

Preventability

Anemia is measurable, monitorable, and treatable.

Anemia and hemoglobin decreased are listed in section 4.8 of the UPTRAVI SmPC as common reported adverse reactions 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.

In addition, the following information is provided in section 4.8 under 'Laboratory abnormalities':

"Haemoglobin decrease

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from -0.34 to -0.02 g/dL in the selexipag group compared to -0.05 to 0.25 g/dL in the placebo group. A decrease from baseline in hemoglobin concentration to below 10 g/dL was reported in 8.6% of selexipag-treated patients and 5.0% of placebo treated patients."

Impact on the Risk-Benefit Balance of the Product

Anemia is measurable, monitorable, and treatable. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Anemia may require blood transfusion.

Important Identified Risk: Hyperthyroidism

Potential Mechanisms

Prostacyclin plays an important role in the modulation of thyroid function (Silva 2009). It was suggested that prostacyclin stimulates TSH secretion (Marvisi 2006). Previous investigations have shown that prostacyclin stimulate intracellular thyroid processes through interaction with specific surface membrane-bound receptors and mimic many of the effects of TSH on the thyroidal metabolism and in vivo stimulate the synthesis and secretion of thyroid hormone (Virgolini 1988).

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.11: Important Identified Risk: Treatment-emergent Adverse Events of Hyperthyroidism in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	15 / 574 (2.6%)	8 / 578 (1.4%)	1.888 (0.807 - 4.419)	0.0203 [936.4]	0.0126 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	0 / 119 (0)	1 / 120 (0.8%)	NA	0 [207.1]	0.0054 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.12: Important Identified Risk: Treatment-emergent Adverse Events of Hyperthyroidism in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	31 / 953 (3.3%)	0.0109 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	0 / 37 (0)	0 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	0 / 119 (0)	0 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.13: Important Identified Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Hyperthyroidism

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Hyperthyroidism										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	15 (1.9%)	9 (1.2%)	15 (2.6%)	8 (1.4%)	0	0	0	1 (0.8%)	0	0
Serious	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0	0
Leading to discontinuation	2 (0.3%)	1 (0.1%)	2 (0.3%)	1 (0.2%)	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.632	-	1.888	-	NA	-	NA	-	NA	-
95% CI	(0.719 - 3.708)		(0.807 - 4.419)							
Number of recurrent AESI	19	12	19	11	0	0	0	1	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0161	0.0110	0.0203	0.0126	0	0	0	0.0054	0	0
Severity (worst)*										
Mild	13 (1.7%)	3 (0.4%)	13 (2.3%)	3 (0.5%)	0	0	0	0	0	0
Moderate	2 (0.3%)	4 (0.5%)	2 (0.3%)	3 (0.5%)	0	0	0	1 (0.8%)	0	0
Severe	0	0	0	0	0	0	0	0	0	0
Missing	0	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.14: Important Identified Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Hyperthyroidism

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Hyperthyroidism						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	31 (2.6%)	31 (3.3%)	0	0	0	0
Serious	5 (0.4%)	5 (0.5%)	0	0	0	0
Leading to discontinuation	2 (0.2%)	2 (0.2%)	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	36	36	0	0	0	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0096	0.0109	0	0	0	0
Severity (worst)*						
Mild	17 (1.4%)	17 (1.8%)	0	0	0	0
Moderate	12 (1.0%)	12 (1.3%)	0	0	0	0
Severe	2 (0.2%)	2 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.15: AESIs: Hyperthyroidism

	NS-304 N = 37 n (%)
No patient observed	

MedDRA version 22.0 was used to classify the AESIs.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Hyperthyroidism.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 97 post-marketing reports including events of hyperthyroidism were received. Taking into account the estimated exposure of 21,142 patients, the estimated cumulative reporting rate is 0.5%. Data from post-marketing data sources were consistent with data observed in the clinical studies.

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.

Preventability

Hyperthyroidism (subclinical or overt) is measurable, monitorable and treatable.

The following information is included in the SmPC:

Section 4.4 ‘Special warnings and precautions for use’

“*Hyperthyroidism*

Hyperthyroidism has been observed with UPTRAVI. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism.”

In section 4.8 ‘Undesirable effects’, hyperthyroidism and TSH decreased are listed as a commonly reported adverse reactions.

In addition, the following information is provided in section 4.8 under 'Laboratory abnormalities':

'Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, hyperthyroidism was reported for 1.6% of patients in the selexipag group, compared to no case in the placebo group (see section 4.4). A reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median TSH was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.'

Impact on the Risk-Benefit Balance of the Product

Hyperthyroidism (subclinical or overt) is measurable, monitorable, and treatable. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Hyperthyroidism requires dedicated treatment and may require hospitalization.

Important Identified Risk: Concomitant use with strong inhibitors of CYP2C8

Potential Mechanisms

Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8. Gemfibrozil is the only known strong CYP2C8 inhibitor based on experimental DDI data obtained with multiple dosing (Niemi 2003).

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

No patient was treated concomitantly with a strong CYP2C8 inhibitor during the GRIPHON, TRITON and TRACE double-blind studies.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of for the list of medications which are strong inhibitors of CYP2C8.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, co-administration of strong CYP2C8 inhibitors with selexipag where patients initiated selexipag on top of ongoing concomitant gemfibrozil was

reported in 3 post-marketing cases. 1 of the patients was unable to titrate selexipag beyond 200 µg bid, due to the severity of prostacyclin-associated events; both gemfibrozil and selexipag were discontinued. In the second patient, the maximum documented dose of selexipag was 1400 µg bid, which was gradually down-titrated due to ADRs; lower doses were reported to be associated with unchanged pulmonary pressures and fewer side effects. The third patient was prescribed gemfibrozil when on selexipag treatment (1200 µg bid) and experienced severe pain after one dose of gemfibrozil; atorvastatin and gemfibrozil were discontinued, and action taken with selexipag was unknown.

Risk Factors and Risk Groups

Patients treated with gemfibrozil and selexipag.

Preventability

Substances that strongly inhibit the activity of these CYP2C8 enzymes should not be used with selexipag and are contraindicated (SmPC section 4.3). The doctor and the patient will be informed about the interaction between selexipag and gemfibrozil in the product information documents.

Impact on the Risk-Benefit Balance of the Product

This identified DDI does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Prescribers need to monitor concomitant treatments given to selexipag-treated patients.

Important Potential Risk: Pulmonary edema associated with PVOD

Potential Mechanisms

Pulmonary edema following administration of any pulmonary vasodilator used for treatment of PAH could be due to previously unrecognized secondary angioproliferative process caused by post-capillary obstruction, eg, PVOD and/or due to combined pre-capillary and post-capillary pulmonary hypertension (Galiè 2015b, Galiè 2016, Opitz 2016).

Evidence Source(s) and Strength of Evidence

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 PVOD. 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 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.

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.16: Important Potential Risk: Treatment-emergent Adverse Events of Pulmonary Edema Associated with PVOD in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	4 / 574 (0.7%)	5 / 578 (0.9%)	0.806 (0.217 - 2.985)	0.0053 [936.4]	0.0069 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	2 / 119 (1.7%)	1 /120 (0.8%)	2.017 (0.185 - 21.945)	0.0145 [207.1]	0.0054 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.17: Important Potential Risk: Treatment-emergent Adverse Events of Pulmonary Edema Associated with PVOD in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	9 / 953 (0.9%)	0.0030 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	2 / 119 (1.7%)	0.0145 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.18: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: PVOD Associated with Pulmonary Edema

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
PVOD Associated with Pulmonary Edema										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	6 (0.8%)	6 (0.8%)	4 (0.7%)	5 (0.9%)	0	0	2 (1.7%)	1 (0.8%)	0	0
Serious	3 (0.4%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0	0	1 (0.8%)	1 (0.8%)	0	0
Leading to discontinuation	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0	0
Fatal outcome	0	1 (0.1%)	0	0	0	0	0	1 (0.8%)	0	0
Relative Risk	0.979	-	0.806	-	NA	-	2.017	-	NA	-
95% CI	(0.317 - 3.024)		(0.217 - 2.985)				(0.185 - 21.945)			
Number of recurrent AESI	8	7	5	6	0	0	3	1	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0068	0.0064	0.0053	0.0069	0	0	0.0145	0.0054	0	0
Severity (worst)*										
Mild	0	0	0	0	0	0	0	0	0	0
Moderate	3 (0.4%)	4 (0.5%)	2 (0.3%)	4 (0.7%)	0	0	1 (0.8%)	0	0	0
Severe	3 (0.4%)	2 (0.3%)	2 (0.3%)	1 (0.2%)	0	0	1 (0.8%)	1 (0.8%)	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.19: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: PVOD Associated with Pulmonary Edema

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
PVOD Associated with Pulmonary Edema						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	11 (0.9%)	9 (0.9%)	0	0	2 (1.7%)	0
Serious	5 (0.4%)	4 (0.4%)	0	0	1 (0.8%)	0
Leading to discontinuation	2 (0.2%)	2 (0.2%)	0	0	0	0
Fatal outcome	2 (0.2%)	2 (0.2%)	0	0	0	0
Number of recurrent AESI	13	10	0	0	3	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0035	0.0030	0	0	0.0145	0
Severity (worst)*						
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0
Moderate	4 (0.3%)	3 (0.3%)	0	0	1 (0.8%)	0
Severe	6 (0.5%)	5 (0.5%)	0	0	1 (0.8%)	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.20: AESIs: PVOD Associated with Pulmonary Edema

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	1 (2.7%)
Moderate	0
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Pulmonary edema associated with PVOD.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 34 post-marketing reports including events of PVOD or veno-occlusive disease have been received, corresponding to a cumulative reporting rate of 0.16% (34 cases / 21,142 exposed patients). Concurrent events of pulmonary edema/acute pulmonary edema were reported in 10 of these 34 cases; selexipag was discontinued in 4 cases and remained ongoing in 6 cases (at a decreased dose in 1 case).

Data from post-marketing data sources were consistent with data observed in the clinical studies.

Risk Factors and Risk Groups

Patients with undiagnosed PVOD and on concurrent medications leading to pulmonary vasodilatation.

Preventability

Undiagnosed pre-existing PVOD or post-capillary pulmonary artery disease may unmask itself with administration of PAH-specific therapies that are pulmonary vasodilators. The use of any PAH-specific therapies in PVOD patients may therefore lead to pulmonary edema.

As stated in SmPC section 4.4 (‘Special warnings and precautions for use’): “Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with

PVOD. Consequently, if signs of pulmonary edema occur when UPTRAVI is administered in patients with PAH, the possibility of PVOD should be considered. If confirmed, treatment is to be discontinued."

Impact on the Risk-Benefit Balance of the Product

Taking into account the severity of the PAH indication, and pathological, genetic, and clinical similarities between PVOD and PAH resulting in a diagnostic and therapeutic challenge, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Some patients with a specific blockage of the blood vessels in the lungs may have a very rare type of high blood pressure in the lungs called PVOD. These patients can get a build-up of fluid in the lungs if they take UPTRAVI or other medicines that widen blood vessels in the lung. If there are signs of a build-up of fluid in the lungs that the doctor thinks might be due to this disease, treatment with UPTRAVI should be stopped.

The diagnosis of PVOD / pulmonary capillary hemangiomatosis can be established with a high probability by the combination of clinical suspicion, physical examination, bronchoscopy, and radiological findings. Diagnosis of PVOD may require hospitalization and change in the therapy administered.

Important Potential Risk: MACE

Potential Mechanisms

No deleterious effect of selexipag on MACE is evident. Neither scientific literature nor non-clinical data indicate a risk of harmful effects of prostacyclin and its analogues on MACE.

Evidence Source(s) and Strength of Evidence

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.

Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.21: Important Potential Risk: Treatment-emergent Adverse Events of MACE in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	25 / 574 (4.4%)	23 / 578 (4.0%)	1.095 (0.629 - 1.905)	0.0310 [936.4]	0.0308 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	3 / 119 (2.5%)	7 /120 (5.8%)	0.432 (0.114 - 1.632)	0.0145 [207.1]	0.0482 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.22: Important Potential Risk: Treatment-emergent Adverse Events of MACE in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	77 / 953 (8.1%)	0.0256 [3315.4]
PAH	NS-304/-02 + NS-304/-03	8 / 41 (19.5%)	0.0473 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	3 / 119 (2.5%)	0.0145 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.23: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: MACE

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
MACE										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	28 (3.6%)	30 (3.9%)	25 (4.4%)	23 (4.0%)	0	0	3 (2.5%)	7 (5.8%)	0	0
Serious	23 (3.0%)	21 (2.8%)	23 (4.0%)	16 (2.8%)	0	0	0	5 (4.2%)	0	0
Leading to discontinuation	12 (1.5%)	5 (0.7%)	12 (2.1%)	4 (0.7%)	0	0	0	1 (0.8%)	0	0
Fatal outcome	15 (1.9%)	12 (1.6%)	15 (2.6%)	10 (1.7%)	0	0	0	2 (1.7%)	0	0
Relative Risk	0.914	-	1.095	-	NA	-	0.432	-	NA	-
95% CI	(0.552 - 1.515)		(0.629 - 1.905)				(0.114 - 1.632)			
Number of recurrent AESI	32	36	29	27	0	0	3	9	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0271	0.0330	0.0310	0.0308	0	0	0.0145	0.0482	0	0
Severity (worst)*										
Mild	3 (0.4%)	4 (0.5%)	1 (0.2%)	3 (0.5%)	0	0	2 (1.7%)	1 (0.8%)	0	0
Moderate	6 (0.8%)	8 (1.0%)	5 (0.9%)	6 (1.0%)	0	0	1 (0.8%)	2 (1.7%)	0	0
Severe	18 (2.3%)	17 (2.2%)	18 (3.1%)	13 (2.2%)	0	0	0	4 (3.3%)	0	0
Missing	1 (0.1%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.24: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: MACE

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
MACE						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	88 (7.3%)	77 (8.1%)	8 (19.5%)	0	3 (2.5%)	0
Serious	76 (6.3%)	68 (7.1%)	8 (19.5%)	0	0	0
Leading to discontinuation	16 (1.3%)	15 (1.6%)	1 (2.4%)	0	0	0
Fatal outcome	59 (4.9%)	53 (5.6%)	6 (14.6%)	0	0	0
Number of recurrent AESI	97	85	9	0	3	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0259	0.0256	0.0473	0	0.0145	0
Severity (worst)*						
Mild	6 (0.5%)	4 (0.4%)	0	0	2 (1.7%)	0
Moderate	12 (1.0%)	10 (1.0%)	1 (2.4%)	0	1 (0.8%)	0
Severe	66 (5.5%)	59 (6.2%)	7 (17.1%)	0	0	0
Missing	4 (0.3%)	4 (0.4%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.25: AESIs: MACE

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	1 (2.7%)
Patients with at least one AESI with a fatal outcome	1 (2.7%)
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	0
Moderate	0
Severe	1 (2.7%)
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of MACE.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 457 post-marketing cases containing MACE have been received. The estimated cumulative reporting rate is 2.2% (457 cases / 21,142 patients exposed).

