Professional Information (PI) Leaflet

SCHEDULING STATUS
Schedule 4

1 NAME OF THE MEDICINE

UPTRAVI® 200 microgram film-coated tablets

UPTRAVI® 400 microgram film-coated tablets

UPTRAVI® 600 microgram film-coated tablets

UPTRAVI® 800 microgram film-coated tablets

UPTRAVI® 1 000 microgram film-coated tablets

UPTRAVI® 1 200 microgram film-coated tablets

UPTRAVI® 1 400 microgram film-coated tablets

UPTRAVI® 1 600 microgram film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

UPTRAVI 200 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 200 micrograms selexipag.

UPTRAVI 400 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 400 micrograms selexipag.

UPTRAVI 600 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 600 micrograms selexipag.

UPTRAVI 800 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 800 micrograms selexipag.

UPTRAVI 1 000 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 1 000 micrograms selexipag.

UPTRAVI 1 200 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 1 200 micrograms selexipag.

UPTRAVI 1 400 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 1 400 micrograms selexipag.

UPTRAVI 1 600 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 1 600 micrograms selexipag.

Contains sugar (mannitol).

UPTRAVI 200 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 72,6 mg mannitol.

UPTRAVI 400 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 72,4 mg mannitol.

UPTRAVI 600 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 72,2 mg mannitol.

UPTRAVI 800 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 72,0 mg mannitol.

UPTRAVI 1 000 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 71,8 mg mannitol.

UPTRAVI 1 200 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 71,6 mg mannitol.

UPTRAVI 1 400 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 71,4 mg mannitol.

UPTRAVI 1 600 microgram film coated tablets:

Each 7,3 mm diameter film-coated tablet contains 71,2 mg mannitol.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

UPTRAVI 200 microgram film coated tablets:

Round, 7,3 mm diameter, light-yellow, film-coated tablets with "2" debossed on one side.

UPTRAVI 400 microgram film coated tablets:

Round, 7,3 mm diameter, red, film-coated tablets with "4" debossed on one side.

UPTRAVI 600 microgram film coated tablets:

Round, 7,3 mm diameter, light-violet, film-coated tablets with "6" debossed on one side.

UPTRAVI 800 microgram film coated tablets:

Round, 7,3 mm diameter, green, film-coated tablets with "8" debossed on one side.

UPTRAVI 1 000 microgram film coated tablets:

Round, 7,3 mm diameter, orange, film-coated tablets with "10" debossed on one side.

UPTRAVI 1 200 microgram film coated tablets:

Round, 7,3 mm diameter, dark-violet, film-coated tablets with "12" debossed on one side.

UPTRAVI 1 400 microgram film coated tablets:

Round, 7,3 mm diameter, dark-yellow, film-coated tablets with "14" debossed on one side.

UPTRAVI 1 600 microgram film coated tablets:

Round, 7,3 mm diameter, brown, film-coated tablets with "16" debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

UPTRAVI is indicated for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult patients with WHO functional class (FC) II–IV to delay disease progression. Disease progression events included: death, hospitalisation for PAH, initiation of prostanoids, or other disease progression events (decrease of 6-minute walk distance [6MWD] associated with either worsened PAH symptoms or need for additional PAH-specific treatment).

UPTRAVI is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy.

4.2 Posology and method of administration

Posology

Individualised dose titration

The goal is to reach the individually appropriate dose for each patient (the individualised maintenance dose).

The recommended starting dose of UPTRAVI is 200 micrograms given twice daily, approximately 12 hours apart. The dose is increased in increments of 200 micrograms given twice daily, usually at weekly intervals, until an acceptable maximum tolerated dose is achieved or adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1 600 micrograms twice daily is reached. While a maximum with an acceptable tolerability is being determined, it is recommended not to discontinue treatment in the event of mild to moderate pharmacological side effects since they are usually transient or manageable with symptomatic treatment (see section 4.8). If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level.

Individualised maintenance dose

The highest tolerated dose reached during dose titration should be maintained. If the therapy over time is less tolerated at a given dose, symptomatic treatment or a dose reduction to the next lower dose should be considered.

Interruptions and discontinuations

If a dose of medication is missed, it should be taken as soon as possible. The missed dose should not be taken if time for the next scheduled dose is within 6 hours.

If treatment is missed for 3 days or more, UPTRAVI should be re-started at a lower dose and then titrated.

Dosage adjustment with co-administration of moderate CYP2C8 inhibitors

When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI to once daily. Revert back to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped (see section 4.5).

Information about special populations

Paediatric use

Paediatric population (< 18 years)

The safety and efficacy of UPTRAVI in children have not been established.

Elderly use

Elderly (≥ 65 years)

No adjustment to the dosing regimen is needed in elderly patients.

Use in other populations

Renal impairment

No adjustment to the dosing regimen is needed in patients with mild or moderate renal impairment.

No change in starting dose is required in patients with severe renal impairment. In patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1,73 m^2) caution should be exercised during dose titration. There is no experience with UPTRAVI in patients undergoing dialysis.

Hepatic impairment

No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

A once daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to UPTRAVI and its active metabolite in this population. There is no clinical experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

Method of administration

The film-coated tablets are to be taken orally in the morning and in the evening.

UPTRAVI may be taken with or without food. Tolerability may be improved when taken with food.

The tablets should not be split, crushed or chewed, and are to be swallowed with water.

4.3 Contraindications

- Hypersensitivity to the active substance, selexipag, or to any of the excipients listed in section 6.1.
- Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil, see section 4.5).

4.4 Special warnings and precautions for use

Hyperthyroidism

Hyperthyroidism has been observed with UPTRAVI. Thyroid function tests are recommended as clinically indicated.

Pulmonary veno-occlusive disease

Should signs of pulmonary oedema occur, consider the possibility of associated pulmonary veno-occlusive disease. If confirmed, discontinue UPTRAVI.

