1 PRODUCT NAME

UPTRAVI® selexipag 200 microgram film coated tablets
UPTRAVI® selexipag 400 microgram film coated tablets
UPTRAVI® selexipag 600 microgram film coated tablets
UPTRAVI® selexipag 800 microgram film coated tablets
UPTRAVI® selexipag 1000 microgram film coated tablets
UPTRAVI® selexipag 1200 microgram film coated tablets
UPTRAVI® selexipag 1400 microgram film coated tablets
UPTRAVI® selexipag 1600 microgram film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

UPTRAVI 200 microgram film coated tablets
Each film coated tablet contains 200 micrograms of selexipag

UPTRAVI 400 microgram film coated tablets
Each film coated tablet contains 400 micrograms of selexipag

UPTRAVI 600 microgram film coated tablets
Each film coated tablet contains 600 micrograms of selexipag

UPTRAVI 800 microgram film coated tablets
Each film coated tablet contains 800 micrograms of selexipag

UPTRAVI 1000 microgram film coated tablets
Each film coated tablet contains 1000 micrograms of selexipag

UPTRAVI 1200 microgram film coated tablets
Each film coated tablet contains 1200 micrograms of selexipag

UPTRAVI 1400 microgram film coated tablets
Each film coated tablet contains 1400 micrograms of selexipag

UPTRAVI 1600 microgram film coated tablets
Each film coated tablet contains 1600 micrograms of selexipag

3 PHARMACEUTICAL FORM

UPTRAVI 200 microgram film coated tablets
Round light yellow, film-coated tablet with '2' debossed on one side

UPTRAVI 400 microgram film coated tablets
Round red yellow, film-coated tablet with '4' debossed on one side

UPTRAVI 600 microgram film coated tablets
Round light violet, film-coated tablet with '6' debossed on one side

UPTRAVI 800 microgram film coated tablets
Round green, film-coated tablet with '8' debossed on one side

UPTRAVI 1000 microgram film coated tablets
Round orange, film-coated tablet with '10' debossed on one side

UPTRAVI 1200 microgram film coated tablets
Round dark violet, film-coated tablet with '12' debossed on one side

UPTRAVI 1400 microgram film coated tablets
Round dark yellow, film-coated tablet with '14' debossed on one side

UPTRAVI 1600 microgram film coated tablets
Round brown, film-coated tablet with '16' debossed on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

UPTRAVI is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue disease
- pulmonary arterial hypertension associated with congenital heart disease with repaired shunts
- pulmonary arterial hypertension associated with drugs and toxins

in patients with WHO functional class II, III or IV symptoms.

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 Dose and method of administration

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Selexipag can be used in combination with an ERA or a PDE-5 inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy.

Dosage

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 adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1600 micrograms twice daily is reached. At the beginning of treatment and at each up-titration step it is recommended to take the first dose in the evening. During dose titration, it is recommended not to discontinue treatment in the event of expected pharmacological side effects since they are usually transient or manageable with symptomatic treatment (see Section 4.8 UNDESIRABLE EFFETCS). 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 is less tolerated at a given dose over time, symptomatic treatment or a dose reduction to the next lower dose should be considered. 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.

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 it is almost time for the next scheduled dose (within approximately 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Dosage adjustment in elderly patients (≥ 65 years)
No adjustment to the dosing regimen is needed in elderly patients.

Dosage adjustment in patients with hepatic impairment
No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (i.e., 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 selexipag and its active metabolite.

Dosage adjustment in patients with 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. Dose titration in these patients should be done with caution.

Method of administration

Oral use.

The film-coated tablets are to be taken orally in the morning and in the evening. UPTRAVI should be taken consistently 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 some water.

4.3 Contraindications

UPTRAVI is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.

- Severe hepatic impairment (Child-Pugh class C).
- 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 (e.g., transient ischaemic attack, stroke) within the last 3 months.

- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.
- Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil)

4.4 Special warnings and precautions for use

Additional Information on Special Populations

Studies with selexipag have been mainly performed in PAH patients classified as WHO functional Class II and III. Selexipag has only been studied in a limited number of patients with WHO functional Class IV. Selexipag has only been studied in a limited number of patients with PAH due to drugs or toxins.

Hypotension

UPTRAVI 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 (e.g., patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).

Increase in heart rate

UPTRAVI may cause a moderate increase in heart rate after each dose.

Hyperthyroidism

Hyperthyroidism has been observed with UPTRAVI (2% patients on selexipag and 0% of placebo-treated patients) and other prostacyclin receptor agonists. 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.