Consistent with data from Study AC-065A302/GRIPHON and all other completed studies, MACE were reported in patients with severe PAH disease, receiving multiple medications, and occurred in a context of other pre-existing cardiovascular comorbidities or prior history of stroke or myocardial infarction, which are known to represent independent factors increasing the risk for adverse cardiovascular or cerebrovascular events. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies or with commercial product.

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, cardiovascular risk factor and underlying cardiovascular comorbidities treatment, is part of general medical management of each patient.

Preventability

Proper management of patients with pre-existing cardiac disease (either in the context of underlying PAH, CTD, or other cardiac co morbidities) should be conducted as per clinical practice.

In addition, as stated in the UPTRAVI SmPC in section 4.3 'Contraindications', selexipag treatment is contraindicated in patients with the following conditions:

- Severe coronary heart disease or unstable angina.
- Myocardial infarction within the last 6 months.
- Decompensated cardiac failure if not under close medical supervision.
- Severe arrhythmias.
- Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months.
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

Impact on the Risk-Benefit Balance of the Product

Taking into account the severity of the PAH indication, and additional impact of the cardiovascular and cerebrovascular comorbidities associated with more severe clinical symptoms and a lower exercise tolerance, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Events may require hospitalization of various duration, conservative and/or surgical treatment, may affect the activities of daily living and prognosis of these patients.

Important Potential Risk: Renal function impairment / acute renal failure

Potential Mechanisms

No deleterious effect of selexipag on renal function is evident. Neither scientific literature nor non-clinical data indicate a risk of harmful effects of prostacyclin and its analogues on renal function. In contrast, the activation of IP receptors by endogenous prostacyclin is critical for normal renal function, including regulating renal blood flow, glomerular filtration rate, secretion of renin, glomerular and tubular growth, tubular transport processes, and cell fate (Nasrallah 2005).

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.26: Important Potential Risk: Treatment-emergent Adverse Events of Renal Function Impairment / Acute Renal Failure in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	33 / 574 (5.7%)	19 / 578 (3.3%)	1.749 (1.007 - 3.039)	0.0406 [936.4]	0.0251 [875.9]
PAH	NS-304/-02	0 / 33 (0)	1 / 10 (10.0%)	NA	0 [13.0]	0.5407 [3.7]
PAH	AC-065A308	12 / 119 (10.1%)	5 /120 (4.2%)	2.420 (0.880 - 6.658)	0.0628 [207.1]	0.0321 [186.9]
PAH	AC-065A404	0 / 53 (0)	1 / 55 (1.8%)	NA	0 [22.2]	0.0390 [25.7]

All selexipag studies

Table SVII.27: Important Potential Risk: Treatment-emergent Adverse Events of Renal Function Impairment / Acute Renal Failure in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	72 / 953 (7.6%)	0.0277 [3315.4]
PAH	NS-304/-02 + NS-304/-03	3 / 41 (7.3%)	0.0158 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	12 / 119 (10.1%)	0.0628 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.28: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Renal Function Impairment / Acute Renal Failure

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Renal Function Impairment / Acute Renal Failure										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	45 (5.8%)	26 (3.4%)	33 (5.7%)	19 (3.3%)	0	1 (10.0%)	12 (10.1%)	5 (4.2%)	0	1 (1.8%)
Serious	14 (1.8%)	9 (1.2%)	10 (1.7%)	7 (1.2%)	0	0	4 (3.4%)	2 (1.7%)	0	0
Leading to discontinuation	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	0	0	0	0	0	0
Fatal outcome	3 (0.4%)	3 (0.4%)	2 (0.3%)	3 (0.5%)	0	0	1 (0.8%)	0	0	0
Relative Risk	1.695	-	1.749	-	NA	-	2.420	-	NA	-
95% CI	(1.057 - 2.719)		(1.007 - 3.039)				(0.880 - 6.658)			
Number of recurrent AESI	51	31	38	22	0	2	13	6	0	1
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0433	0.0284	0.0406	0.0251	0	0.5407	0.0628	0.0321	0	0.0390
Severity (worst)*										
Mild	13 (1.7%)	9 (1.2%)	11 (1.9%)	6 (1.0%)	0	0	2 (1.7%)	2 (1.7%)	0	1 (1.8%)
Moderate	20 (2.6%)	10 (1.3%)	14 (2.4%)	7 (1.2%)	0	1 (10.0%)	6 (5.0%)	2 (1.7%)	0	0
Severe	12 (1.5%)	6 (0.8%)	8 (1.4%)	5 (0.9%)	0	0	4 (3.4%)	1 (0.8%)	0	0
Missing	0	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.29: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Renal Function Impairment / Acute Renal Failure

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Renal function impairment / acute renal failure						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	87 (7.3%)	72 (7.6%)	3 (7.3%)	0	12 (10.1%)	0
Serious	23 (1.9%)	18 (1.9%)	1 (2.4%)	0	4 (3.4%)	0
Leading to discontinuation	2 (0.2%)	2 (0.2%)	0	0	0	0
Fatal outcome	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Number of recurrent AESI	108	92	3	0	13	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0288	0.0277	0.0158	0	0.0628	0
Severity (worst)*						
Mild	28 (2.3%)	26 (2.7%)	0	0	2 (1.7%)	0
Moderate	39 (3.3%)	31 (3.3%)	2 (4.9%)	0	6 (5.0%)	0
Severe	19 (1.6%)	14 (1.5%)	1 (2.4%)	0	4 (3.4%)	0
Missing	1 (0.1%)	1 (0.1%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.30: AESIs: Renal Function Impairment / Acute Renal Failure

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	1 (2.7%)
Moderate	0
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Renal function impairment/acute renal failure.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 592 post-marketing cases describing renal function impairment / acute renal failure events have been received. The estimated cumulative post-marketing reporting rate is 2.8% (592 cases / 21,142 exposed patients).

Consistent with data from Study AC-065A302/GRIPHON and all other completed studies, the majority of these events were temporally associated with hemodynamic compromise due to PAH disease progression / right ventricular failure, or in association with other concurrent illnesses (eg, sepsis, hypovolemic shock) that can result in a transient effect on renal function as a secondary complication, or were attributed to other concomitant medications (ie, diuretics, digoxin) that can affect renal function.

Reported events of renal failure or renal function impairment are considered unlikely to be related to selexipag administration. The absence of an adverse effect of selexipag on renal function is supported by the short term and reversible nature of the majority of these events while selexipag treatment was continued. Renal function usually improved with improved cardiac function.

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.

Preventability

Regular monitoring of renal functions of each patient with acute heart failure or other concurrent illnesses leading to hemodynamic decompensation should be conducted, as per standard medical care.

Impact on the Risk-Benefit Balance of the Product

Taking into account the severity of the indication and high prevalence of associated renal function impairment in PAH patients, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Impaired renal function is measurable, monitorable and treatable. Acute renal failure / renal impairment requires therapeutic intervention, hospitalization or dialysis. Measuring renal function in PAH patients during regular monitoring is recommended in the current *ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension* as part of the comprehensive evaluation for any evidence of clinical deterioration due to progression of PH (right ventricular dysfunction, right ventricular failure, and/or secondary organ dysfunction) or due to a concomitant illness (Galiè 2016).

Important Potential Risk: Bleeding events

Potential Mechanisms

Selexipag is a weak platelet aggregation inhibitor (UPTRAVI SmPC, 2024). In healthy participants, selexipag did not show any effects on PD and PK of warfarin. In healthy participants and PAH or chronic thromboembolic pulmonary hypertension patients, selexipag use was associated with a decrease in mean plasma vWF; however, no decrease in individual vWF below the lower limit of the normal range was observed, nor were associated hemorrhagic AEs of concern reported.

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.31: Important Potential Risk: Treatment-emergent Adverse Events of Bleeding Events in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	95 / 574 (16.6%)	96 / 578 (16.6%)	0.996 (0.769 - 1.291)	0.1602 [936.4]	0.1530 [875.9]
PAH	NS-304/-02	3 / 33 (9.1%)	2 / 10 (20.0%)	0.455 (0.088 - 2.351)	0.2301 [13.0]	0.8111 [3.7]
PAH	AC-065A308	26 / 119 (21.8%)	27 /120 (22.5%)	0.971 (0.604 - 1.562)	0.2028 [207.1]	0.2034 [186.9]
PAH	AC-065A404	7 / 53 (13.2%)	7 / 55 (12.7%)	1.038 (0.391 - 2.758)	0.4062 [22.2]	0.3116 [25.7]

All selexipag studies

Table SVII.32: Important Potential Risk: Treatment-emergent Adverse Events of Bleeding Events in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	196 / 953 (20.6%)	0.0995 [3315.4]
PAH	NS-304/-02 + NS-304/-03	14 / 41 (34.1%)	0.0945 [190.4]
PAH	AC-065A201	18 / 37 (48.6%)	0.3667 [111.8]
PAH	AC-065A304	4 / 34 (11.8%)	0.2842 [14.1]
PAH	AC-065A308	26 / 119 (21.8%)	0.2028 [207.1]
PAH	AC-065A404	7 / 53 (13.2%)	0.4062 [22.2]

Table SVII.33: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Bleeding Events

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Bleeding Events										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	131 (16.8%)	132 (17.3%)	95 (16.6%)	96 (16.6%)	3 (9.1%)	2 (20.0%)	26 (21.8%)	27 (22.5%)	7 (13.2%)	7 (12.7%)
Serious	30 (3.9%)	27 (3.5%)	23 (4.0%)	22 (3.8%)	0	0	7 (5.9%)	5 (4.2%)	0	0
Leading to discontinuation	2 (0.3%)	5 (0.7%)	2 (0.3%)	4 (0.7%)	0	0	0	1 (0.8%)	0	0
Fatal outcome	2 (0.3%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0	0	0	1 (0.8%)	0	0
Relative Risk	0.972	-	0.996	-	0.455	-	0.971	-	1.038	-
95% CI	(0.780 - 1.211)		(0.769 - 1.291)		(0.088 - 2.351)		(0.604 - 1.562)		(0.391 - 2.758)	
Number of recurrent AESI	204	183	150	134	3	3	42	38	9	8
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.1731	0.1676	0.1602	0.1530	0.2301	0.8111	0.2028	0.2034	0.4062	0.3116
Severity (worst)*										
Mild	67 (8.6%)	70 (9.2%)	49 (8.5%)	46 (8.0%)	1 (3.0%)	1 (10.0%)	11 (9.2%)	18 (15.0%)	6 (11.3%)	5 (9.1%)
Moderate	45 (5.8%)	42 (5.5%)	31 (5.4%)	35 (6.1%)	2 (6.1%)	1 (10.0%)	11 (9.2%)	4 (3.3%)	1 (1.9%)	2 (3.6%)
Severe	19 (2.4%)	20 (2.6%)	15 (2.6%)	15 (2.6%)	0	0	4 (3.4%)	5 (4.2%)	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.34: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Bleeding Events

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Bleeding Events						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	247 (20.6%)	196 (20.6%)	14 (34.1%)	4 (11.8%)	26 (21.8%)	7 (13.2%)
Serious	73 (6.1%)	61 (6.4%)	4 (9.8%)	1 (2.9%)	7 (5.9%)	0
Leading to discontinuation	6 (0.5%)	6 (0.6%)	0	0	0	0
Fatal outcome	10 (0.8%)	9 (0.9%)	1 (2.4%)	0	0	0
Number of recurrent AESI	403	330	18	4	42	9
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.1075	0.0995	0.0945	0.2842	0.2028	0.4062
Severity (worst)*						
Mild	109 (9.1%)	87 (9.1%)	3 (7.3%)	2 (5.9%)	11 (9.2%)	6 (11.3%)
Moderate	88 (7.3%)	67 (7.0%)	8 (19.5%)	1 (2.9%)	11 (9.2%)	1 (1.9%)
Severe	50 (4.2%)	42 (4.4%)	3 (7.3%)	1 (2.9%)	4 (3.4%)	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.35: AESIs: Bleeding Events

	NS-304 N = 37 n (%)
Patients with at least one AESI	18 (48.6%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	1 (2.7%)
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	41
Patient-years of observation	111.81
Average annualized event rate	0.3667
Severity (worst) (b)	
Asymptomatic	3 (8.1%)
Mild	11 (29.7%)
Moderate	4 (10.8%)
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Bleeding events.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 1,329 post-marketing cases containing bleeding events have been received; the estimated cumulative reporting rate is stable at 6.3% (1,329 cases / 21,142 exposed patients).

Consistent with data from Study AC-065A302/GRIPHON and all other completed studies, the post-marketing data sources showed that the majority of the bleeding events at various sites occurred in PAH patients with pre-existing risk factors, such as concomitant use of anticoagulants and antithrombotic agents, or occurred in a temporal association with underlying PAH disease progression / right ventricular failure, other concurrent illnesses (eg, gastritis, pre-existing vascular abnormalities in patients with CTD, infections), or in association with diagnostic or surgical procedures or injuries.

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.

Preventability

As no specific risk factors other than the underlying PAH disease have been identified to date, no proposal for preventability is feasible.

Impact on the Risk-Benefit Balance of the Product

Taking into account the severity of the indication and high prevalence of concomitant use of anticoagulant and antithrombotic medications in PAH patients, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

The public health impact depends on the nature and severity of the bleeding event that may require hospitalization, therapeutic or surgical intervention.

Important Potential Risk: Light-dependent non-melanoma skin malignancies

Potential Mechanisms

No propensity of selexipag for the development of malignancies, including skin malignancies was observed in non-clinical carcinogenicity studies in animals. The observed clinical pattern and incidence of BCC in GRIPHON is consistent with the expected incidence in the general and connective tissue disease patient populations. There is currently no evidence of causal association between selexipag treatment and occurrence of light-dependent non-melanoma skin malignancies.

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.36: Important Potential Risk: Treatment-emergent Adverse Events of Light-dependent Non-melanoma Skin Malignancies in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	4 / 574 (0.7%)	0 / 578 (0)	NA	0.0075 [936.4]	0 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	1 / 119 (0.8%)	2 / 120 (1.7%)	0.504 (0.046 - 5.486)	0.0048 [207.1]	0.0107 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.37: Important Potential Risk: Treatment-emergent Adverse Events of Light-dependent Non-melanoma Skin Malignancies in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	6 / 953 (0.6%)	0.0027 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	1 / 119 (0.8%)	0.0048 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.38: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Light-dependent Non-melanoma Skin Malignancies

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Light-dependent Non-melanoma Skin Malignancies										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	5 (0.6%)	2 (0.3%)	4 (0.7%)	0	0	0	1 (0.8%)	2 (1.7%)	0	0
Serious	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	2.449	-	NA	-	NA	-	0.504	-	NA	-
95% CI	(0.477 - 12.583)						(0.046 - 5.486)			
Number of recurrent AESI	8	2	7	0	0	0	1	2	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0068	0.0018	0.0075	0	0	0	0.0048	0.0107	0	0
Severity (worst)*										
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0	1 (0.8%)	1 (0.8%)	0	0
Moderate	3 (0.4%)	1 (0.1%)	3 (0.5%)	0	0	0	0	1 (0.8%)	0	0
Severe	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.