Intolerance

UPTRAVI contains mannitol that may have a laxative effect or cause diarrhoea. Patients with the rare hereditary condition of mannitol intolerance should not take UPTRAVI.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants or inhibitors of platelet aggregation: Selexipag and its active metabolite inhibited platelet aggregation *in vitro*. In the Phase 3 placebo-controlled study in patients with PAH, no increased risk of bleeding was detected with selexipag compared to placebo, including when selexipag was administered with anticoagulants (such as heparin, coumarin-type anticoagulants) or inhibitors of platelet aggregation. In a study in healthy subjects, selexipag (400 micrograms twice a day) did not alter the exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 20 mg warfarin. Selexipag did not influence the pharmacodynamic effect of warfarin on the international normalised ratio. The pharmacokinetics of selexipag and its active metabolite were not affected by warfarin.

Interaction with other medicines

Selexipag is hydrolysed to its active metabolite by carboxylesterase (see section 5.2). Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter breast cancer resistance protein (BCRP).

Selexipag and its active metabolite do not inhibit or induce cytochrome P450 enzymes or transport proteins at clinically relevant concentrations.

Interaction with enzyme inhibitors

Lopinavir/ritonavir: In the presence of 400/100 mg lopinavir/ritonavir, twice a day, a strong CYP3A4, OATP (OATP1B1 and OATP1B3) and P-gp inhibitor, exposure to selexipag increased approximately 2-fold, whereas the exposure to the active metabolite of selexipag did not change.

Gemfibrozil: 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. Concomitant administration of selexipag with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated (see section 4.3).

Clopidogrel: Concomitant administration of selexipag with clopidogrel (300 mg as a loading dose or maintenance dose of 75 mg once a day), a moderate inhibitor of CYP2C8, had no

relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2,2-fold and 2,7-fold following loading dose and maintenance dose, respectively (see section 4.2).

Interaction with enzyme inducers

Rifampicin: In the presence of 600 mg rifampicin, once a day, 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.

Midazolam: At steady state after up-titration to 1 600 µg UPTRAVI twice a day, no change in exposure to midazolam, a sensitive intestinal and hepatic CYP3A4 substrate, or its metabolite, 1-hydroxymidazolam, was observed. Concomitant administration of UPTRAVI with CYP3A4 substrates does not require dose adjustment.

Pharmacodynamic interactions: Reductions in blood pressure may occur when UPTRAVI is administered with diuretics, antihypertensive medicines, or other vasodilators.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should practice effective contraception while taking UPTRAVI.

Pregnancy

Safety and/or efficacy in pregnancy has not been established. There are limited data on the use of UPTRAVI in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Breastfeeding

It is unknown whether selexipag or its metabolites are excreted in human milk.

In rats, selexipag or its metabolites are excreted in the milk (see section 5.3).

Breastfeeding is not recommended during treatment with UPTRAVI.

Fertility

There are no clinical data available. In rat studies, selexipag at high doses caused transient disturbances in oestrus cycles that did not affect fertility (see section 5.3). The relevance for humans is not known.

4.7 Effects on the ability to drive and use machines

No studies on the effect of UPTRAVI on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions related to the pharmacological effects of UPTRAVI are headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in the extremity, flushing, and arthralgia. These reactions are more frequent during the dose titration phase. The majority of these reactions are of mild to moderate intensity.

Tabulated list of adverse reactions

The safety of UPTRAVI has been evaluated in a long-term, Phase 3, placebo-controlled study enrolling 1 156 patients with symptomatic PAH. The mean treatment duration was 76,4 weeks (median 70,7 weeks) for patients receiving UPTRAVI versus 71,2 weeks (median 63,7 weeks) for patients on placebo. The exposure to UPTRAVI was up to 4,2 years.

Adverse reactions associated with UPTRAVI over the entire treatment period in this study are presented in the table below. Frequency is reported according to CIOMS: very common ≥ 1/10, common ≥ 1/100 to < 1/10, uncommon ≥ 1/1 000 to < 1/100, rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000).

Table 1: Adverse reactions§

System organ class	Very common	Common	Uncommon
Blood and lymphatic disorders		Anaemia	
Endocrine disorders		Hyperthyroidism	
Metabolism and nutrition disorders		Decreased appetite	
Nervous system disorders	Headache *		
Vascular disorders	Flushing*	Hypotension	
Gastro-intestinal disorders	Diarrhoea* Vomiting* Nausea*	Abdominal pain Dyspepsia	
Skin and subcutaneous tissue disorders	Rash[1]		
Musculoskeletal and connective tissue disorders	Jaw pain* Myalgia* Arthralgia*		

	Pain in extremity*		
General disorders and administration site conditions		Pain	

§ reported by 3 % more in the active group versus placebo and/or if confirmed by laboratory findings (as appropriate) and/or if the adverse event is consistent with the pharmacology of the medicine and hence a causal relationship was deemed at least as possible.

* See description of selected adverse reactions

[1] Based on the MedDRA high level group terms of rash

Description of selected adverse reactions

Pharmacological effects associated with titration and maintenance treatment

Adverse reactions associated with the pharmacological action of selexipag have been observed frequently, in particular during the phase of individualised dose titration. The placebo-corrected incidence during the titration and maintenance phase, respectively, were: headache (36 and 20 %), diarrhoea (24 and 16 %), jaw pain (22 and 17 %), nausea (16 and 10 %), myalgia (10 and 6 %), vomiting (10 and 2 %), pain in extremity (9 and 7 %), flushing (7 and 7 %) and arthralgia (2 and 4 %). These effects are usually transient or manageable with symptomatic treatment.

Laboratory abnormalities

Haemoglobin

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in haemoglobin 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 haemoglobin concentration to below 10 g/dL was reported in 8,6 % of patients treated with UPTRAVI and 5,0 % of placebo-treated patients.

Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH. Signs of overactive thyroid gland were seen in 2% of patients on selexipag versus none in the placebo group.

A reduction (up to −0,3 MU/L from a baseline median of 2,5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent.

Combination treatment of UPTRAVI with macitentan and tadalafil in newly diagnosed PAH patients

Safety of triple combination treatment (UPTRAVI, macitentan and tadalafil) versus double combination (macitentan, tadalafil and placebo) in newly diagnosed PAH patients was evaluated in the double -blind, placebo-controlled TRITON clinical study. Treatment was initiated with macitentan 10 mg and tadalafil 20 mg (increased to 40 mg, if tolerated). Treatment with UPTRAVI (N=119) or placebo (N=120) was initiated on Day 15 and patients were uptitrated per the current UPTRAVI titration and dosing regimen (see Dosage and Administration). The median exposure was 90 weeks for patients receiving UPTRAVI versus 78 weeks for patients on placebo.

While the safety and tolerability profile of UPTRAVI was similar in both TRITON and GRIPHON studies, the frequencies for dyspepsia and anaemia were higher in TRITON. Dyspepsia was reported in 16,8 % of patients in the triple therapy group and 8,3 % in the double therapy group, and anaemia was reported in 13,4 % of patients in the triple therapy group and 8,3 % in the double therapy group.

The adverse reactions that occurred in at least 10 % of patients in triple therapy group and ≥5 % more commonly on UPTRAVI, macitentan and tadalafil than on placebo, macitentan, and tadalafil are shown in Table 2.

Table 2 Adverse Reactions Reported in atleast 10 % of patients and more commonly (≥ 5 %) on UPTRAVI + Macitentan + Tadalafil than on Placebo + Macitentan + Tadalafil in TRITON study.

Table 2 **Adverse Reactions Reported in at least 10% of patients and More Commonly (≥ 5 %) on UPTRAVI + Macitentan + Tadalafil than on Placebo+Macitentan + Tadalafil in TRITON study**

	Double-blind PAH AC-065A308/TRITON		
System organ class	**UPTRAVI + Macitentan + Tadalafil combination therapy N=119**	**Placebo + Macitentan + Tadalafil combination therapy N=120**	**Frequency category**
Nervous system disorders			
Headache	55,5 % (66)	31,7 % (38)	Very common
Gastrointestinal disorders			
Diarrhoea	49,6 % (59)	26,7 % (32)	Very common
Nausea	41,2 % (49)	21,7 % (26)	Very common
Vomiting	24,4 % (29)	10,8 % (13)	Very common
Dyspepsia	16,8 % (20)	8,3 % (10)	Very common
Musculoskeletal and connective tissue disorders			
Jaw pain	26,1 % (31)	11,7 % (14)	Very common
Pain in extremity	23,5 % (28)	11,7 % (14)	Very common
Vascular disorders			

Flushing	16,0 % (19)	7,5 % (9)	Very common
Blood and lymphatic system disorders			
Anaemia	13,4 % (16)	8,3 % (10)	Very common

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience: hypersensitivity reactions, urticaria and angioedema. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and e-Reporting platform (who-umc.org) found on SAHPRA website.

Alternatively, adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose

Isolated cases of overdose up to 3 200 microgram were reported. The patient should be monitored for adverse events as per section 4.8. In the event of overdose, supportive

measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein-bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin,

ATC code: B01AC27

Mechanism of action

The vasculo-protective effects of prostacyclin (PGI_2) are mediated by the prostacyclin receptor (IP receptor). Decreased expression of IP receptors and decreased synthesis of prostacyclin contribute to the pathophysiology of PAH.

Selexipag is an oral, selective, IP receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogs. Selexipag is hydrolysed 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). Selectivity against EP_1, EP_3, FP and TP is important because these are well-described contractile receptors in gastro-intestinal tract and blood vessels. Selectivity against EP_2, EP_4 and DP_1 is important because these receptors mediate immune depressive effects.

Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. Selexipag improves haemodynamic variables and prevents cardiac and pulmonary remodeling in a rat model of PAH. In these PAH rats, pulmonary and peripheral vasodilation in response to selexipag correlate, indicating that peripheral vasodilation reflects pulmonary pharmacodynamic efficacy. Selexipag does not cause IP receptor desensitization *in vitro* nor tachyphylaxis in a rat model.

PAH patients have variable degrees of IP receptor expression. Differences in maintenance dose of selexipag between individuals may be related to differences in IP receptor expression levels.

Pharmacodynamic effects

Pulmonary haemodynamics

A Phase 2 double-blind, placebo-controlled clinical study assessed haemodynamic variables after 17 weeks of treatment in patients with PAH WHO FC II–III and concomitantly receiving endothelin receptor antagonist (ERAs) and/or phosphodiesterase-5 (PDE-5) inhibitors. Patients titrating selexipag to an individually tolerated dose (200 micrograms twice daily increments up to 800 micrograms twice daily; N = 33) achieved a statistically significant mean reduction in pulmonary vascular resistance of 30,3 % (95 % confidence interval [CI]: −44,7 %, −12,2 %; p = 0,0045) and an increase in cardiac index

(mean treatment effect) of 0,48 L/min/m^2, (95 % CI: 0,13; 0,83) compared to placebo (N = 10).

Clinical studies / pharmacological properties

Clinical efficacy and safety

Efficacy in patients with PAH

The effect of selexipag on progression of PAH was demonstrated in a multi-center, long-term (maximum duration of exposure approximately 4,2 years), double-blind, placebo-controlled, parallel group, event-driven Phase 3 study in 1156 patients with symptomatic [WHO FC I–IV] PAH. Patients were randomised to either placebo (N = 582), or selexipag (N = 574) twice a day. The dose was increased in weekly intervals by increments of 200 micrograms given twice a day to determine the individualised maintenance dose (200–1600 micrograms twice a day).