Elderly

There is limited clinical experience with selexipag in patients over the age of 75 years, therefore UPTRAVI should be used with caution in this population.

Paediatric

The safety and efficacy of UPTRAVI in children (<18 years) has not been established.

Genotoxicity

Selexipag and its active metabolite are not genotoxic under *in vivo* conditions. The weight of evidence from a battery of genotoxicity studies indicates no cause for clinical concern.

Patients with 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 selexipag and its active metabolite in this population. There is no experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

Patients with 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.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies

Selexipag is hydrolysed to its active metabolite by carboxylesterases) [see Section 5.2 PHARMACOKINETIC PROPERTIES]. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalysed by UGT1A3 and UGT2B7. 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.

In vivo studies

PAH-specific therapies: In the Phase 3 placebo-controlled study in patients with PAH, no relevant changes in the exposure (area under the plasma concentration-time curve during a dose interval) to selexipag and its active metabolite were observed when administered in combination with an ERA and/or PDE-5 inhibitor.

Anticoagulants or inhibitors of platelet aggregation: Selexipag is an inhibitor of 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.

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.

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 1600 µg selexipag 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 selexipag with CYP3A4 substrates does not require dose adjustment.

Inhibitors of UGT1A3 and UG2B7: The effect of strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration may result in a significant increase in exposure or its active metabolite.

Inhibitors of CYP2C8: 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 UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Concomitant administration of selexipag with clopidogrel (loading dose 300 mg 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. Dosing frequency of UPTRAVI should be reduced to once daily when co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide). Dosing frequency of UPTRAVI should be reverted back to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Dosage adjustment with co-administration of moderate CYP2C8 inhibitors).

Hormonal contraceptives: Specific drug-drug interaction studies with hormonal contraceptives have not been conducted. Since selexipag did not affect the exposure to the CYP3A4 substrates midazolam and R-warfarin or the CYP2C9 substrate S-warfarin, reduced efficacy of hormonal contraceptives is not expected**.**

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

4.6 Fertility, pregnancy and lactation

Effects on Fertility
Selexipag 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.

Use in pregnancy (Category B)
There are limited data on the use of selexipag in pregnant women. Selexipag was not teratogenic in rats and rabbits. As a precautionary measure, it is preferable - unless clearly needed - to avoid the use of UPTRAVI during pregnancy.

Use in Lactation
It is unknown whether selexipag or its metabolites are excreted in human milk.
In rats, selexipag and/or its metabolites are excreted in the milk. Breastfeeding is not recommended during treatment with UPTRAVI.

4.7 Effects on ability to drive and use machines

No studies on the effect of UPTRAVI on the ability to drive and use machines have been performed. UPTRAVI has a minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of selexipag (such as headache or hypotension) should be kept in mind when considering the patient's ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse drug 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.

The safety of selexipag has been evaluated in a long-term, Phase 3 placebo-controlled study enrolling 1156 patients with symptomatic PAH. The mean treatment duration was 76.4 weeks

(median 70.7 weeks) for patients receiving selexipag versus 71.2 weeks (median 63.7 weeks) for patients on placebo. The exposure to selexipag was up to 4.2 years.

Table 1 presents adverse events over the entire treatment period in the Phase 3 study.

Table 1 Adverse events occurring in ≥ 5 % of selexipag or placebo treated subjects (during treatment and up to 7 days after treatment discontinuation)

	Double blind PAH GRIPHON	
System organ class	Selexipag N = 575	Placebo N = 577
Blood and lymphatic system disorders		
Anaemia	8% (48)	5% (31)
Cardiac disorders		
Right ventricular failure	8% (46)	10% (58)
Palpitations	6% (34)	6% (32)
Gastrointestinal disorders		
Diarrhoea	42% (244)	18% (106)
Nausea	33% (192)	18% (105)
Vomiting	18% (104)	9% (49)
Abdominal pain	8% (48)	6% (33)
Dyspepsia	4% (25)	2% (14)
General disorders and administration site conditions		
Oedema peripheral	14% (79)	18% (103)
Fatigue	8% (46)	10% (59)
Chest pain	7% (39)	7% (42)
Asthenia	5% (31)	4% (24)
Infections and Infestations		
Upper respiratory tract infection	13% (75)	14% (79)
Nasopharyngitis	13% (75)	11% (63)
Bronchitis	8% (47)	8% (43)
Pneumonia	5% (30)	6% (33)
Urinary tract infection	5% (26)	5% (30)