AEs are coded using MedDRA Version 22.0

Table SVII.39: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Light-dependent Non-melanoma Skin Malignancies

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Light-dependent Non-melanoma Skin Malignancies						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	7 (0.6%)	6 (0.6%)	0	0	1 (0.8%)	0
Serious	1 (0.1%)	1 (0.1%)	0	0	0	0
Leading to discontinuation	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	10	9	0	0	1	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0027	0.0027	0	0	0.0048	0
Severity (worst)*						
Mild	2 (0.2%)	1 (0.1%)	0	0	1 (0.8%)	0
Moderate	3 (0.3%)	3 (0.3%)	0	0	0	0
Severe	2 (0.2%)	2 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.

* The event experienced by the patient with the worst severity is used.

AEs are coded using MedDRA Version 22.0

Table SVII.40: AESIs: Light-dependent Non-melanoma Skin Malignancies

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	1 (2.7%)
Moderate	0
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Light-dependent non-melanoma skin malignancies.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 17 post-marketing reports including events denoting non-melanoma skin malignancies have been received. The incidence of reported skin malignancies appears consistent with the expected incidence in the general population, with an expected higher rate in patients with CTD compared to other PAH etiologies.

At present, there is no evidence that selexipag is associated with an increased risk of skin malignancies.

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.

Preventability

Regular skin check as per clinical practice.

Impact on the Risk-Benefit Balance of the Product

Considering the severity of the indication, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Intervention or hospitalization.

Important Potential Risk: Ophthalmological effects associated with retinal vascular system

Potential Mechanisms

Retinal vessel tortuosity in rats is considered to reflect exaggerated PD resulting in continuous blood vessel dilatation for the whole lifespan. There is no evidence of retinal vascular abnormalities associated with selexipag treatment in humans.

Evidence Source(s) and Strength of Evidence

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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.41: Important Potential Risk: Treatment-emergent Adverse Events of Ophthalmological Effects Associated with Retinal Vascular System in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	24 / 574 (4.2%)	15 / 578 (2.6%)	1.611 (0.854 - 3.039)	0.0299 [936.4]	0.0194 [875.9]
PAH	NS-304/-02	1 / 33 (3.0%)	0 / 10 (0)	NA	0.0767 [13.0]	0 [3.7]
PAH	AC-065A308	6 / 119 (5.0%)	8 / 120 (6.7%)	0.756 (0.271 - 2.114)	0.0386 [207.1]	0.0428 [186.9]
PAH	AC-065A404	0 / 53 (0)	2 / 55 (3.6%)	NA	0 [22.2]	0.0779 [25.7]

All selexipag studies

Table SVII.42: Important Potential Risk: Treatment-emergent Adverse Events of Ophthalmological Effects Associated with Retinal Vascular System in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	37 / 953 (3.9%)	0.0124 [3315.4]
PAH	NS-304/-02 + NS-304/-03	1 / 41 (2.4%)	0.0053 [190.4]
PAH	AC-065A201	4 / 37 (10.8%)	0.0358 [111.8]
PAH	AC-065A304	2 / 34 (5.9%)	0.1421 [14.1]
PAH	AC-065A308	6 / 119 (5.0%)	0.0386 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.43: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Ophthalmological Effects Associated with Retinal Vascular System

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Ophthalmological Effects Associated with Retinal Vascular System										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	31 (4.0%)	25 (3.3%)	24 (4.2%)	15 (2.6%)	1 (3.0%)	0	6 (5.0%)	8 (6.7%)	0	2 (3.6%)
Serious	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0	1 (0.8%)	0	0	1 (1.8%)
Leading to discontinuation	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.215	-	1.611	-	NA	-	0.756	-	NA	-
95% CI	(0.724 - 2.037)		(0.854 - 3.039)				(0.271 - 2.114)			
Number of recurrent AESI	37	27	28	17	1	0	8	8	0	2
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0314	0.0247	0.0299	0.0194	0.0767	0	0.0386	0.0428	0	0.0779
Severity (worst)*										
Mild	19 (2.4%)	17 (2.2%)	15 (2.6%)	9 (1.6%)	0	0	4 (3.4%)	7 (5.8%)	0	1 (1.8%)
Moderate	9 (1.2%)	8 (1.0%)	7 (1.2%)	6 (1.0%)	1 (3.0%)	0	1 (0.8%)	1 (0.8%)	0	1 (1.8%)
Severe	2 (0.3%)	0	1 (0.2%)	0	0	0	1 (0.8%)	0	0	0
Missing	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.44: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Ophthalmological Effects Associated with Retinal Vascular System

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Ophthalmological Effects Associated with Retinal Vascular System						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	46 (3.8%)	37 (3.9%)	1 (2.4%)	2 (5.9%)	6 (5.0%)	0
Serious	4 (0.3%)	3 (0.3%)	0	0	1 (0.8%)	0
Leading to discontinuation	1 (0.1%)	1 (0.1%)	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	52	41	1	2	8	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0139	0.0124	0.0053	0.1421	0.0386	0
Severity (worst)*						
Mild	29 (2.4%)	23 (2.4%)	0	2 (5.9%)	4 (3.4%)	0
Moderate	13 (1.1%)	11 (1.2%)	1 (2.4%)	0	1 (0.8%)	0
Severe	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Missing	1 (0.1%)	1 (0.1%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.45: AESIs: Ophthalmological Effects Associated with Retinal Vascular System

	NS-304 N = 37 n (%)
Patients with at least one AESI	4 (10.8%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	4
Patient-years of observation	111.81
Average annualized event rate	0.0358
Severity (worst) (b)	
Asymptomatic	0
Mild	3 (8.1%)
Moderate	1 (2.7%)
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Ophthalmological effects associated with retinal vascular system.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 440 post-marketing cases containing events under the 'Retinal disorders' SMQ (broad search) have been received. There were 40 post-marketing cases identified using the 'Retinal disorders' SMQ (narrow scope). None of these events were confirmed to be associated with retinal arterial tortuosity.

At present, there is no evidence that selexipag is associated with the occurrence of ophthalmological effects associated with the retinal vascular system.

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.

Preventability

Not applicable.

Impact on the Risk-Benefit Balance of the Product

Considering the severity of the indication, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

More severe cases of symptomatic retinal vascular abnormality may require therapeutic and/or surgical intervention, and/or modification in the concomitant treatment (eg, anticoagulants).

Important Potential Risk: GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

Potential Mechanisms

Intestinal intussusception was identified in young dogs, but not in rodents. This can be ascribed to IP-mediated effects on intestinal motility in a sensitive species at a particularly sensitive age; therefore, it is unlikely to be of relevance to the adult target population. Due to the known susceptibility of young dogs to develop intussusception and the safety margin of 2-fold (ie, corrected for potency; at 180-fold based on total exposure) for the active metabolite, the finding is considered as not relevant for adult humans.

Evidence Source(s) and Strength of Evidence

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 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.

Characterization of the Risk

Randomized, double-blind studies

Table SVII.46: Important Potential Risk: Treatment-emergent Adverse Events of GI Disturbances Denoting Intestinal Intussusception in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	1 / 574 (0.2%)	1 / 578 (0.2%)	1.007 (0.063 - 16.060)	0.0011 [936.4]	0.0023 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	1 / 119 (0.8%)	0 / 120 (0)	NA	0.0097 [207.1]	0 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.47: Important Potential Risk: Treatment-emergent Adverse Events of GI Disturbances Denoting Intestinal Intussusception in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	3 / 953 (0.3%)	0.0009 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	0 / 37 (0)	0 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	1 / 119 (0.8%)	0.0097 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.48: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	1 (0.8%)	0	0	0
Serious	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	1 (0.8%)	0	0	0
Leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.959	-	1.007	-	NA	-	NA	-	NA	-
95% CI	(0.178 - 21.559)		(0.063 - 16.060)							
Number of recurrent AESI	3	2	1	2	0	0	2	0	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0025	0.0018	0.0011	0.0023	0	0	0.0097	0	0	0
Severity (worst)*										
Mild	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	1 (0.8%)	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.

AEs are coded using MedDRA Version 22.0

Table SVII.49: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	4 (0.3%)	3 (0.3%)	0	0	1 (0.8%)	0
Serious	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Leading to discontinuation	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	5	3	0	0	2	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0013	0.0009	0	0	0.0097	0
Severity (worst)*						
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.

* The event experienced by the patient with the worst severity is used.

AEs are coded using MedDRA Version 22.0

Table SVII.50: AESIs: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)

	NS-304 N = 37 n (%)
No patient observed	

MedDRA version 22.0 was used to classify the AESIs.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction).

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 72 post-marketing cases including 1 or more GI disturbances suggestive of intestinal obstruction have been reported. Overall, 3 cases involved the PT Intestinal intussusception: (1) One elderly patient was diagnosed with appendix cancer; the event was assessed as not related by the reporter. (2) One case referred to an adult patient with ulcerative colitis who experienced intestinal intussusception after starting selexipag, with no causality assessment reported. (3) The 3rd case pertained to a patient diagnosed with diffuse large B-cell lymphoma 1.5 years after selexipag initiation who 1 year later experienced bilateral pneumonia, abdominal pain and developed life-threatening invagination of intestine. The reporter assessed these events as not related to selexipag and possibly associated with intestinal lesions due to diffuse large B-cell lymphoma. The remaining 69 cases pertained to other relevant comorbidities known to be associated with GI obstruction, such as partial colectomy, intestinal resection, gallstone ileus, diverticulitis; intestinal polyps, *Clostridium difficile* infection, or a medical history of connective tissue disease or scleroderma.

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).

Preventability

As no specific risk factors other than the underlying PAH disease associated with SSc have been identified to date, no proposal for preventability is feasible. In the current PIP, a waiver was granted for children from birth to less than 2 years (EMEA-000997-PIP01-10-M07).

See UPTRAVI SmPC, section 4.2:

"*Pediatric population*

The safety and efficacy of selexipag in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of selexipag in the pediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown (see section 5.3)."

Impact on the Risk-Benefit Balance of the Product

Taking into account the severity of the indication, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

Occurrence of intestinal obstruction requires prompt therapeutic and/or surgical intervention.

Important Potential Risk: Medication error

Potential Mechanisms

Selexipag is available only on prescription. A total of 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets) have been approved.

Evidence Source(s) and Strength of Evidence

As compared to controlled clinical trials in adult patients, 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) have been approved. 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 HCPs. Information regarding medication errors during selexipag initial titration and transition to maintenance dose is therefore only collected from post-approval use.

Characterization of the Risk

Selexipag has been approved in 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets), and the commercial presentations for UPTRAVI include the following: one titration pack of 140 tablets (200 µg) , one titration pack of 140 tablets (100 µg) for adult patients concomitantly treated with moderate CYP2C8 inhibitors or with moderate hepatic impairment, one pack of 10 tablets (200 µg), and 9 different packs of 60 tablets each (100, 200, 400, 600, 800, 1000, 1200, 1400, 1600 µg).

Starting patients on UPTRAVI involves dose titration, according to tolerability, to reach the individually appropriate dose for each patient.

General Population

For the general population, the recommended starting dose of UPTRAVI is 200 µg bid, approximately 12 hours apart. The dose is increased in increments of 200 µg bid, usually at weekly intervals until adverse pharmacological effects that cannot be tolerated or medically managed are experienced or until a maximum dose of 1600 µg bid is reached. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level (down-titration).

To aid the titration stage, UPTRAVI 200 µg bid film-coated tablets are used for up-titration to a dose of 800 µg bid. If a patient reaches a dose above 800 µg bid during the titration period, UPTRAVI 200 µg film-coated tablets together with one UPTRAVI 800 µg film-coated tablet should be used.

Once the maintenance dose is achieved, an equivalent single-tablet strength for the individualized maintenance dose can be prescribed (200-1600 µg tablets available). This allows the patient to take one tablet in the morning and one in the evening.

In clinical practice, the administration of multiple units (eg, tablets) required to achieve a single dose may be associated with dosing errors because of users making miscalculations or forgetting how many units have already been administered. For patients reaching doses of 300, 500 or 700 µg bid, the individualized maintenance dose will require prescription of 2 tablet strengths.

Patients concomitantly treated with moderate CYP2C8 inhibitors and patients with moderate hepatic impairment requiring a 50% reduction in the daily dose of selexipag

When co-administered with moderate CYP2C8 inhibitors, the total daily dose of selexipag is reduced by half. This can be achieved by either administering half the dose of selexipag bid or reducing the dosing frequency of selexipag to qd (SmPC section 4.2). The dosing frequency is based on the physician's choice.

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of treatment should be 100 µg bid or 200 µg qd and increased at weekly intervals by increments of 100 µg bid or 200 µg qd until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced (SmPC section 4.2). The starting dose (100 µg bid or 200 µg qd) is based on physician choice.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Medication error associated with selexipag tablets.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 2,005 post-marketing cases containing events denoting medication errors have been received from worldwide sources. Of these, 162 cases originated from EEA.

In 134 out of 162 cases reported from EEA, the reported medication error referred to a single occasion of accidental error, such as drug dose omission, extra dose, wrong technique in product usage process, wrong strength and/or voluntary/intentional change in selexipag dose or dosing regimen, accidental overdose or unspecified incorrect dose/dosage, inappropriate schedule of product administration, product prescribing error, also commonly seen with other medications without an initial up-titration process.

Twenty-eight out of 162 cases reported events denoting medication errors which reportedly occurred during selexipag initiation, titration and transition to maintenance dose. Nine cases referred to medication errors associated with selexipag titration and 19 cases referred to voluntary/intentional change in selexipag dose or dosing scheme modifications during titration phase that were reported as medication errors.

Analysis of cases of medication errors suggestive of selexipag titration errors did not indicate any trend for a specific systematic medication error during the selexipag initial titration phase. If associated AEs were reported, they mostly referred to non-serious well known ADRs with selexipag which also commonly occur in patients following initial up-titration scheme as described in the SmPC. No unanticipated pattern of medication error or AEs was identified.

Taking into account the estimated cumulative exposure since approval/launch in the EEA the estimated cumulative reporting rate of medication errors during selexipag initiation, titration and transition to maintenance dose was at 0.19% (9 cases/ 4,815 exposed patients).

Risk Factors and Risk Groups

Patients during initial selexipag up-titration phase.

Preventability

Treatment with selexipag should only be initiated by a certified physician experienced in the treatment of PAH and familiar with educational materials included in the Prescriber Kit.

Clear instructions on recommended daily dosing, titration and transition to maintenance dose are given in the respective national UPTRAVI product labelling documents and corresponding patient information leaflets. In addition, further educational materials are provided to patients and HCPs.

In the EU/EEA, as documented in Annex 6, all HCPs identified via a Controlled Access System (implemented nationally) who intend to prescribe and/or dispense selexipag are provided with educational material in a Prescriber Kit containing the following:

- Cover letter to the HCP.
- The SmPC.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 100 µg bid.

- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 200 µg bid.
- Patient Titration Guide included in the titration pack of the 100 µg tablets.
- Patient Titration Guide included in the titration pack of the 200 µg tablets.
- Package leaflet.

Impact on the Risk-Benefit Balance of the Product

This potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact

If a medication error is detected, correction and treatment adjustment may need to be performed.

At present, routine and additional risk minimization measures in place clearly and extensively educate HCPs as well as patients and appropriately address its purpose to minimize the occurrence of medication errors during initial selexipag up-titration or transition to individual maximum tolerated maintenance dose in the clinical practice.

A Category 3 PASS (EDUCATE) with the objective of evaluating medication error risk minimization measures during the selexipag titration phase is ongoing (see Part III.2.). The objectives in the current EDUCATE PASS protocol address the concepts of the educational materials for treatment initiation using 200 µg. These objectives are also considered applicable to the 100 µg selexipag tablets because the additional risk minimization measures are replicated for treatment initiation with the 100 µg selexipag tablets. Therefore, no modifications to the EDUCATE PASS are deemed necessary.

Furthermore, following introduction of the 100 µg selexipag tablet, the MAH will continue to provide dedicated analyses on all cases of medication error in the upcoming PBRERs, including information on the selexipag starting dose (100 µg or 200 µg), if available.

SVII.3.2. Presentation of the Missing Information

Missing Information: Use in pediatric patients

Evidence Source

Based on current medical practice and due to the lack of registered treatments for pediatric PAH as well as the high medical need (Abman 2015, Hansmann 2016, Hansmann 2017), it is not uncommon for treating physicians to prescribe pediatric patients drugs approved in adult PAH.

Cumulatively, since IBD up to 20 December 2020, 514 post-marketing cases have been received for children.

Consistent with the adult and elderly patient population, the most frequently reported AEs in pediatric patients were those reflecting the mode of action of selexipag, and typically occurred during the initial selexipag dose titration. The nature of the reported events in pediatric patients

was similar to other age groups, and consistent with expected events in patients with PAH and its associated comorbidities.

Population in Need of Further Characterization

Pediatric patients under the age of 18 years. In the current PIP, a waiver was granted for children from birth to less than 2 years (EMEA-000997-PIP01-10-M07).

Anticipated Risk/Consequence of the Missing Information

To date, no safety concern has been identified from the review of selexipag use in this patient population. There is no evidence that the safety profile of selexipag is expected to be different from that in the general (adult) target population.

To date, no safety concern has been identified from the review of selexipag use in this patient population.

Missing Information: Use in elderly patients over 75 years old

Evidence Source

In the pivotal Phase 3 AC-065A302/GRIPHON study, 99 elderly patients were treated with selexipag and 107 with placebo. Of the 99 patients on selexipag, 91 were aged between 65 and 74 years, and 8 patients were ≥75 years old (range 75–80 years).

In the TRITON study, 27 (22.0%) and 26 (21.0%) participants in the selexipag and placebo groups, respectively, were ≥65 years-of-age. No patients were >75 years old (range 21-75 years). In the TRACE study, 11 (20.8%) and 12 (21.8%) participants in the selexipag and placebo groups, respectively, were ≥65 years-of-age. No patients were >75 years old (range 19-75 years).

No patients >80 years were exposed to selexipag during the clinical development program.

There is no clinically relevant effect of age on the PK of selexipag and its active metabolite in healthy participants or PAH patients. Therefore, no adjustment to the dosing regimen is needed in elderly patients. No important differences regarding efficacy or safety were observed between elderly and non-elderly patients.

Cumulatively, since IBD up to 20 December 2020, 3339 post-marketing cases have been received for patients aged ≥75 years.

Cumulative safety information pertaining to patients aged ≥75 years showed that the nature and pattern of reported events were comparable between patients aged ≥18 to <75 years and those aged ≥75 years. As expected, the majority of AEs reflected the mode of action of selexipag, ie, known prostacyclin-like reactions typically occurring during initial dose titration, and symptoms of the underlying PAH disease.

Population in Need of Further Characterization

Patients >75 years old.

Anticipated Risk/Consequence of the Missing Information

There is no evidence that the safety profile of selexipag is expected to be different than that in the general (adult) target population. To date, no safety concern has been identified from the review of selexipag use in this patient population.

Missing Information: Use during pregnancy and lactation

Evidence Source

Pregnant or breast-feeding women were excluded from the clinical trials with selexipag.

As described in the current ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, pregnancy is associated with a very high risk to mother and fetus, and should be discouraged. Effective contraception is considered mandatory (Galiè 2016).

Per UPTRAVI SmPC, section 4.6 'Fertility, pregnancy and lactation':

Women of Childbearing Potential

Women of childbearing potential should practice effective contraception while taking selexipag (see section 4.4).

Pregnancy

There are no data from the use of selexipag in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Selexipag and its main metabolite showed 20- to 80-times lower IP receptor potency in vitro for animal species used in reproductive toxicity testing compared to humans. Therefore, safety margins for potential IP receptor-mediated effects on reproduction are accordingly lower than for non-IP-related effects (see section 5.3).

UPTRAVI is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, selexipag or its metabolites are excreted in milk (see section 5.3). A risk to the suckling child cannot be excluded. UPTRAVI should not be used during breast-feeding."

Cumulatively, since IBD (21 December 2015) and up to the data cut-off point for the most recent PBRER/PSUR (20 December 2020), 46 confirmed pregnancies in selexipag-treated patients have been reported, including 11 from interventional clinical trials, 17 from noninterventional solicited clinical studies, and 18 from spontaneous source (1 spontaneous case was from a literature source). Drug exposure was during the first trimester in 22 cases; selexipag was started 6 weeks prior to birth in 1 case; time of exposure was unknown in 19 cases; and pregnancy was confirmed after selexipag discontinuation in 4 cases.

To date, 15 pregnant patients gave birth. Of these, 1 case reported live birth of a term baby, 3 cases reported live births with gestational age not reported and the remaining 11 cases reported live births of premature neonates. Eleven patients gave birth via Caesarean section: 8 babies were premature, born at Week 26 (1 case), Week 28 (1 case), Week 31 (2 cases), Week 33, Week 35,

probably Week 36, and Week 36+3 days of gestation; 1 baby was born at Week 37; and gestational age was not reported for 2 babies.

Three of the prematurely born babies had respiratory distress syndrome and foetal distress syndrome: 1 baby (born at Week 35) required continuous positive airway pressure and had secundum atrial septal defect seen on neonatal echocardiogram; however, the baby was "doing well" at 10 weeks of age. One baby (born at Week 31) was admitted to a neonatal intensive care unit with neonatal respiratory distress syndrome, requiring positive pressure ventilation due to cyanosis, then continuous positive airway pressure and doses of surfactant. The remaining baby case (born at Week 28) reported that the mother was admitted to the hospital as the baby was in distress; the baby was a female with a birth weight of 815 grams, Apgar scores were not provided, and the mother died after birth.

There were no neonatal abnormalities reported for the remaining babies.

Eighteen pregnancies had an outcome of abortion (10 induced abortions, 8 spontaneous/missed abortions), ongoing pregnancy was reported in 10 cases, 1 pregnancy was lost to follow-up in a patient who died, 1 case of pregnancy had an unknown outcome, 1 case reported ectopic pregnancy.

No safety concern has been identified from the review of data referring to patients who became pregnant while being treated with selexipag.

To date, no reports of selexipag use during lactation have been received.

Population in Need of Further Characterization

Pregnant and lactating women.

Anticipated Risk/Consequence of the Missing Information

To date, no safety concern has been identified from the review of selexipag use in this patient population. Studies in animals do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Missing Information: Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

Evidence Source

Based on non-clinical data, CYP2C8 and CYP3A4 were considered to be involved in the metabolism of both selexipag and its active metabolite, ACT-333679. CYP2C8 was identified as the only CYP isoform catalyzing the aromatic hydroxylation of ACT 333679 to P10, one of the major metabolites detected in human feces and in vitro with human liver microsomes. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite.

The effect of inhibitors of UGT1A3 and UGT2B7 (such as valproic acid, probenecid, and fluconazole) on exposure to selexipag or its active metabolite has not been studied.

Cumulatively, since IBD up to 20 December 2020, 51 cases with concomitant use of UGT1A3 and UGT2B7 inhibitors, ie, fluconazole (19 cases), valproate/valpromide (28 cases), valproic acid (2 cases) or probenecid (2 cases) were reported.

To date, no safety concern has been identified from the review of data referring to selexipag patients concomitantly treated with inhibitors of UGT1A3 and UGT2B7.

Population in Need of Further Characterization

Patients treated with inhibitors of UGT1A3 and UGT2B7 (such as valproic acid, probenecid and fluconazole).

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Hypotension
	Anemia
	Hyperthyroidism
	Concomitant use with strong inhibitors of CYP2C8
Important Potential Risks	Pulmonary edema associated with PVOD
	MACE
	Renal functional impairment / acute renal failure
	Bleeding events
	Light-dependent non-melanoma skin malignancies
	Ophthalmological effects associated with retinal vascular system
	GI 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

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires

Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective(s)	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Study name and title	AC-065A401 EXPOSURE: EXPloratory Observational Study of Uptravi in Real-lifE PASS: observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice.
Rationale and study objectives	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 MACE rates with PAH patients not treated with UPTRAVI.
Safety concern(s) addressed	The safety concerns addressed are: • Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old
Study design	This is a multicenter, prospective, real-world, observational cohort study.
Study population	The cohort study includes patients with PAH who either initiated treatment with UPTRAVI less than 1 month prior to enrolment, at enrolment, or during

	observation, or initiated any other PAH-specific therapy less than 1 month prior to enrolment or at enrolment and who were never treated with UPTRAVI.
Milestones	• Seq0129\m1\eu\18-pharmacovigilance\182-riskmgt-system • Start of data collection: 2017 • Registration in the EU PAS register (ENCePP): 2017 • Regular updates for mortality data in selexipag cohort: Reporting within the PBRERs • Annual updates: Progress reports on enrolment and intermediate analysis results will be provided yearly[1] • End of data collection: at time of PRAC agreement that commitment is fulfilled • Final study report: 12 months after PRAC agreement that commitment is fulfilled

Study name and title	AC-065A403 EDUCATE PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice.
Rationale and study objectives	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.
Safety concern(s) addressed	The safety concern addressed is the occurrence of medication errors during the UPTRAVI titration phase.
Study design	The study is an observational, cross-sectional survey of awareness, knowledge, and self-reported behavior.
Study population	The study population will involve patients and HCPs from Europe and Australia, including centralized healthcare systems (ie, national PAH reference centers) and decentralized systems.
Milestones	• Seq0107\m1\eu\18-pharmacovigilance\182-riskmgt-system • Start of data collection: 02 December 2022 • Collection of targeted number (60) of HCP surveys completed: 16 June 2023 • Second interim report submission: Once 100 patients' questionnaires are completed • End of data collection: At time of PRAC agreement that commitment is fulfilled • Final study report submission: 12 months after PRAC agreement

[1] As per agreement with the PRAC Rapporteur received on 01 September 2025, the next interim analysis will be provided once the full sample size is reached.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3: Required additional pharmacovigilance activities				
AC-065A401 EXPOSURE PASS: observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. Ongoing	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 MACE rates with PAH patients not treated with UPTRAVI.	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old	Annual updates	Progress reports on enrolment and intermediate analysis results will be provided yearly, including mortality data.[1]
			Final study report	Final study report: 12 months after PRAC agreement that commitment is fulfilled.
AC-065A403 EDUCATE PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration	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	Occurrence of medication errors during the UPTRAVI titration phase.	Collection of targeted number (60) of HCP surveys	Completed: 16 June 2023
			Second interim report submission	Once 100 patients' questionnaires are completed

[1] As per agreement with the PRAC Rapporteur received on 01 September 2025, the next annual interim analysis will be provided once the full sample size is reached.

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
phase in patients with pulmonary arterial hypertension (PAH) in clinical practice. Ongoing	patient-reported "wrong dose" medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration.		Final study report	Final study report submission: 12 months after PRAC agreement.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no ongoing or planned imposed postauthorization efficacy studies included in the selexipag pharmacovigilance plan.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Hypotension
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Anemia
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Hyperthyroidism
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.

Concomitant use with strong inhibitors of CYP2C8
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Pulmonary edema associated with PVOD
Routine risk communication SmPC section 4.4: 'Special warnings and precautions for use'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
MACE
Routine risk communication SmPC section 4.3: 'Contraindications'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Renal function impairment / acute renal failure
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Bleeding events
Routine risk communication 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’.

Routine risk minimization activities recommending specific clinical measures to address the risk

None

Other routine risk minimization activities beyond the Product Information

Legal status: Medicinal product subject to restricted medical prescription.

Light-dependent non-melanoma skin malignancies

Routine risk communication

None

Routine risk minimization activities recommending specific clinical measures to address the risk

None

Other routine risk minimization activities beyond the Product Information

Legal status: Medicinal product subject to restricted medical prescription.

Ophthalmological effects associated with retinal vascular system

Routine risk communication

SmPC section 5.3: ‘Preclinical safety data’.

Routine risk minimization activities recommending specific clinical measures to address the risk

None

Other routine risk minimization activities beyond the Product Information

Legal status: Medicinal product subject to restricted medical prescription.

GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

Routine risk communication

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’.

Routine risk minimization activities recommending specific clinical measures to address the risk

None

Other routine risk minimization activities beyond the Product Information

Legal status: Medicinal product subject to restricted medical prescription.

Medication error

Routine risk communication

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’.

Routine risk minimization activities recommending specific clinical measures to address the risk

None

Other routine risk minimization activities beyond the Product Information

Legal status: Medicinal product subject to restricted medical prescription.

The authorized pack size is chosen to ensure that the medicine is used correctly.
Missing information in use in pediatric patients
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Missing information in use in elderly over 75 years old
Routine risk communication 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Missing information in use during pregnancy and lactation
Routine risk communication SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 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'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.
Missing information in concomitant use with strong inhibitors of UGT1A3 and UGT2B7
Routine risk communication SmPC section 4.5: 'Interactions with other medicinal products and other forms of interaction'. SmPC section 5.2: 'Pharmacokinetic properties'. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization activities beyond the Product Information** Legal status: Medicinal product subject to restricted medical prescription.

V.2. Additional Risk Minimization Measures

Educational material in a Prescriber Kit:

- Cover letter to the HCP.
- The SmPC.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 100 µg bid.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 200 µg bid.
- Patient Titration Guide included in the titration pack of the 100 µg tablets.
- Patient Titration Guide included in the titration pack of the 200 µg tablets.
- Package leaflet.