The mean age was 48,1 years (range 18–80 years of age) with the majority of subjects being Caucasian (65,0 %) and female (79,8 %). Approximately 1 %, 46 %, 53 % and 1 % of patients were in WHO FC I, II, III and IV, respectively, at baseline.

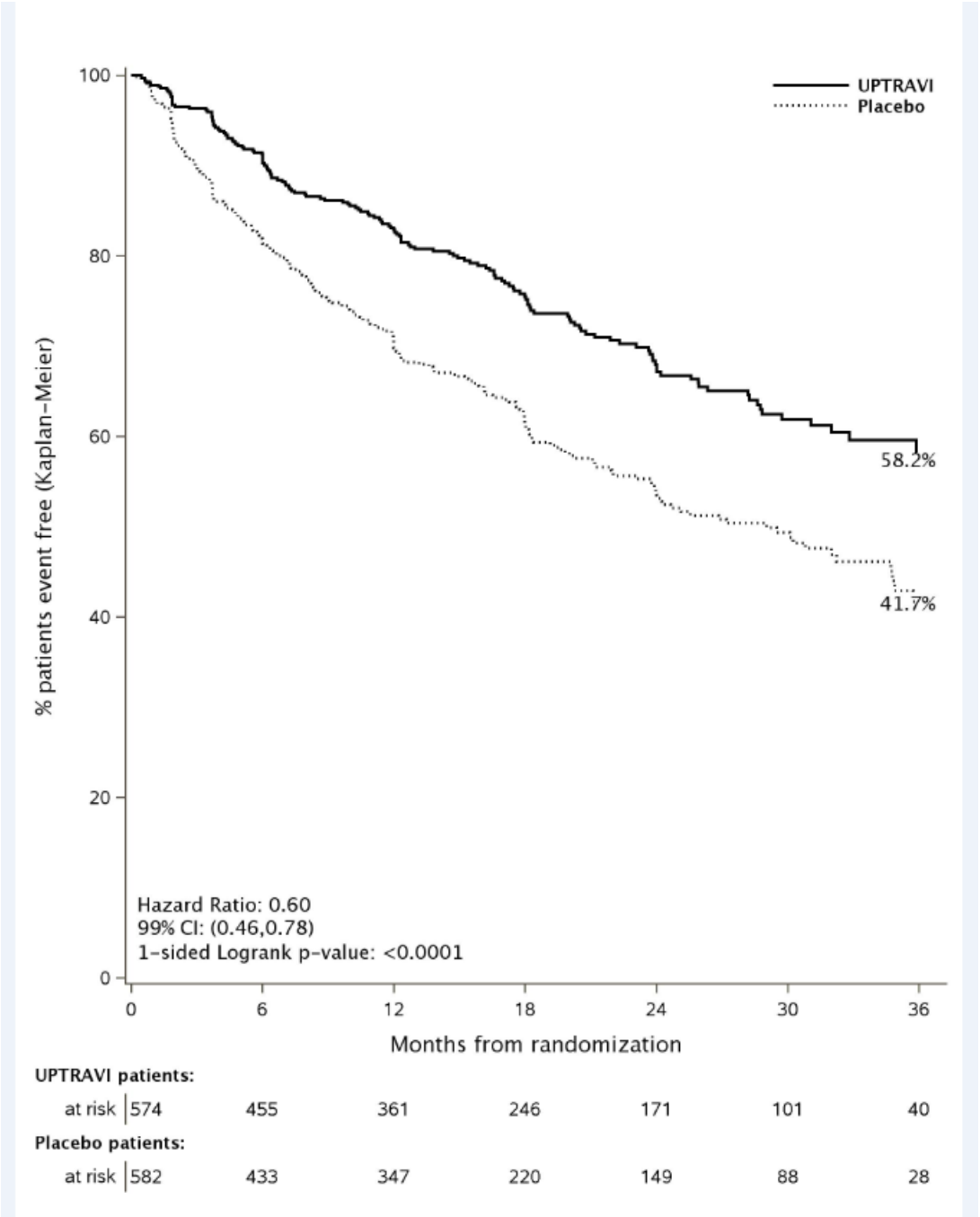
Idiopathic or heritable PAH was the most common etiology in the study population (58 %) followed by PAH due to connective tissue disorders (29 %), PAH associated with congenital heart disease with repaired shunts (10 %), and PAH associated with other etiologies (medicines and toxins [2 %] and HIV [1 %]).

At baseline, the majority of enrolled patients (80 %) were being treated with a stable dose of a specific therapy for PAH, either with an ERA (15 %) or with a PDE-5 inhibitor (32 %) or with both an ERA and a PDE-5 inhibitor (33 %).

The overall median double-blind treatment duration was 63,7 weeks for the placebo group and 70,7 weeks for the group on selexipag.

Treatment with selexipag 200–1600 micrograms twice a day resulted in a 40% reduction (hazard ratio [HR] 0,60; 99 % CI: 0,46, 0,78; one-sided log-rank p-value < 0,0001) of the occurrence of morbidity or mortality events up to 7 days after last dose compared to placebo [Figure 1]. The beneficial effect of selexipag was primarily attributable to a reduction in hospitalisation for PAH and a reduction in other disease progression events).

Figure 1 Kaplan-Meier estimates of the first morbidity-mortality event in GRIPHON



The observed effect of selexipag versus placebo on the primary endpoint was independent of the achieved individualised maintenance dose (IMD):

IMD 200–400 µg twice daily (23,2 % of patients): HR 0.60 (95 % CI: 0,41, 0,88, one-sided log-rank p = 0,0038)

IMD 600–1000 µg twice daily (31,4 % of patients: HR 0,53 (95 % CI: 0,38, 0,72, one-sided log-rank p < 0,0001)

IMD 1200–1600 µg twice daily (4,9 % of patients): HR 0,64 (95 % CI: 0,49, 0,82, one-sided log-rank p = 0,0002).