	Double blind PAH **GRIPHON**	
System organ class	Selexipag N = 575	Placebo N = 577
Respiratory tract infection	4% (21)	5% (28)
Metabolism and nutrition disorders		
Decreased appetite	6% (34)	3% (19)
Hypokalaemia	4% (25)	5% (28)
Musculoskeletal and connective tissue disorders		
Jaw pain	26% (148)	6% (33)
Pain in extremity	17% (97)	8% (44)
Myalgia	16% (92)	6% (34)
Arthralgia	11% (62)	8% (44)
Back pain	6% (35)	6% (35)
Nervous system disorders		
Headache	65% (375)	32% (182)
Dizziness	15% (86)	15% (85)
Syncope	6% (37)	9% (51)
Psychiatric disorders		
Insomnia	4% (23)	5% (28)
Respiratory, thoracic and mediastinal disorders		
Pulmonary arterial hypertension	22% (125)	36% (206)
Dyspnoea	16% (91)	21% (121)
Cough	10% (56)	12% (67)
Epistaxis	5% (30)	5% (29)
Skin and subcutaneous tissue disorders		
Rash	11% (64)	8% (48)
Vascular disorders		
Flushing	12% (70)	5% (28)
Hypotension	5% (29)	3% (18)

Table 2 presents adverse drug reactions reported in selexipag-treated subjects at an incidence ≥ 3 % and with a placebo-corrected difference ≥ 1 % (during treatment and up to 7 days after treatment discontinuation).

Table 2 Adverse drug reactions reported by ≥ 3% of selexipag treated patients with a placebo-corrected difference ≥ 1% (during treatment and up to 7 days after treatment discontinuation) §

	Double blind PAH GRIPHON	
System organ class	Selexipag N = 575	Placebo N = 577
Infections and Infestations		
Nasopharyngitis	13% (75)	11% (63)
Influenza	4% (20)	2% (14)
Blood and lymphatic system disorders		
Anaemia	8% (48)	5% (31)
Hemoglobin decreased	10 % (55)	7% (42)
Nervous system disorders		
Headache*****	65% (375)	32% (182)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	3% (17)	2% (11)
Gastrointestinal disorders		
Diarrhoea*	42% (244)	18% (106)
Nausea*	33% (192)	18% (105)
Vomiting*	18% (104)	9% (49)
Abdominal pain*	8% (48)	6% (33)
Dyspepsia	4% (25)	2% (14)
Abdominal discomfort	4% (21)	2% (14)
Metabolism and nutrition disorders		
Decreased appetite	6% (34)	3% (19)
Musculoskeletal and connective tissue disorders		
Jaw pain*	26% (148)	6% (33)
Pain in extremity*	17% (97)	8% (44)

	Double blind PAH GRIPHON	
System organ class	Selexipag N = 575	Placebo N = 577
Myalgia*	16% (92)	6% (34)
Arthralgia*	11% (62)	8% (44)
Musculoskeletal pain	3% (18)	2% (12)
Vascular disorders		
Flushing*	12% (70)	5% (28)
Hypotension	5% (29)	3% (18)
Skin and subcutaneous tissue disorders		
Rash	11% (64)	8% (48)
General disorders and administration site conditions		
Asthenia	5% (31)	4% (24)
Pyrexia	4% (23)	3% (17)
Pain	3% (18)	1% (3)
Investigation		
Weight decrease	3% (17)	1% (8)

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

* see section Description of selected adverse reactions.

Table 3 presents adverse reactions occurring in selexipag-treated subjects at an incidence < 3 % respectively and with a placebo-corrected difference ≥ 1 % (during treatment and up to 7 days after treatment discontinuation). Adverse reactions are listed by system organ class and frequency category, using the convention: common (≥ 1/100 and < 1/10). Frequency determination does not account for other factors including varying study duration, pre-existing conditions, and baseline patient characteristics.

Table 3 Adverse reactions occurring in selexipag-treated subjects at an incidence < 3 % and with a placebo-corrected difference ≥ 1%‡

System Organ Class	Common ≥ 1/100 and < 1/10
Cardiac disorder*	Sinus tachycardia
Nervous system disorders	Burning sensation
Eye disorders	Eye pain

Vascular disorders	Hot flush
Musculoskeletal and connective tissue disorders	Neck pain, bone pain
Endocrine disorders	Hyperthyroidism Thyroid-stimulating Hormone decreased

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

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 (Table 4). These effects usually are transient or manageable with symptomatic treatment.