Objective(s)	To explain that the purpose of the educational materials is to reduce the risk of medication error due to the availability of multiple tablets and dose strengths. To provide a list of the content of the prescriber kit. To provide the HCP with information on the dosing and titration concept, the move to the maintenance dose, and expectations and management of AEs. To encourage the HCP to communicate clearly with the patient during their first visit; and to take responsibility to contact the patient during the titration phase, facilitating communication between HCP and the patient. To demonstrate and discuss with patients the safe and effective use of UPTRAVI. To be aware of the information and the titration guide that the patient will receive in the pack together with the package leaflet. To ensure that patients receive the patient titration guide in lay language. The patient titration guide will facilitate UPTRAVI use and serve as a reminder for the patients (eg, to contact her/his doctor), and a place to record intake of tablets.
Rationale for the additional risk minimization activity	These efforts reinforce patient knowledge regarding the safe use of UPTRAVI, thereby mitigating the risks associated with UPTRAVI treatment.
Target audience and planned distribution path	Prescribers and other HCPs (eg, pharmacists, nurses) involved in the prescription and delivery of UPTRAVI or in the education of patients who are prescribed UPTRAVI.

Plans to evaluate the effectiveness of the interventions and criteria for success	Title: Category 3 PASS, EDUCATE, AC-065A403 "PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice." The study is an observational, cross-sectional survey of awareness, knowledge and self-reported behavior in the following groups: • HCPs (physicians, pharmacists and nurses); collection of targeted number (60) of HCP surveys was completed on 16 June 2023 • Patients at completion of titration or discontinuation of UPTRAVI during titration (ie, ≤4 weeks after reaching individual maintenance dose or ≤4 weeks after discontinuation during titration). 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 surveys will contain questions about: a. Process indicators: • Whether and how HCPs and patients use the respective materials, b. Impact assessment: • Measuring HCPs' and patients' awareness and knowledge (understanding) of the UPTRAVI titration c. Outcome indicator: • Patient self-reported occurrence of medication errors

Controlled Access System	
Objective(s)	To facilitate the identification of prescribers and approach them with the appropriate information on the safe and effective use of UPTRAVI, and provide them with risk minimization tools, especially regarding the potential risk of medication error.
Rationale for the additional risk minimization activity	The Controlled Access System includes three key principles that will be incorporated within each system in all Member States. These are: • The identification and maintenance of a list of all UPTRAVI prescribers. • The distribution of kits to all identified prescribers to minimize the risks of medication error. • Tracking of the receipt of the kits by prescribers.
Target audience and planned distribution path	UPTRAVI prescribers and other HCPs.

Plans to evaluate the effectiveness of the interventions and criteria for success	There are no regulatory commitments regarding measuring the effectiveness.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures

Table Part V.3: Summary of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hypotension	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Anemia	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hyperthyroidism	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Concomitant use with strong inhibitors of CYP2C8	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** None
Pulmonary edema associated with PVOD	**Routine risk minimization activities** SmPC section 4.4: 'Special warnings and precautions for use'. **Additional risk minimization activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
MACE	**Routine risk minimization activities** • SmPC section 4.3: 'Contraindications'. • PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Renal function impairment / acute renal failure	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Bleeding events	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Light-dependent non-melanoma skin malignancies	**Routine risk minimization activities** None **Additional risk minimization activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Ophthalmological effects associated with retinal vascular system	**Routine risk minimization activities** • SmPC section 5.3: 'Preclinical safety data'. **Additional risk minimization activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Medication error	**Routine risk minimization activities** • 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 activities** Controlled Access System Educational material in a Prescriber Kit containing: • Cover Letter to the HCP and pharmacist • A4 laminated card HCP titration guide (specific for starting doses of 100 µg or 200 µg) • SmPC • Package leaflet and patient titration guide Specific patient titration guides are included in the titration packs of the 100 µg and 200 µg tablets.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A403 EDUCATE

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in pediatric patients	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** None
Use in elderly over 75 years old	**Routine risk minimization activities** • 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** AC-065A401 EXPOSURE
Use during pregnancy and lactation	**Routine risk minimization activities** • SmPC section 4.4: 'Special warnings and precautions for use'. • SmPC section 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 activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** None
Concomitant use with strong inhibitors of UGT1A3 and UGT2B7	**Routine risk minimization activities** • SmPC section 4.5: 'Interactions with other medicinal products and other forms of interactions'. • SmPC section 5.2: 'Pharmacokinetic properties'. **Additional risk minimization activities** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** None

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 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 PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI 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.
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 RHF hospitalization. Four-fold increase of in-hospital mortality for patients with systolic blood pressure <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 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	AC-065A401 EXPOSURE 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	AC-065A401 EXPOSURE 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 on 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	AC-065A401 EXPOSURE 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 PVOD	
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 PVOD. 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 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. 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.
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
Additional pharmacovigilance activities	AC-065A401 EXPOSURE See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: MACE	
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
Additional pharmacovigilance activities	AC-065A401 EXPOSURE 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	**Routine 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
Additional pharmacovigilance activities	AC-065A401 EXPOSURE 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
Additional pharmacovigilance activities	AC-065A401 EXPOSURE 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	**Routine risk minimization measures** None **Additional risk minimization measures** None
Additional pharmacovigilance activities	AC-065A401 EXPOSURE See Section II.C. of this summary for an overview of the 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	AC-065A401 EXPOSURE See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: GI 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 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. 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	AC-065A401 EXPOSURE 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 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets) have been approved. 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 Prescriber Kit containing: • Cover Letter to the HCP and pharmacist • A4 laminated card HCP titration guide (specific for starting doses of 100 µg or 200 µg) • SmPC • Package leaflet and patient titration guide Specific patient titration guides are included in the titration packs of the 100 µg and 200 µg tablets.
Additional pharmacovigilance activities	AC-065A403 EDUCATE 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	AC-065A401 EXPOSURE 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 section 4.4: 'Special warnings and precautions for use'. SmPC section 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 That are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligations of UPTRAVI.

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

1. **AC-065A401 EXPOSURE**

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 MACE rates with PAH patients not treated with UPTRAVI.

2. AC-065A403 EDUCATE

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.

PART VII: ANNEXES

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[redacted]
Annex 4 Specific Adverse Reaction Follow-up Questionnaires
[redacted]
Annex 6 Details of Additional Risk Minimization Activities
[redacted]

Annex 1: EudraVigilance Interface

Submission of Annex 1 has been suspended per EMA instruction.

Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Studies in the Pharmacovigilance Study Program

Table 1 Annex 2: Planned and Ongoing Studies

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Protocol Reference and Milestones
AC-065A401 EXPOSURE PASS: observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical	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 MACE rates with	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events	Seq0129\m1\eu\18-pharmacovigilance\182-riskmgt-system Regular updates for mortality data within annual PBRERs. Annual updates: Progress reports

Table 1 Annex 2: Planned and Ongoing Studies

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Protocol Reference and Milestones
practice. Category 3 Ongoing	PAH patients not treated with UPTRAVI.	• Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with the retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old	on enrolment and intermediate analysis results will be provided yearly.[1] Final study report: 12 months after PRAC agreement that commitment is fulfilled
AC-065A403 EDUCATE PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice. Category 3 Ongoing	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.	Occurrence of medication errors during the UPTRAVI titration phase.	Seq0107\m1\eu\18-pharmacovigilance\182-riskmgt-system Collection of targeted number (60) of HCP surveys completed: 16 June 2023 Second interim report submission: Once 100 patients' questionnaires are completed Final study report submission: 12 months after PRAC agreement

[1] As per agreement with the PRAC Rapporteur received on 01 September 2025, the next annual interim analysis will be provided once the full sample size is reached.

Table 2 Annex 2: Completed Studies

Study	Summary of Objectives	Safety Concern(s) Addressed	Date of Final Study Report Submission Reference
PASS: AC-065-117 A single-center, open-label, two treatment, one-sequence, cross-over study to investigate the effect of clopidogrel on the PK of selexipag and its active metabolite, ACT-333679, in healthy male subjects Category 3	• To evaluate the effect of multiple-dose treatment with clopidogrel on the PK of multiple-dose selexipag and its active metabolite, ACT-333679, in healthy male participants. • To evaluate the safety and tolerability of selexipag when administered alone or with clopidogrel in healthy male participants.	Interactions between selexipag and moderate inhibitors of CYP2C8 (Clopidogrel)	Date of report: 14 November 2018 eCTD reference sequence: 0043
67896049PAH0002 EXTRACT PASS: retrospective medical chart review of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy. Category 3	The purpose of this PASS was 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.	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old	Final study report submission: 21 March 2024 eCTD location of the final study report: Seq0105/Mod5.3.6

Annex 3: Protocols for Proposed and Ongoing Studies in the Pharmacovigilance Plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan submitted for regulatory review with this updated version of the RMP

Not applicable

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed or approved by the competent authority

Previously agreed protocols for ongoing studies

Study Name and Title	Procedure Number	Date of Procedure Outcome	Protocol Reference
EXPOSURE (AC-065A401) PASS: observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice	EMA/PAM/0000256686	13 November 2025	Seq0129/m1/eu/18 - pharmacovigilance/182-riskmgt-system
EDUCATE (AC-065A403) PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice	EMEA/H/C/003774/MEA/003.6	25 July 2024	Seq0107/m1/eu/18 - pharmacovigilance/182-riskmgt-system

Final protocols not reviewed or not approved by the competent authority

Not applicable

Annex 4: Specific Adverse Reaction Follow-up Questionnaires

Not applicable.

[redacted]

Annex 6: Details of Additional Risk Minimization Activities

Key Messages of Additional Risk Minimization Activities

Physician Educational Material:

1. The SmPC will contain information on approved indications and posology in order to ensure appropriate prescription of UPTRAVI, the warnings and the precautions as well as symptoms and signs of any potential ADRs.
2. Cover letter to HCPs
   a. To explain that the purpose of the educational materials is to reduce the risk of medication error due to the availability of multiple tablets and dose strengths. The Cover letter will include an explanation regarding availability of 100 µg or 200 µg tablet strengths for initial up-titration.
   b. To provide a list of the content of the prescriber kit.
3. HCP A4 laminated titration guides describing treatment initiation and titration with UPTRAVI 100 µg or with UPTRAVI 200 µg dosage strengths
   a. To provide the HCP with information on the dosing and titration concept, the move to the maintenance dose, and expectations and management of AEs.
   b. To encourage the HCP to communicate clearly with the patient during their first visit; as well as to take responsibility to contact the patient during the titration phase, facilitating communication between HCP and the patient.
   c. To demonstrate and discuss with patients the safe and effective use of UPTRAVI.
4. Patient Titration Guide and patient leaflet to be used by the HCP during discussions with the patient (included in the titration packs containing 140 tablets of 100 µg or 200 µg selexipag specifically for patients initiating UPTRAVI at starting dose of 100 µg or 200 µg bid).
   a. To demonstrate and discuss with patients the safe and effective use of UPTRAVI.
   b. To be aware of the information and the titration guide that the patient will receive in the pack together with the package leaflet.

Controlled Access System:

1. To facilitate the identification of prescribers and approach them with the appropriate information on the safe and effective use of UPTRAVI, and provide them with risk minimization tools, especially regarding the potential risk of medication error.

Bone marrow myelogram abnormal
Bone marrow necrosis
Bone marrow toxicity
Cardiac haemolytic anaemia
Cold type haemolytic anaemia
Congenital anaemia
Congenital aplastic anaemia
Congenital dyserythropoietic anaemia
Coombs negative haemolytic anaemia
Coombs positive haemolytic anaemia
Cytopenia
Deficiency anaemia
Erythroblast count abnormal
Erythroblast count decreased
Erythroid maturation arrest
Erythropenia
Erythropoiesis abnormal
Febrile bone marrow aplasia
Foetal anaemia
Full blood count decreased
Gelatinous transformation of the bone marrow
Haematocrit abnormal
Haematocrit decreased
Haematotoxicity
Haemoglobin abnormal
Haemoglobin decreased
Haemolytic anaemia
Haemolytic anaemia enzyme specific
Haemolytic icteroanaemia
Hand and foot syndrome secondary to sickle cell anaemia
Hereditary haemolytic anaemia
Hereditary sideroblastic anaemia
Hexokinase deficiency anaemia
Hyperchromic anaemia
Hypochromic anaemia
Hypoplastic anaemia
Immune-mediated pancytopenia
Iron deficiency anaemia
Leukoerythroblastic anaemia
Melanaemia
Microangiopathic haemolytic anaemia
Microcytic anaemia
Myelodysplastic syndrome
Myelodysplastic syndrome transformation

Myelofibrosis
Myeloid metaplasia
Nephrogenic anaemia
Normochromic anaemia
Normochromic normocytic anaemia
Normocytic anaemia
Pancytopenia
Panmyelopathy
Pernicious anaemia
Plasmablast count decreased
Primary myelofibrosis
Proerythroblast count abnormal
Proerythroblast count decreased
Protein deficiency anaemia
Pyruvate kinase deficiency anaemia
Red blood cell count abnormal
Red blood cell count decreased
Refractory anaemia with an excess of blasts
Refractory anaemia with ringed sideroblasts
Reticulocyte count abnormal
Reticulocyte count decreased
Reticulocyte percentage decreased
Reticulocytopenia
Scan bone marrow abnormal
Sickle cell anaemia
Sickle cell anaemia with crisis
Sideroblastic anaemia
Spherocytic anaemia
Spur cell anaemia
Warm type haemolytic anaemia

Bleeding events

Cases including events denoting haemorrhage or GI haemorrhage are retrieved from the safety database for analysis if they contain an event PT within either of the following MedDRA SMQs: 'Haemorrhage terms (excl. laboratory terms)', or 'Gastrointestinal haemorrhage', ie, any of the following MedDRA PTs:

Abdominal wall haematoma
Abdominal wall haemorrhage
Abnormal withdrawal bleeding
Achenbach syndrome
Acute haemorrhagic leukoencephalitis
Acute haemorrhagic ulcerative colitis

Administration site bruise
Administration site haematoma
Administration site haemorrhage
Adrenal haematoma
Adrenal haemorrhage
Anal fissure haemorrhage
Anal haemorrhage
Anal ulcer haemorrhage
Anastomotic haemorrhage
Anastomotic ulcer haemorrhage
Aneurysm ruptured
Angina bullosa haemorrhagica
Anorectal varices haemorrhage
Aortic aneurysm rupture
Aortic dissection rupture
Aortic intramural haematoma
Aortic perforation
Aortic rupture
Aponeurosis contusion
Application site bruise
Application site haematoma
Application site haemorrhage
Application site purpura
Arterial haemorrhage
Arterial intramural haematoma
Arterial perforation
Arterial rupture
Arteriovenous fistula site haematoma
Arteriovenous fistula site haemorrhage
Arteriovenous graft site haematoma
Arteriovenous graft site haemorrhage
Astringent therapy
Atrial rupture
Auricular haematoma
Basal ganglia haematoma
Basal ganglia haemorrhage
Basilar artery perforation
Bladder tamponade
Bleeding varicose vein
Blood blister
Blood loss anaemia
Blood urine
Blood urine present
Bloody discharge