Figure 2 Kaplan-Meier estimates of the first morbidity-mortality event in GRIPHON by individual maintenance dose group

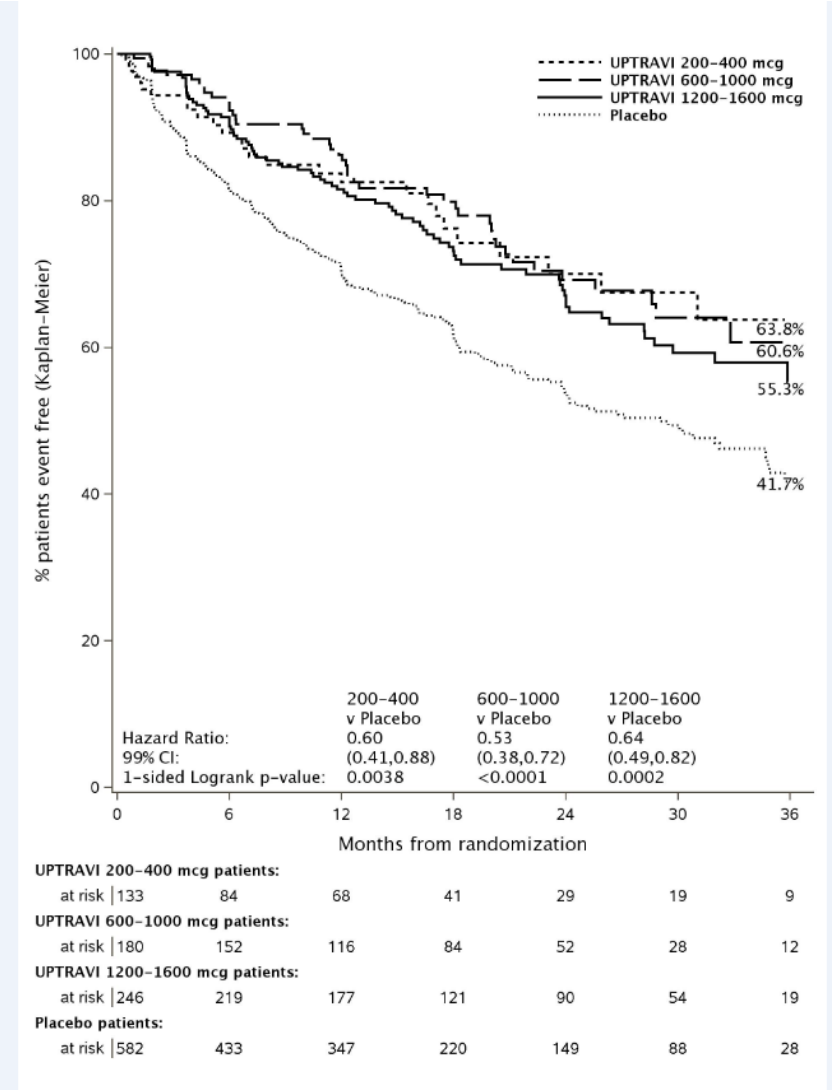
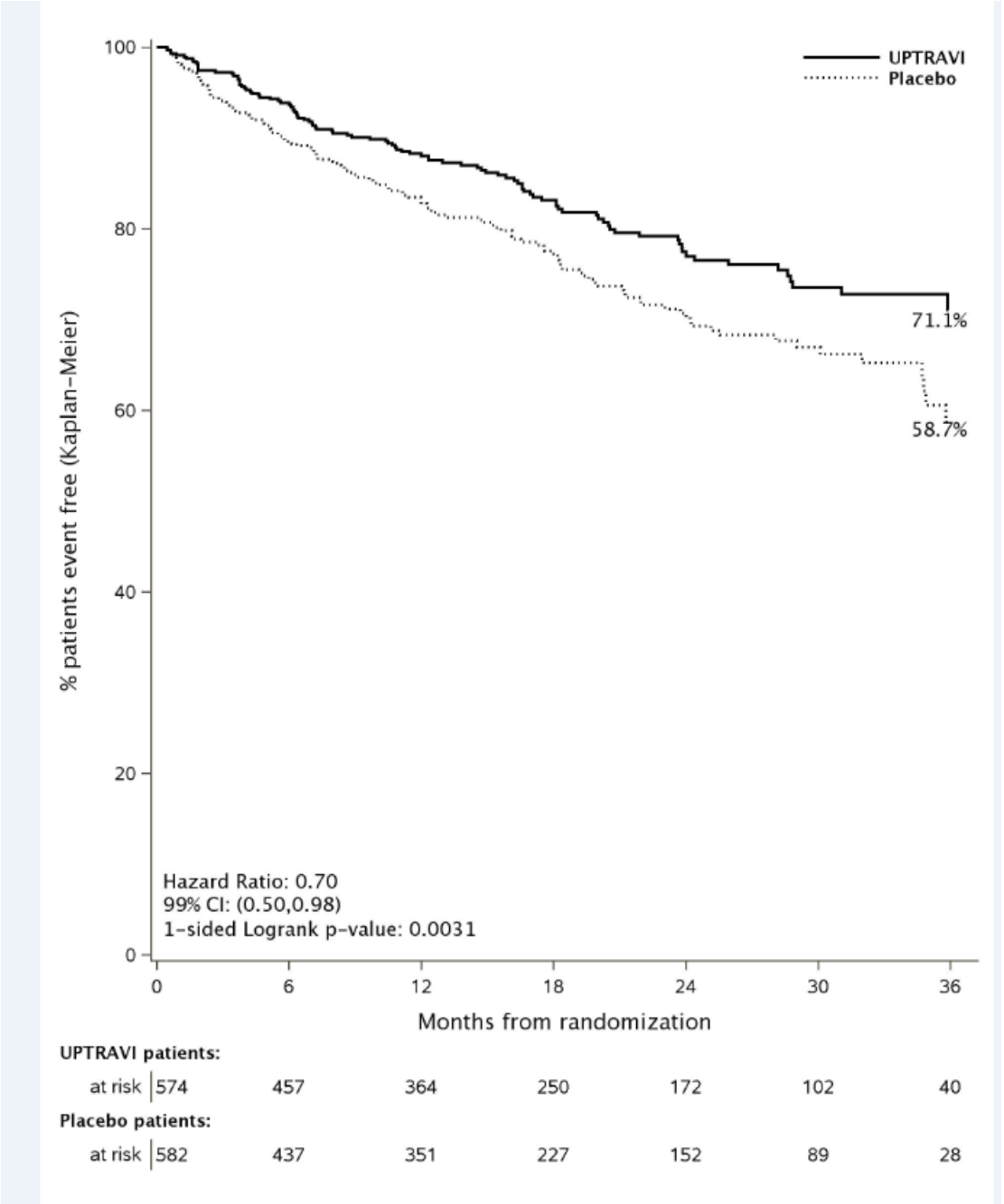