Bloody peritoneal effluent
Bone contusion
Bone marrow haemorrhage
Brain contusion
Brain stem haematoma
Brain stem haemorrhage
Brain stem microhaemorrhage
Breast haematoma
Breast haemorrhage
Broad ligament haematoma
Bronchial haemorrhage
Bronchial varices haemorrhage
Bursal haematoma
Cardiac contusion
Carotid aneurysm rupture
Carotid artery perforation
Catheter site bruise
Catheter site haematoma
Catheter site haemorrhage
Central nervous system haemorrhage
Cephalhaematoma
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar microhaemorrhage
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery perforation
Cerebral cyst haemorrhage
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral microhaemorrhage
Cervix haematoma uterine
Cervix haemorrhage uterine
Chest wall haematoma
Choroidal haematoma
Choroidal haemorrhage
Chronic gastrointestinal bleeding
Chronic pigmented purpura
Ciliary body haemorrhage
Coital bleeding
Colonic haematoma

Conjunctival haemorrhage
Contusion
Corneal bleeding
Cullen's sign
Cystitis haemorrhagic
Deep dissecting haematoma
Diarrhoea haemorrhagic
Disseminated intravascular coagulation
Diverticulitis intestinal haemorrhagic
Diverticulum intestinal haemorrhagic
Duodenal operation
Duodenal ulcer haemorrhage
Duodenal vascular ectasia
Duodenitis haemorrhagic
Dysfunctional uterine bleeding
Ear haemorrhage
Ecchymosis
Encephalitis haemorrhagic
Enterocolitis haemorrhagic
Epidural haemorrhage
Epistaxis
Exsanguination
Extra-axial haemorrhage
Extradural haematoma
Extradural haematoma evacuation
Extravasation blood
Eye contusion
Eye haematoma
Eye haemorrhage
Eyelid bleeding
Eyelid contusion
Eyelid haematoma
Femoral artery perforation
Femoral vein perforation
Foetal-maternal haemorrhage
Fothergill sign positive
Gastric antral vascular ectasia
Gastric haemangioma
Gastric haemorrhage
Gastric occult blood positive
Gastric ulcer haemorrhage
Gastric ulcer haemorrhage, obstructive
Gastric varices haemorrhage
Gastritis alcoholic haemorrhagic

Gastritis haemorrhagic
Gastroduodenal haemorrhage
Gastrointestinal anastomotic leak
Gastrointestinal angiectasia
Gastrointestinal haemorrhage
Gastrointestinal polyp haemorrhage
Gastrointestinal ulcer haemorrhage
Gastrointestinal vascular malformation haemorrhagic
Genital contusion
Genital haemorrhage
Gingival bleeding
Graft haemorrhage
Grey Turner's sign
Haemarthrosis
Haematemesis
Haematochezia
Haematocoele
Haematoma
Haematoma evacuation
Haematoma infection
Haematoma muscle
Haematosalpinx
Haematospermia
Haematotympanum
Haematuria
Haematuria traumatic
Haemobilia
Haemophilic arthropathy
Haemophilic pseudotumour
Haemoptysis
Haemorrhage
Haemorrhage coronary artery
Haemorrhage foetal
Haemorrhage in pregnancy
Haemorrhage intracranial
Haemorrhage neonatal
Haemorrhage subcutaneous
Haemorrhage subepidermal
Haemorrhage urinary tract
Haemorrhagic adrenal infarction
Haemorrhagic arteriovenous malformation
Haemorrhagic ascites
Haemorrhagic breast cyst
Haemorrhagic cerebral infarction

Haemorrhagic cyst
Haemorrhagic diathesis
Haemorrhagic disease of newborn
Haemorrhagic disorder
Haemorrhagic erosive gastritis
Haemorrhagic hepatic cyst
Haemorrhagic infarction
Haemorrhagic necrotic pancreatitis
Haemorrhagic ovarian cyst
Haemorrhagic stroke
Haemorrhagic thyroid cyst
Haemorrhagic transformation stroke
Haemorrhagic tumour necrosis
Haemorrhagic urticaria
Haemorrhagic vasculitis
Haemorrhoidal haemorrhage
Haemostasis
Haemothorax
Henoch-Schonlein purpura
Hepatic haemangioma rupture
Hepatic haematoma
Hepatic haemorrhage
Hereditary haemorrhagic telangiectasia
Hyperfibrinolysis
Hyphaema
Iliac artery perforation
Iliac artery rupture
Iliac vein perforation
Immune thrombocytopenic purpura
Implant site bruising
Implant site haematoma
Implant site haemorrhage
Incision site haematoma
Incision site haemorrhage
Increased tendency to bruise
Induced abortion haemorrhage
Inferior vena cava perforation
Infusion site bruising
Infusion site haematoma
Infusion site haemorrhage
Injection site bruising
Injection site haematoma
Injection site haemorrhage
Instillation site bruise

Instillation site haematoma
Instillation site haemorrhage
Internal haemorrhage
Intestinal haematoma
Intestinal haemorrhage
Intestinal varices haemorrhage
Intra-abdominal haematoma
Intra-abdominal haemorrhage
Intracerebral haematoma evacuation
Intracranial haematoma
Intracranial tumour haemorrhage
Intraocular haematoma
Intrapartum haemorrhage
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal
Iris haemorrhage
Joint microhaemorrhage
Kidney contusion
Lacrimal haemorrhage
Large intestinal haemorrhage
Large intestinal ulcer haemorrhage
Laryngeal haematoma
Laryngeal haemorrhage
Lip haematoma
Lip haemorrhage
Liver contusion
Lower gastrointestinal haemorrhage
Lower limb artery perforation
Lymph node haemorrhage
Mallory-Weiss syndrome
Mediastinal haematoma
Mediastinal haemorrhage
Medical device site bruise
Medical device site haematoma
Medical device site haemorrhage
Melaena
Melaena neonatal
Meningorrhagia
Menometrorrhagia
Menorrhagia
Mesenteric haematoma
Mesenteric haemorrhage
Metrorrhagia
Mouth haemorrhage

Mucocutaneous haemorrhage
Mucosal haemorrhage
Muscle contusion
Muscle haemorrhage
Myocardial haemorrhage
Myocardial rupture
Naevus haemorrhage
Nail bed bleeding
Nasal septum haematoma
Neonatal gastrointestinal haemorrhage
Nephritis haemorrhagic
Nipple exudate bloody
Occult blood positive
Ocular retrobulbar haemorrhage
Oesophageal haemorrhage
Oesophageal intramural haematoma
Oesophageal ulcer haemorrhage
Oesophageal varices haemorrhage
Oesophagitis haemorrhagic
Optic disc haemorrhage
Optic nerve sheath haemorrhage
Oral contusion
Oral mucosa haematoma
Osteorrhagia
Ovarian haematoma
Ovarian haemorrhage
Palpable purpura
Pancreatic haemorrhage
Pancreatitis haemorrhagic
Papillary muscle haemorrhage
Paranasal sinus haematoma
Paranasal sinus haemorrhage
Parathyroid haemorrhage
Parotid gland haemorrhage
Pelvic haematoma
Pelvic haematoma obstetric
Pelvic haemorrhage
Penile contusion
Penile haematoma
Penile haemorrhage
Peptic ulcer haemorrhage
Pericardial haemorrhage
Perineal haematoma
Periorbital haematoma

Periorbital haemorrhage
Periosteal haematoma
Peripartum haemorrhage
Peripheral artery aneurysm rupture
Peripheral artery haematoma
Perirenal haematoma
Peritoneal haematoma
Peritoneal haemorrhage
Periventricular haemorrhage neonatal
Petechiae
Pharyngeal contusion
Pharyngeal haematoma
Pharyngeal haemorrhage
Pituitary apoplexy
Pituitary haemorrhage
Placenta praevia haemorrhage
Polymenorrhagia
Post abortion haemorrhage
Post procedural contusion
Post procedural haematoma
Post procedural haematuria
Post procedural haemorrhage
Post transfusion purpura
Postmenopausal haemorrhage
Postpartum haemorrhage
Post-traumatic punctate intraepidermal haemorrhage
Premature separation of placenta
Procedural haemorrhage
Proctitis haemorrhagic
Prostatic haemorrhage
Pulmonary alveolar haemorrhage
Pulmonary contusion
Pulmonary haematoma
Pulmonary haemorrhage
Pulmonary haemorrhage neonatal
Puncture site bruise
Puncture site haematoma
Puncture site haemorrhage
Purpura
Purpura fulminans
Purpura neonatal
Purpura non-thrombocytopenic
Purpura senile
Putamen haemorrhage

Radiation associated haemorrhage
Rectal haemorrhage
Rectal ulcer haemorrhage
Renal artery perforation
Renal cyst haemorrhage
Renal haematoma
Renal haemorrhage
Respiratory tract haemorrhage
Respiratory tract haemorrhage neonatal
Retinal aneurysm rupture
Retinal haemorrhage
Retinopathy haemorrhagic
Retroperitoneal haematoma
Retroperitoneal haemorrhage
Retroplacental haematoma
Ruptured cerebral aneurysm
Scleral haemorrhage
Scrotal haematocoele
Scrotal haematoma
Scrotal haemorrhage
Shock haemorrhagic
Skin haemorrhage
Skin neoplasm bleeding
Skin ulcer haemorrhage
Small intestinal haemorrhage
Small intestinal ulcer haemorrhage
Soft tissue haemorrhage
Spermatic cord haemorrhage
Spinal cord haematoma
Spinal cord haemorrhage
Spinal epidural haematoma
Spinal epidural haemorrhage
Spinal subarachnoid haemorrhage
Spinal subdural haematoma
Spinal subdural haemorrhage
Spleen contusion
Splenic artery perforation
Splenic haematoma
Splenic haemorrhage
Splenic varices haemorrhage
Splinter haemorrhages
Spontaneous haematoma
Spontaneous haemorrhage
Stoma site haemorrhage

Stomatitis haemorrhagic
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subchorionic haematoma
Subchorionic haemorrhage
Subclavian artery perforation
Subclavian vein perforation
Subcutaneous haematoma
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subdural haemorrhage neonatal
Subendocardial haemorrhage
Subgaleal haematoma
Subgaleal haemorrhage
Subretinal haematoma
Superior vena cava perforation
Testicular haemorrhage
Thalamus haemorrhage
Third stage postpartum haemorrhage
Thoracic haemorrhage
Thrombocytopenic purpura
Thrombotic thrombocytopenic purpura
Thyroid haemorrhage
Tongue haematoma
Tongue haemorrhage
Tonsillar haemorrhage
Tooth pulp haemorrhage
Tooth socket haemorrhage
Tracheal haemorrhage
Traumatic haematoma
Traumatic haemorrhage
Traumatic haemothorax
Traumatic intracranial haematoma
Traumatic intracranial haemorrhage
Tumour haemorrhage
Ulcer haemorrhage
Umbilical cord haemorrhage
Umbilical haematoma
Umbilical haemorrhage
Upper gastrointestinal haemorrhage
Ureteric haemorrhage
Urethral haemorrhage

Urinary bladder haemorrhage
Urogenital haemorrhage
Uterine haematoma
Uterine haemorrhage
Vaccination site bruising
Vaccination site haematoma
Vaccination site haemorrhage
Vaginal haematoma
Vaginal haemorrhage
Varicose vein ruptured
Vascular access site bruising
Vascular access site haematoma
Vascular access site haemorrhage
Vascular access site rupture
Vascular graft haemorrhage
Vascular pseudoaneurysm ruptured
Vascular purpura
Vascular rupture
Vein rupture
Venous haemorrhage
Venous perforation
Ventricle rupture
Vertebral artery perforation
Vessel puncture site bruise
Vessel puncture site haematoma
Vessel puncture site haemorrhage
Vitreous haematoma
Vitreous haemorrhage
Vulval haematoma
Vulval haematoma evacuation
Vulval haemorrhage
White nipple sign
Withdrawal bleed
Wound haematoma
Wound haemorrhage

Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

Cases including events denoting GI disturbances are retrieved from the safety database for analysis if they contain an event with any MedDRA PT containing the text ‘ileus’ (with the exception of 1 PT: “Keratomileusis"), ‘intestinal obstruction’, ‘intussusception’, or ‘volvulus’, ie, any of the following MedDRA PTs:

Congenital intestinal obstruction
Distal intestinal obstruction syndrome
Gallbladder volvulus
Gallstone ileus
Gastric ileus
Gastric volvulus
Gastrointestinal obstruction
Ileus
Ileus paralytic
Ileus spastic
Intestinal obstruction
Intestinal pseudo-obstruction
Intussusception
Large intestinal obstruction
Large intestinal obstruction reduction
Malignant gastrointestinal obstruction
Mechanical ileus
Meconium ileus
Neonatal intestinal obstruction
Postoperative ileus
Small intestinal intussusception reduction
Small intestinal obstruction
Small intestinal obstruction reduction
Subileus
Volvulus
Volvulus of small bowel
Volvulus repair

Hyperthyroidism

Cases including events of hyperthyroidism are retrieved from the safety database for analysis if they contain an event PT within the 'Hyperthyroidism' SMQ (narrow and broad scope), ie, any of the following MedDRA PTs:

Anti-thyroid antibody
Anti-thyroid antibody positive
Antithyroid arthritis syndrome
Autoimmune thyroid disorder
Autoimmune thyroiditis
Basedow's disease
Biopsy thyroid gland abnormal
Blood thyroid stimulating hormone abnormal
Blood thyroid stimulating hormone decreased
Blood thyroid stimulating hormone increased

Butanol-extractable iodine decreased
Butanol-extractable iodine increased
Congenital thyroid disorder
Endocrine ophthalmopathy
Euthyroid sick syndrome
Exophthalmos
Free thyroxine index abnormal
Free thyroxine index decreased
Free thyroxine index increased
Gamma radiation therapy to thyroid
Goitre
Hashimoto's encephalopathy
Hyperthyroidism
Immune-mediated thyroiditis
Inappropriate thyroid stimulating hormone secretion
Infectious thyroiditis
Iodine uptake abnormal
Iodine uptake decreased
Iodine uptake increased
Malignant exophthalmos
Marine Lenhart syndrome
Orbital decompression
Photon radiation therapy to thyroid
Polyglandular autoimmune syndrome type II
Polyglandular autoimmune syndrome type III
Primary hyperthyroidism
Protein bound iodine decreased
Protein bound iodine increased
Radioactive iodine therapy
Radiotherapy to thyroid
Reverse tri-iodothyronine decreased
Reverse tri-iodothyronine increased
Secondary hyperthyroidism
Silent thyroiditis
Thyreostatic therapy
Thyroglobulin absent
Thyroglobulin decreased
Thyroglobulin increased
Thyroglobulin present
Thyroid dermatopathy
Thyroid disorder
Thyroid dysfunction in pregnancy
Thyroid electron radiation therapy
Thyroid function test abnormal

Thyroid gland scan abnormal
Thyroid hemiagenesis
Thyroid hormone replacement therapy
Thyroid hormones increased
Thyroid operation
Thyroid pain
Thyroid releasing hormone challenge test abnormal
Thyroid stimulating immunoglobulin increased
Thyroid therapy
Thyroid tuberculosis
Thyroidectomy
Thyroiditis
Thyroiditis acute
Thyroiditis chronic
Thyroiditis fibrous chronic
Thyroiditis subacute
Thyrotoxic cardiomyopathy
Thyrotoxic crisis
Thyrotoxic myopathy
Thyrotoxic periodic paralysis
Thyroxin binding globulin abnormal
Thyroxin binding globulin decreased
Thyroxin binding globulin increased
Thyroxine abnormal
Thyroxine decreased
Thyroxine free abnormal
Thyroxine free decreased
Thyroxine free increased
Thyroxine increased
Thyroxine therapy
Toxic goitre
Toxic nodular goitre
Tri-iodothyronine abnormal
Tri-iodothyronine decreased
Tri-iodothyronine free abnormal
Tri-iodothyronine free decreased
Tri-iodothyronine free increased
Tri-iodothyronine free normal
Tri-iodothyronine increased
Tri-iodothyronine uptake abnormal
Tri-iodothyronine uptake decreased
Tri-iodothyronine uptake increased
Ultrasound thyroid abnormal
X-ray therapy to thyroid

Hypotension

The case will be included in this subgroup if it contains an event with any of the following MedDRA PTs:

Blood pressure ambulatory decreased
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure immeasurable
Blood pressure orthostatic decreased
Blood pressure systolic decreased
Blood pressure systolic inspiratory decreased
CT hypotension complex
Diastolic hypotension
Hypotension
Mean arterial pressure decreased
Neonatal hypotension
Orthostatic hypotension
Postoperative hypotension
Procedural hypotension

Light-dependent non-melanoma skin malignancies

Cases including events denoting non-melanoma skin malignancies are retrieved from the safety database for analysis if they contain an event PT within the MedDRA High Level Term ‘Skin neoplasms malignant and unspecified (excl. melanoma)’, or if they contain the MedDRA PT ‘Squamous cell carcinoma’, ie, any of the following MedDRA PTs:

Atypical fibroxanthoma
Basal cell carcinoma
Basal cell naevus syndrome
Basosquamous carcinoma of skin
Bowen's disease
Carcinoma in situ of skin
Dysplastic naevus syndrome
Eccrine carcinoma
Epidermal naevus syndrome
Extramammary Paget's disease
Hidradenocarcinoma
Keratoacanthoma
Malignant sweat gland neoplasm
Marjolin's ulcer
Mastocytoma
Neoplasm skin
Neuroendocrine carcinoma of the skin

Pilomatrix carcinoma
Porocarcinoma
Sebaceous carcinoma
Skin angiosarcoma
Skin cancer
Skin cancer metastatic
Skin neoplasm bleeding
Skin squamous cell carcinoma metastatic
Skin squamous cell carcinoma recurrent
Squamous cell carcinoma
Squamous cell carcinoma of skin
Trichoblastic carcinoma

MACE

Cases including MACE are retrieved from the safety database for analysis if they contain an event PT within any of the following MedDRA SMQs: 'Conditions associated with central nervous system haemorrhages and cerebrovascular accidents' (broad scope), 'Haemorrhagic central nervous system vascular conditions' (narrow scope), 'Ischaemic central nervous system vascular conditions' (narrow scope), or 'Myocardial infarction' (narrow scope), or an event with any of the following MedDRA PTs: 'Cardiac arrest', 'Cardiac death', 'Cardio-respiratory arrest', 'Coronary artery disease', 'Coronary artery insufficiency', 'Coronary vein stenosis', 'Myocardial ischaemia', 'Pseudostroke', 'Sudden cardiac death', and 'Sudden death', ie, any of the following MedDRA PTs:

Acute cardiac event
Acute coronary syndrome
Acute myocardial infarction
Agnosia
Amaurosis fugax
Angina unstable
Angiogram cerebral abnormal
Aphasia
Balint's syndrome
Basal ganglia haematoma
Basal ganglia haemorrhage
Basal ganglia infarction
Basal ganglia stroke
Basilar artery aneurysm
Basilar artery occlusion
Basilar artery perforation
Basilar artery stenosis
Basilar artery thrombosis
Blood creatine phosphokinase MB abnormal

Blood creatine phosphokinase MB increased
Brachiocephalic arteriosclerosis
Brachiocephalic artery occlusion
Brachiocephalic artery stenosis
Brain hypoxia
Brain injury
Brain stem embolism
Brain stem haematoma
Brain stem haemorrhage
Brain stem infarction
Brain stem ischaemia
Brain stem microhaemorrhage
Brain stem stroke
Brain stem thrombosis
Brain stent insertion
CADASIL
Capsular warning syndrome
CARASIL syndrome
Cardiac arrest
Cardiac death
Cardio-respiratory arrest
Carotid aneurysm rupture
Carotid angioplasty
Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery aneurysm
Carotid artery bypass
Carotid artery disease
Carotid artery dissection
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery perforation
Carotid artery restenosis
Carotid artery stenosis
Carotid artery stent insertion
Carotid artery stent removal
Carotid artery thrombosis
Carotid endarterectomy
Carotid revascularisation
Central nervous system haemorrhage
Central pain syndrome
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar embolism

Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar infarction
Cerebellar ischaemia
Cerebellar microhaemorrhage
Cerebellar stroke
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral arteriosclerosis
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery perforation
Cerebral artery restenosis
Cerebral artery stenosis
Cerebral artery stent insertion
Cerebral artery thrombosis
Cerebral cyst haemorrhage
Cerebral endovascular aneurysm repair
Cerebral gas embolism
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral haemosiderin deposition
Cerebral infarction
Cerebral infarction foetal
Cerebral ischaemia
Cerebral microembolism
Cerebral microhaemorrhage
Cerebral reperfusion injury
Cerebral revascularisation
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vascular occlusion
Cerebral vasoconstriction
Cerebral venous thrombosis
Cerebral ventricular rupture
Cerebrovascular accident
Cerebrovascular accident prophylaxis
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular stenosis

Charcot-Bouchard microaneurysms
Congenital hemiparesis
Coronary artery disease
Coronary artery embolism
Coronary artery insufficiency
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery thrombosis
Coronary bypass thrombosis
Coronary vascular graft occlusion
Coronary vein stenosis
CSF bilirubin positive
CSF red blood cell count positive
Delayed ischaemic neurological deficit
Diplegia
Dysarthria
Embolic cerebral infarction
Embolic stroke
Epidural haemorrhage
Extra-axial haemorrhage
Extradural haematoma
Extradural haematoma evacuation
Extraischaemic cerebral haematoma
Foville syndrome
Haemorrhage intracranial
Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Hemianaesthesia
Hemiasomatognosia
Hemiataxia
Hemidysaesthesia
Hemihyperaesthesia
Hemiparaesthesia
Hemiparesis
Hemiplegia
Hypoxic-ischaemic encephalopathy
Inner ear infarction
Internal carotid artery deformity
Intra-cerebral aneurysm operation
Intracerebral haematoma evacuation
Intracranial aneurysm
Intracranial artery dissection
Intracranial haematoma

Intracranial tumour haemorrhage
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal
Ischaemic cerebral infarction
Ischaemic stroke
Jugular vein embolism
Kounis syndrome
Lacunar infarction
Lacunar stroke
Lateral medullary syndrome
Lateropulsion
Meningorrhagia
Migrainous infarction
Millard-Gubler syndrome
Modified Rankin score decreased
Modified Rankin score increased
Monoparesis
Monoplegia
Moyamoya disease
Myocardial infarction
Myocardial ischaemia
Myocardial necrosis
Myocardial reperfusion injury
Myocardial stunning
NIH stroke scale abnormal
NIH stroke scale score decreased
NIH stroke scale score increased
Papillary muscle infarction
Paralysis
Paraparesis
Paraplegia
Paresis
Perinatal stroke
Periprocedural myocardial infarction
Periventricular haemorrhage neonatal
Pituitary apoplexy
Pituitary haemorrhage
Post cardiac arrest syndrome
Post procedural myocardial infarction
Post procedural stroke
Post stroke depression
Posthaemorrhagic hydrocephalus
Postinfarction angina
Precerebral arteriosclerosis

Precerebral artery occlusion
Pseudostroke
Putamen haemorrhage
Quadriparesis
Quadriplegia
Reversible cerebral vasoconstriction syndrome
Reversible ischaemic neurological deficit
Right hemisphere deficit syndrome
Ruptured cerebral aneurysm
Silent myocardial infarction
Spinal artery embolism
Spinal artery thrombosis
Spinal cord haematoma
Spinal cord haemorrhage
Spinal cord infarction
Spinal cord ischaemia
Spinal epidural haematoma
Spinal epidural haemorrhage
Spinal stroke
Spinal subarachnoid haemorrhage
Spinal subdural haematoma
Spinal subdural haemorrhage
Stroke in evolution
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subclavian steal syndrome
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subdural haemorrhage neonatal
Sudden cardiac death
Sudden death
Superficial siderosis of central nervous system
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke
Transient ischaemic attack
Troponin I increased
Troponin increased
Troponin T increased
Vascular encephalopathy
Vascular stent occlusion

Vascular stent stenosis
Vein of Galen aneurysmal malformation
Vertebral artery aneurysm
Vertebral artery dissection
Vertebral artery occlusion
Vertebral artery perforation
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar insufficiency
Vertebrobasilar stroke
Visual agnosia
Visual midline shift syndrome

Medication error

Cases with events of medication errors with selexipag tablets are retrieved from the safety database for analysis if they contain an event PT within the 'Medication errors' SMQ (narrow scope), ie, any of the following MedDRA PTs:

Accidental device ingestion
Accidental device ingestion by a child
Accidental exposure to product
Accidental exposure to product by child
Accidental exposure to product packaging
Accidental exposure to product packaging by child
Accidental overdose
Accidental poisoning
Accidental underdose
Accidental use of placebo
Booster dose missed
Circumstance or information capable of leading to device use error
Circumstance or information capable of leading to medication error
Contraindicated device used
Contraindicated product administered
Contraindicated product prescribed
Deprescribing error
Device dispensing error
Device monitoring procedure not performed
Device programming error
Device use confusion
Device use error
Dietary supplement prescribing error
Discontinued product administered
Documented hypersensitivity to administered product

Dose calculation error
Drug administered in wrong device
Drug dispensed to wrong patient
Drug dose omission by device
Drug dose titration not performed
Drug monitoring procedure incorrectly performed
Drug monitoring procedure not performed
Drug titration error
Duplicate therapy error
Expired device used
Expired product administered
Exposure via direct contact
Exposure via eye contact
Exposure via skin contact
Extra dose administered
Failure of child resistant mechanism for pharmaceutical product
Failure to suspend medication
Inadequate aseptic technique in use of product
Inappropriate schedule of product administration
Incomplete course of vaccination
Incorrect disposal of product
Incorrect dosage administered
Incorrect dose administered
Incorrect dose administered by device
Incorrect dose administered by product
Incorrect drug administration rate
Incorrect product administration duration
Incorrect product dosage form administered
Incorrect product formulation administered
Incorrect route of product administration
Intercepted accidental exposure to product by child
Intercepted medication error
Intercepted product administration error
Intercepted product dispensing error
Intercepted product monitoring error
Intercepted product preparation error
Intercepted product prescribing error
Intercepted product selection error
Intercepted product storage error
Intercepted wrong patient selected
Labelled drug-disease interaction medication error
Labelled drug-drug interaction medication error
Labelled drug-food interaction medication error
Lack of administration site rotation

Lack of application site rotation
Lack of infusion site rotation
Lack of injection site rotation
Lack of vaccination site rotation
Medical device monitoring error
Medication error
Multiple use of single-use product
Paravenous drug administration
Poor quality product administered
Product administered at inappropriate site
Product administered to patient of inappropriate age
Product administration error
Product appearance confusion
Product barcode issue
Product confusion
Product design confusion
Product dispensing error
Product dosage form confusion
Product dose omission
Product label confusion
Product monitoring error
Product name confusion
Product packaging confusion
Product preparation error
Product prescribing error
Product selection error
Product storage error
Product substitution error
Recalled product administered
Single component of a two-component product administered
Therapeutic drug monitoring analysis incorrectly performed
Therapeutic drug monitoring analysis not performed
Transcription medication error
Transfusion with incompatible blood
Unintentional use for unapproved indication
Vaccination error
Wrong device used
Wrong dosage form
Wrong dosage formulation
Wrong dose
Wrong drug
Wrong patient received product
Wrong product administered
Wrong product procured

Wrong product stored
Wrong rate
Wrong schedule
Wrong strength
Wrong technique in device usage process
Wrong technique in product usage process

Ophthalmological effects associated with retinal vascular system

Cases describing ophthalmological effects associated with the retinal vascular system are retrieved from the safety database for analysis if they contain an event PT within the 'Retinal disorders' SMQ (narrow and broad scope), which includes the PTs 'Vision blurred' and 'Visual impairment', ie, any of the following MedDRA PTs:

Acquired pigmented retinopathy
Acute macular outer retinopathy
Acute zonal occult outer retinopathy
Age-related macular degeneration
AIDS retinopathy
Amaurosis fugax
Angiogram retina abnormal
Arteriosclerotic retinopathy
Autoimmune retinopathy
Benign neoplasm of retina
Biopsy retina abnormal
Birdshot chorioretinopathy
Cholesterolosis bulbi
Chorioretinal atrophy
Chorioretinal disorder
Chorioretinal scar
Chorioretinitis
Chorioretinopathy
Colour blindness
Colour blindness acquired
Colour vision tests abnormal
Colour vision tests abnormal blue-yellow
Colour vision tests abnormal red-green
Commotio retinae
Cystoid macular oedema
Delayed light adaptation
Detachment of macular retinal pigment epithelium
Detachment of retinal pigment epithelium
Diabetic retinal oedema
Diabetic retinopathy

Diffuse uveal melanocytic proliferation
Disruption of the photoreceptor inner segment-outer segment
Dry age-related macular degeneration
Extraocular retinoblastoma
Exudative retinopathy
Eye naevus
Fundoscopy abnormal
Hypotony maculopathy
Immune recovery uveitis
Internal limiting membrane peeling
IRVAN syndrome
Leukaemic retinopathy
Lipaemia retinalis
Macular cyst
Macular degeneration
Macular detachment
Macular fibrosis
Macular hole
Macular ischaemia
Macular oedema
Macular opacity
Macular pigmentation
Macular pseudohole
Macular reflex abnormal
Macular rupture
Macular scar
Macular telangiectasia
Maculopathy
Malignant neoplasm of retina
Metamorphopsia
Myopic chorioretinal degeneration
Myopic traction maculopathy
Necrotising retinitis
Neovascular age-related macular degeneration
Neuropathy, ataxia, retinitis pigmentosa syndrome
Noninfective chorioretinitis
Noninfective retinitis
Non-proliferative retinopathy
Paraneoplastic retinopathy
Photopsia
Pupillary light reflex tests abnormal
Purtscher retinopathy
Radiation retinopathy
Retinal aneurysm