Figure 3 Kaplan-Meier estimates of the occurrence of death due to PAH or first hospitalization for PAH in GRIPHON



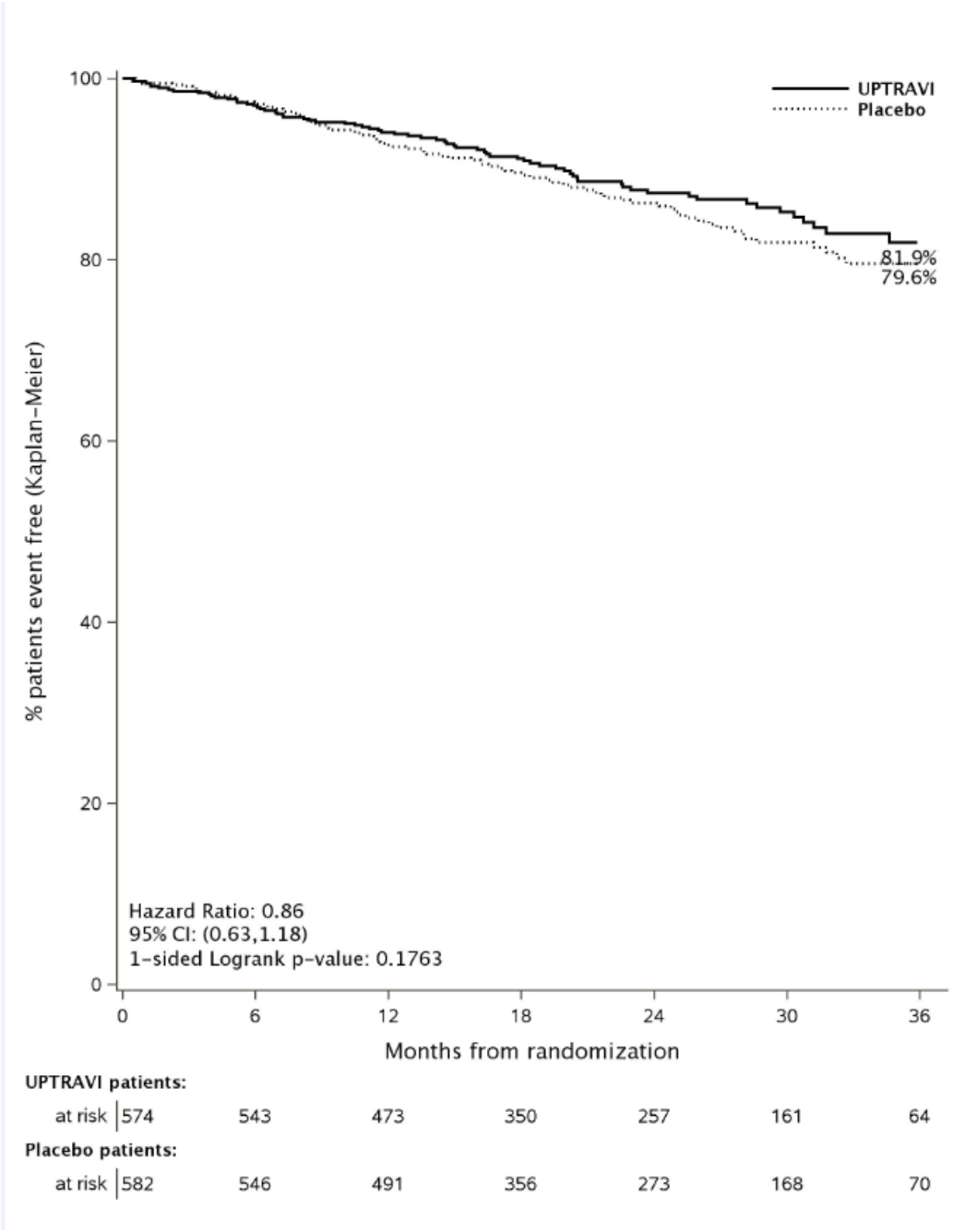
The number of patients who experienced as a first event, death due to PAH or hospitalisation for PAH up to end of treatment was 102 (17,8 %) in the selexipag group,

and 137 (23,5 %) in the placebo group. Death due to PAH as a component of the endpoint was observed in 16 (2,8 %) patients on selexipag and 14 (2,4 %) on placebo. Hospitalisation for PAH was observed in 86 (15 %) of patients on selexipag and 123 (21,1 %) of patients on placebo. UPTRAVI reduced the risk of hospitalisation for PAH as first outcome event compared to placebo (HR 0,67, 99 % CI: 0,46, 0,98); one-sided log-rank p = 0,04).