Retinal aneurysm rupture
Retinal arteriovenous malformation
Retinal artery embolism
Retinal artery occlusion
Retinal artery spasm
Retinal artery stenosis
Retinal artery thrombosis
Retinal collateral vessels
Retinal coloboma
Retinal cryoablation
Retinal cyst
Retinal cyst excision
Retinal degeneration
Retinal depigmentation
Retinal deposits
Retinal detachment
Retinal disorder
Retinal drusen
Retinal dystrophy
Retinal exudates
Retinal fibrosis
Retinal function test abnormal
Retinal haemorrhage
Retinal implant
Retinal infarction
Retinal infiltrates
Retinal injury
Retinal ischaemia
Retinal laser coagulation
Retinal melanocytoma
Retinal melanoma
Retinal migraine
Retinal neoplasm
Retinal neovascularisation
Retinal oedema
Retinal operation
Retinal pallor
Retinal perivascular sheathing
Retinal phototoxicity
Retinal pigment epithelial tear
Retinal pigment epitheliopathy
Retinal pigmentation
Retinal scar
Retinal tear

Retinal telangiectasia
Retinal thickening
Retinal toxicity
Retinal transplant
Retinal tumour excision
Retinal vascular disorder
Retinal vascular occlusion
Retinal vascular thrombosis
Retinal vasculitis
Retinal vein occlusion
Retinal vein thrombosis
Retinal vein varices
Retinal vessel avulsion
Retinal white without pressure
Retinitis
Retinitis pigmentosa
Retinoblastoma
Retinogram abnormal
Retinopathy
Retinopathy haemorrhagic
Retinopathy hypertensive
Retinopathy hyperviscosity
Retinopathy of prematurity
Retinopathy proliferative
Retinopathy sickle cell
Retinopathy solar
Retinopexy
Retinoschisis
Rhegmatogenous retinal detachment
Scintillating scotoma
Scleral buckling surgery
Serous retinal detachment
Serous retinopathy
Serpiginous choroiditis
Subretinal fibrosis
Subretinal fluid
Subretinal haematoma
Subretinal hyperreflective exudation
Tractional retinal detachment
Tunnel vision
Venous stasis retinopathy
Visual field tests abnormal
Vitreal cells
Vitrectomy

Vitreomacular interface abnormal
Vitreoretinal traction syndrome
Vitreous adhesions
Vitreous detachment
Vitreous disorder
Vitreous floaters
Vitreous haematoma
Vitreous haemorrhage
Vitreous haze
Vitritis
Autoimmune eye disorder
Blindness
Blindness transient
Blindness unilateral
Central vision loss
Chromatopsia
Ciliary body melanoma
Dyschromatopsia
Eye disorder
Eye haematoma
Eye haemorrhage
Eye infarction
Eye opacity
Fluorescence angiogram abnormal
Foveal reflex abnormal
Hyperaesthesia eye
Hypertensive cerebrovascular disease
Immune-mediated uveitis
Intraocular haematoma
Intra-ocular injection complication
Intravitreal implant
Leukocoria
Low luminance best-corrected visual acuity decreased
Ocular ischaemic syndrome
Ocular lymphoma
Ocular stem cell transplant
Ophthalmic artery thrombosis
Ophthalmic vein thrombosis
Optic disc traction syndrome
Optical coherence tomography abnormal
Pars plana cyst
Pathologic myopia
Photophobia
Red reflex abnormal

Sclerotomy
Susac's syndrome
Uveal melanoma
Vision blurred
Visual acuity reduced
Visual acuity tests abnormal
Visual field defect
Visual impairment
Vogt-Koyanagi-Harada disease
Xanthopsia

Pregnancy and lactation

Pregnancy

Cases referring to pregnancy are retrieved from the safety database for analysis if they meet any of the following conditions:

The case contains an event with a primary MedDRA System Organ Class containing the text: 'pregnancy' (but excluding the MedDRA PTs: 'Pregnancy test urine negative', 'Pregnancy test negative', or 'Pregnancy test false positive'),

OR

It contains an event with a MedDRA primary High-Level Term or PT containing the following text: 'abortion', or 'pregnancy' (but excluding the PT 'Woman of childbearing potential').

OR

It contains an event with any of the following MedDRA PTs: 'Maternal drugs affecting foetus', 'Miscarriage of partner', or 'Paternal drugs affecting foetus', ie, any of the following MedDRA PTs:

Abnormal labour
Abnormal labour affecting foetus
Abnormal product of conception
Aborted pregnancy
Abortion
Abortion complete
Abortion complete complicated
Abortion complicated
Abortion early
Abortion incomplete
Abortion incomplete complicated

Abortion induced
Abortion induced complete
Abortion induced complete complicated
Abortion induced complicated
Abortion induced incomplete
Abortion induced incomplete complicated
Abortion infected
Abortion late
Abortion missed
Abortion of ectopic pregnancy
Abortion spontaneous
Abortion spontaneous complete
Abortion spontaneous complete complicated
Abortion spontaneous complicated
Abortion spontaneous incomplete
Abortion spontaneous incomplete complicated
Abortion threatened
Acute fatty liver of pregnancy
Adrenocortical insufficiency neonatal
Afterbirth pain
Amniorrhexis
Amniorrhoea
Amniotic cavity disorder
Anaemia of pregnancy
Anaesthetic complication neonatal
Anaphylactoid syndrome of pregnancy
Anembryonic gestation
Arrested labour
Asynclitic presentation
Bacteriuria in pregnancy
Biochemical pregnancy
Birth trauma
Birth weight normal
Bottle feeding
Breast engorgement in newborn
Breast feeding
Breech delivery
Breech presentation
Brow presentation
Caput succedaneum
Cephalhaematoma
Cephalo-pelvic disproportion
Cervical dilatation
Cervical incompetence

Cervix dystocia
Child born to unmarried parents
Cholestasis of pregnancy
Chorioamniotic separation
Chronic villitis of unknown etiology
Complication of delivery
Complication of pregnancy
Cranial nerve injury secondary to birth trauma
Decidual cast
Delayed delivery
Delivery
Delivery outside health facility
Diabetes complicating pregnancy
Discordant twin
Drug exposure before pregnancy
Eclampsia
Ectopic pregnancy
Ectopic pregnancy termination
Ectopic pregnancy under hormonal contraception
Ectopic pregnancy with contraceptive device
Elderly primigravida
Exposure during pregnancy
Exposure via breast milk
Exposure via father
Face presentation
Facial nerve injury due to birth trauma
Failed induction of labour
Failed trial of labour
False labour
False negative pregnancy test
Fear of pregnancy
First trimester pregnancy
Foetal acidosis
Foetal arm prolapse
Foetal cardiac disorder
Foetal compartment fluid collection
Foetal damage
Foetal death
Foetal disorder
Foetal distress syndrome
Foetal exposure during delivery
Foetal exposure during pregnancy
Foetal exposure timing unspecified
Foetal growth abnormality

Foetal growth restriction
Foetal hypokinesia
Foetal macrosomia
Foetal malnutrition
Foetal malposition
Foetal malpresentation
Foetal placental thrombosis
Foetal-maternal haemorrhage
Gestational diabetes
Gestational hypertension
Gestational oedema
Gestational trophoblastic detachment
Glucose tolerance impaired in pregnancy
Glycosuria during pregnancy
Habitual abortion
Haemorrhage foetal
Haemorrhage in pregnancy
HELLP syndrome
Heterotopic pregnancy
High foetal head
High risk pregnancy
Hydrops foetalis
Hyperemesis gravidarum
Hypothermia neonatal
Imminent abortion
Incoordinate uterine action
Indeterminate pregnancy test result
Induced abortion failed
Induced abortion haemorrhage
Induced abortion infection
Induced labour
Injury to spinal cord secondary to birth trauma
Intrapartum haemorrhage
Jaundice neonatal
Labour complication
Labour pain
Lack of prenatal care
Lactation normal
Large for dates baby
Leukopenia neonatal
Lithopedion
Live birth
Locked twins
Low birth weight baby

Maternal cancer in pregnancy
Maternal condition affecting foetus
Maternal death affecting foetus
Maternal death during childbirth
Maternal distress during labour
Maternal drugs affecting foetus
Maternal exposure before pregnancy
Maternal exposure during breast feeding
Maternal exposure during delivery
Maternal exposure during pregnancy
Maternal exposure timing unspecified
Meconium abnormal
Meconium in amniotic fluid
Meconium increased
Meconium stain
Mirror syndrome
Miscarriage of partner
Missed labour
Molar abortion
Morning sickness
Multigravida
Multiparous
Multiple pregnancy
Neonatal disorder
Neonatal thyrotoxicosis
Normal foetus
Normal labour
Normal newborn
Nulli gravida
Nulliparous
Oblique presentation
Obstructed labour
Oligohydramnios
Omphalorrhexis
Parity
Paternal drugs affecting foetus
Paternal exposure before pregnancy
Paternal exposure during pregnancy
Paternal exposure timing unspecified
Pelvic haematoma obstetric
Perinatal brain damage
Perineal repair breakdown
Peripartum cardiomyopathy
Peripartum haemorrhage

Placenta accreta
Placenta duplex
Placenta praevia
Placenta praevia haemorrhage
Placental calcification
Placental disorder
Placental dysplasia
Placental hypertrophy
Placental infarction
Placental insufficiency
Placental lake
Placental necrosis
Placental polyp
Planning to become infertile
Planning to become pregnant
Polyhydramnios
Polymorphic eruption of pregnancy
Poor weight gain neonatal
Post abortion complication
Post abortion haemorrhage
Post abortion infection
Postmature baby
Postpartum disorder
Postpartum haemorrhage
Postpartum state
Postpartum uterine subinvolution
Precipitate labour
Pre-eclampsia
Pregnancy
Pregnancy after post coital contraception
Pregnancy in habitual aborter
Pregnancy of partner
Pregnancy of unknown location
Pregnancy on contraceptive
Pregnancy on oral contraceptive
Pregnancy test
Pregnancy test positive
Pregnancy test urine
Pregnancy test urine positive
Pregnancy with advanced maternal age
Pregnancy with contraceptive device
Pregnancy with contraceptive patch
Pregnancy with implant contraceptive
Pregnancy with injectable contraceptive

Pregnancy with young maternal age
Premature baby
Premature delivery
Premature labour
Premature rupture of membranes
Premature separation of placenta
Preterm premature rupture of membranes
Previous caesarean section
Primigravida
Primiparous
Prolonged labour
Prolonged pregnancy
Prolonged rupture of membranes
Prophylaxis of abortion
Pseudomenstruation neonatal
Renal disorder in pregnancy
Retained placenta or membranes
Retained products of conception
Retroplacental haematoma
Risk of future pregnancy miscarriage
Rubella in pregnancy
Ruptured ectopic pregnancy
Second trimester pregnancy
Selective abortion
Short interpregnancy interval
Shoulder dystocia
Small for dates baby
Small size placenta
Somatic symptom disorder of pregnancy
Stillbirth
Subchorionic haematoma
Subchorionic haemorrhage
Term baby
Term birth
Third stage postpartum haemorrhage
Third trimester pregnancy
Threatened labour
Thyroid dysfunction in pregnancy
Transverse presentation
Traumatic delivery
Tubal rupture
Twin pregnancy
Umbilical cord abnormality
Umbilical cord around neck

Umbilical cord compression
Umbilical cord cyst
Umbilical cord haemorrhage
Umbilical cord occlusion
Umbilical cord prolapse
Umbilical cord short
Umbilical cord thrombosis
Umbilical cord vascular disorder
Umbilical granuloma
Unintended pregnancy
Unstable foetal lie
Unwanted pregnancy
Uterine atony
Uterine contractions abnormal
Uterine contractions during pregnancy
Uterine hyperstimulation
Uterine hypertonus
Uterine hypokinesia
Uterine hypotonus
Uterine inversion
Uterine irritability
Uterine tachysystole
Vanishing twin syndrome
Vasa praevia
Velamentous cord insertion
Venous thrombosis in pregnancy
Weight decrease neonatal

Lactation

Cases with events denoting lactation were retrieved from the safety database for analysis if they contained an event within the 'Neonatal exposures via breast milk' SMQ, ie, either of the following MedDRA PTs: 'Exposure via breast milk' or 'Maternal exposure during breast feeding' or 'Intoxication by breast feeding'.

Pulmonary veno-occlusive disease associated with pulmonary oedema

The case will be included in this subgroup if it contains an event with the following MedDRA PT:

Acute lung injury
Acute pulmonary oedema
Acute respiratory distress syndrome
Negative pressure pulmonary oedema

Non-cardiogenic pulmonary oedema
Pulmonary congestion
Pulmonary oedema
Pulmonary oedema neonatal
Reexpansion pulmonary oedema
Pulmonary veno-occlusive disease
Venoocclusive disease
Pulmonary vein occlusion

Renal function impairment/ acute renal failure

Cases including events denoting renal function impairment / acute renal failure are retrieved from the safety database for analysis if they contain an event PT within the MedDRA SMQ 'Acute renal failure' (narrow scope, including the PT 'Renal impairment') or it contains an event with any of the following MedDRA PTs: 'Blood creatinine abnormal', 'Blood creatinine increased', 'Creatinine renal clearance abnormal', 'Creatinine renal clearance decreased', 'Glomerular filtration rate abnormal', 'Glomerular filtration rate decreased', 'Renal function test abnormal', 'Renal transplant', 'Renal tubular injury', 'Renal tubular necrosis', and 'Urine output decreased', ie, any of the following MedDRA PTs:

Acute kidney injury
Acute phosphate nephropathy
Anuria
Azotaemia
Blood creatinine abnormal
Blood creatinine increased
Continuous haemodiafiltration
Creatinine renal clearance abnormal
Creatinine renal clearance decreased
Dialysis
Foetal renal impairment
Glomerular filtration rate abnormal
Glomerular filtration rate decreased
Haemodialysis
Haemofiltration
Neonatal anuria
Nephropathy toxic
Oliguria
Peritoneal dialysis
Prerenal failure
Renal failure
Renal failure neonatal
Renal function test abnormal
Renal impairment

Renal impairment neonatal
Renal transplant
Renal tubular injury
Renal tubular necrosis
Subacute kidney injury
Urine output decreased

Use in Pediatric Patients

Cases referring to patients with an age of less than 18 years or patients in the age group Adolescent or younger, ie, Adolescent, Child, Infant, Neonate, or Foetus (with exclusion of cases referring to exposure during pregnancy).

Use in Elderly Over 75 Years of Age

Cases referring to patients with an age greater or equal to 75 years.

Concomitant Use With Strong Inhibitors of CYP2C8

Cases containing medication which is the strong inhibitor of CYP2C8: gemfibrozil.

Concomitant Use With Strong Inhibitors of UGT1A3 and UGT2B7

Cases containing the following medications which are inhibitors of UGT1A3 and UGT2B7: valproic acid, valproate, valpromide, probenecid, and fluconazole.