The total number of deaths of all causes up to study closure was 100 (17,4 %) for the UPTRAVI group and 105 (18,0 %) for the placebo group (HR 0,97, 99 % CI: 0,68, 1,39).

The number of deaths due to PAH up to study closure was 70 (12,2 %) for the UPTRAVI group and 83 (14,3 %) for the placebo group.

Figure 4 Kaplan-Meier estimates of the occurrence of death due to PAH up to study closure



Symptomatic endpoint

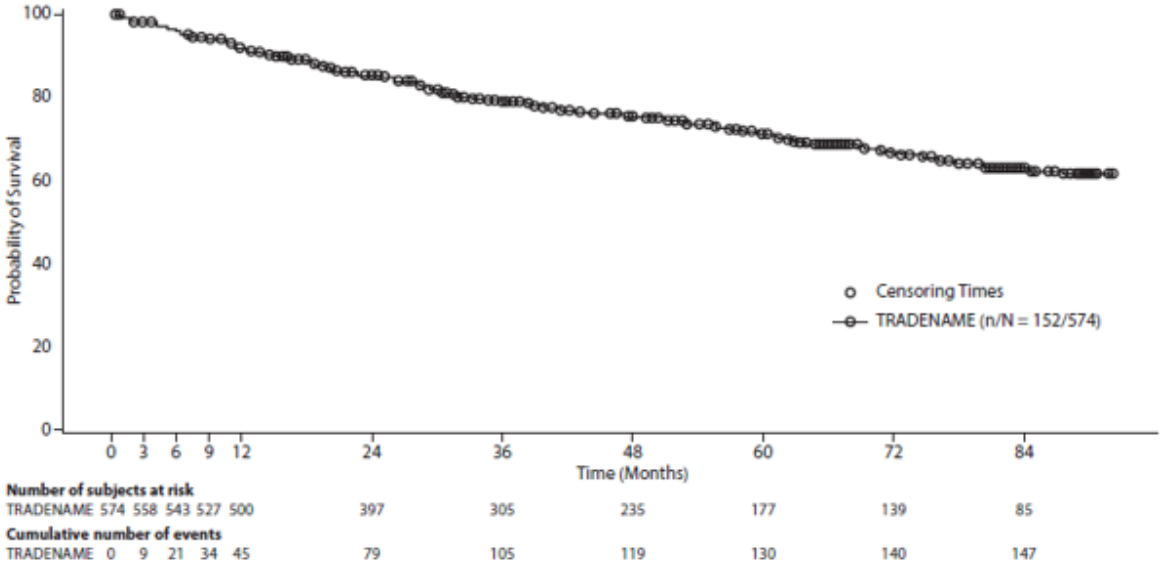
Exercise capacity was evaluated as a secondary endpoint. Treatment with UPTRAVI resulted in a placebo-corrected median increase in 6MWD measured at trough (i.e., approximately 12 hours post-dose) of 12 meters at Week 26 (99 % CI: 1, 24 meters,

one-sided p value = 0, 0027). In patients without concurrent PAH-specific therapy, the treatment effect measured at trough was 34 meters (99 % CI: 10, 63 meters).

Long-Term Treatment of PAH

Patients enrolled into the pivotal study (GRIPHON) were eligible to enter a long-term open-label extension study. A total of 574 patients were treated with Uptravi in the GRIPHON study; of these, 330 patients continued Uptravi treatment in the open-label extension study. Kaplan-Meier estimates of survival of these patients across the GRIPHON and the long-term extension study at 1, 2, 5 and 7 years were 92 %, 85 %, 71 %, and 63 %, respectively (Figure 5). The median follow-up duration was 4,5 years and the median exposure to Uptravi was 3 years. Most patients were WHO FC II or III (47,6% and 51,2 %, respectively); less than 1% of patients were in FC I (0,7 %) or IV (0,5 %) at baseline. The Kaplan-Meier estimates of survival at 1, 2, 5, and 7 years for patients of WHO FC I-II at baseline of the pivotal study were 97 %, 91 %, 81 % and 70 %, respectively, and for patients of WHO FC III-IV at baseline were 88 %, 80 %, 61% and 56 %, respectively.

Figure 5 Kaplan-Meier estimates of time to death (all-causes) in long-term follow-up of UPTRAVI treatment



5.2 Pharmacokinetic properties

The pharmacokinetics of selexipag and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of selexipag and the active metabolite, both after single- and multiple-dose administration, were dose-proportional up to a single dose of 800 micrograms and multiple doses of up to 1 800 micrograms twice daily. After multiple-dose administration, steady-state conditions of selexipag and active metabolite were reached within 3 days. No accumulation in plasma, either of parent compound or active metabolite, occurred after multiple-dose administration.

In healthy subjects, inter-subject variability in exposure (area under the curve over a dosing interval) at steady-state was 43 % and 39 % for selexipag and the active metabolite, respectively. Intra-subject variability in exposure was 24 % and 19 % for selexipag and the active metabolite, respectively.

Exposure to selexipag and the active metabolite at steady-state in Pulmonary Arterial Hypertension (PAH) patients and healthy subjects was similar. The pharmacokinetics of selexipag and the active metabolite in PAH patients were not influenced by the severity of the disease and did not change with time.

Absorption

Selexipag is rapidly absorbed and is hydrolysed by carboxylesterases to its active metabolite.

Maximum observed plasma concentrations of selexipag and its active metabolite after oral administration are reached within 1–3 h and 3–4 h, respectively.

The absolute bioavailability of selexipag is approximately 49 %.

In the presence of food, the exposure to selexipag after a single dose of 400 micrograms was increased by 10 % in Caucasian subjects and decreased by 15 % in Japanese subjects, whereas exposure to the active metabolite was decreased by 27 % (Caucasian subjects) and 12 % (Japanese subjects). More subjects reported adverse events after administration in the fasted than in the fed state.

Distribution

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). The volume of distribution of selexipag at steady state is 11,7 L.

Biotransformation

Selexipag is hydrolysed to its active metabolite in the liver and in the intestine by carboxylesterases. Oxidative metabolism catalysed mainly by CYP2C8 and to a smaller extent by CYP3A4 leads to the formation of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceeds 3 % of the total medicine-related material. Both in healthy subjects and PAH patients, after oral administration, exposure at steady-state to the active metabolite is approximately 3- to 4-fold higher than to the parent compound.

Elimination

Elimination of selexipag is predominantly via metabolism with a mean terminal half-life of 0,8–2,5 h. The active metabolite has a half-life of 6,2–13,5 h. The total body clearance of selexipag is 17,9 L/h. Excretion in healthy subjects was complete 5 days after administration and occurred primarily via faeces (accounting for 93 % of the administered dose) compared to 12 % in urine.

Renal impairment

A 1,4- to 1,7-fold increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1,73 m^2).

Hepatic impairment

In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, after a single dose administration of 400 micrograms of selexipag, exposure to selexipag was 2- and 4-fold higher, respectively, when compared to healthy subjects. Exposure to the active metabolite remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. Only two subjects with severe (Child-Pugh class C) hepatic impairment were dosed with selexipag. Exposure to selexipag and its active metabolite in these two subjects was similar to that in subjects with moderate (Child-Pugh class B) hepatic impairment.

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in subjects with moderate hepatic impairment during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice daily regimen.

5.3 Pre-clinical safety data

In the repeated-dose toxicity studies in rodents, strong blood pressure decrease as a result of exaggerated pharmacology induced transient clinical signs and reduced food consumption and body-weight gain. In adult and juvenile dogs, intestine and bone / bone marrow were identified as the main target organs after treatment with selexipag. In dogs less than 1 year of age, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. The effect occurred at 5-fold the human exposure (i.e., corrected for potency; 415-fold based on total exposure) (active metabolite). 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 (i.e., corrected for potency; 180-fold based on total exposure) in relation to human exposure at a dose of 1 600 micrograms of selexipag twice a day. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific sensitivity of dogs to develop intussusception and the safety margin, this finding is considered not relevant for adult humans.

Increased bone ossification and related changes in the bone marrow in dog studies are considered to be due to the activation of EP_4 receptors in dogs. As human EP_4 receptors are not activated by selexipag or its active metabolite, this effect is species-specific and, therefore, not relevant to humans.

Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.

In the 2-year carcinogenicity studies, selexipag caused an increased incidence of thyroid adenomas in mice and Leydig cell adenomas in rats. The mechanisms are rodent-specific. The findings were observed at exposures that were more than 25-fold above human exposure and are, therefore, not relevant for humans. Tortuosity of retinal arterioles was noted after 2 years of treatment only in rats. Mechanistically, the effect is considered to be induced by life-long vasodilation and subsequent changes in ocular hemodynamics. The finding is considered to be species-specific.

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.

Selexipag and its active metabolite were phototoxic *in vitro*. A dedicated clinical study did not indicate a phototoxic potential of selexipag in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

D-mannitol

Maize starch

Low substituted hydroxypropyl cellulose

Hydroxypropyl cellulose

Magnesium stearate

Film coating

UPTRAVI 200 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide yellow

Carnauba wax

UPTRAVI 400 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide red

Carnauba wax

UPTRAVI 600 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide red

Iron oxide black

Carnauba wax

UPTRAVI 800 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide yellow

Iron oxide black

Carnauba wax

UPTRAVI 1 000 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide red

Iron oxide yellow

Carnauba wax

UPTRAVI 1 200 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide black

Iron oxide red

Carnauba wax

UPTRAVI 1 400 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide yellow

Carnauba wax

UPTRAVI 1 600 microgram film-coated tablet

Hypromellose

Propylene glycol

Titanium dioxide

Iron oxide black

Iron oxide red

Iron oxide yellow

Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Store film-coated tablets in the original blisters and keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

UPTRAVI film-coated tablets are packed in alu/alu blisters with desiccant consisting of:

- 25 µm Polyamide/ 45 µm aluminium/high-density polyethylene/polyethylene with an embedded desiccant agent/high-density polyethylene forming foil
- Aluminium lid foil, push through 20 µm.

The blisters are packed in an outer carton as secondary functional packaging.

Pack sizes:

UPTRAVI 200/ 400/ 600/ 800/ 1 000/ 1 200/ 1 400 & 1600 µg tablets are packed in blisters containing 60 tablets.

UPTRAVI titration pack comprises of 200 µg tablets only, packed in blisters containing 140 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty) Ltd

(Reg. No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand, 1685

Tel: +27 (0)11 518 7000

ra-medinfoemmarkets@its.jnj.com

8 REGISTRATION NUMBERS

UPTRAVI 200 microgram: 53/7.1.3/0631

UPTRAVI 400 microgram: 53/7.1.3/0632

UPTRAVI 600 microgram: 53/7.1.3/0633

UPTRAVI 800 microgram: 53/7.1.3/0634

UPTRAVI 1 000 microgram: 53/7.1.3/0635

UPTRAVI 1 200 microgram: 53/7.1.3/0636

UPTRAVI 1 400 microgram: 53/7.1.3/0637

UPTRAVI 1 600 microgram: 53/7.1.3/0638

9 DATE OF FIRST AUTHORISATION

17 May 2022

10 DATE OF REVISION OF TEXT

05 May 2026