Table 4 Adverse reactions associated with pharmacological action of selexipag during titration and maintenance phase (> 3% placebo-corrected incidence in decreasing order)

	Selexipag	
Adverse reaction	Titration phase (≤ 12 weeks) N = 509	Maintenance phase (> 12 weeks) N = 509
Headache	36%	20%
Diarrhoea	24%	16%
Jaw pain	22%	17%
Nausea	16%	10%
Myalgia	10%	6%
Vomiting	10%	2%
Pain in extremity	9%	7%
Flushing	7%	7%
Arthralgia	2%	4%

Increase in heart rate:
In the Phase 3 placebo-controlled study in patients with PAH a transient increase in mean heart rate

of 3–4 bpm at 2-4 hours post-dose was observed. ECG investigations showed sinus tachycardia in 11.3% of patients in the selexipag group compared to 8.8% in the placebo group.

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 −3.4 to −0.2 g/L in the selexipag group compared to −0.5 to 2.5 g/L in the placebo group. A decrease from baseline in haemoglobin concentration to below 100 g/L was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests
In a Phase 3 placebo-controlled study in patients with PAH, 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. There were no mean changes in triiodothyronine or thyroxine in either group.

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

Safety of triple combination treatment (selexipag, 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.

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

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

	Double-blind PAH **AC-065A308/TRITON**		
System organ class	**Selexipag + 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 (Table 6). 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 drug exposure. In the table, the frequencies are provided according to the following convention:

Very common ≥ 1/10 (≥ 10%)

Common ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare ≥ 1/10000 and < 1/1000 (≥0.01 and < 0.1%)
Very rare < 1/10000, including isolated reports (< 0.01%)
Not known Cannot be estimated from the available data

Table 6 Adverse reactions identified during postmarketing experience with selexipag

System Organ Class Adverse Reaction	Frequency category calculated from clinical trials with selexipag
Immune system disorders	
Hypersensitivity reactions	Common
Skin and subcutaneous tissue disorders	
Urticaria	Common
Angioedema	Common

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. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Isolated cases of overdose up to 3200 µg were reported. Mild, transient nausea was the only reported consequence. 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose. Contact the NZ National Poisons Centre on 0800 POISON (0800 764766) for advice on management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, platelet aggregation inhibitors excluding herapin, ACT 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 pulmonary arterial hypertension (PAH).

Selexipag is an oral, selective, IP prostacyclin receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogues. 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 parameters 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 desensitisation 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.

Pharmacodynamics

Cardiac electrophysiology:
In a thorough QT study in healthy subjects, repeated doses of 800 and 1600 micrograms of selexipag twice daily did not show an effect on cardiac repolarisation (the QT_c interval) or conduction (PR and QRS intervals) and had a mild accelerating effect on heart rate. The placebo-corrected increase from time-matched baseline heart rate 1.5 to 3 hours post-dose was 6–7 bpm at 800 µg twice daily and 9–10 bpm at 1600 µg twice daily.

Pulmonary Haemodynamics:
A Phase 2 double-blind, placebo-controlled clinical study assessed haemodynamic parameters after

17 weeks of treatment in patients with PAH WHO functional classes II–III and concomitantly receiving ERAs and/or PDE-5 inhibitor. 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% CL −44.7%, −12.2%; P = 0.0045) and an increase in cardiac index (mean treatment effect) 0.48 L/min/m^2, 95% CL 0.13, 0.83 compared to placebo (N=10).

Clinical Efficacy and Safety

Efficacy in Patients with Pulmonary Arterial Hypertension

The effect of selexipag on progression of PAH was demonstrated in a multi-centre, long-term (mean duration of exposure approximately 1.5 years up to maximum of 4.2 years), double-blind, placebo-controlled, parallel group, event-driven Phase 3 study (GRIPHON) 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 primary study endpoint was the time to first occurrence of a morbidity or mortality event up to end of treatment defined as a composite of death (all-causes); or hospitalisation for PAH; or progression of PAH resulting in need for lung transplantation or balloon atrial septostomy; or initiation of parenteral prostanoid therapy or chronic oxygen therapy; or other disease progression events (patients in modified NYHA/WHO FC II or III at baseline) confirmed by decrease in 6MWD from baseline (≥ 15%) and worsening of NYHA/WHO FC or (patients in modified NYHA/WHO FC III or IV at baseline) confirmed by decrease in 6MWD from baseline (≥ 15%) and need for additional PAH specific therapy.

All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

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 aetiology 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 aetiologies (drugs and toxins [2%] and HIV [1%]). Patients with left ventricular dysfunction, moderate or severe obstructive or restrictive lung disease, moderate or severe hepatic impairment, or severe renal insufficiency were excluded from the study.

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

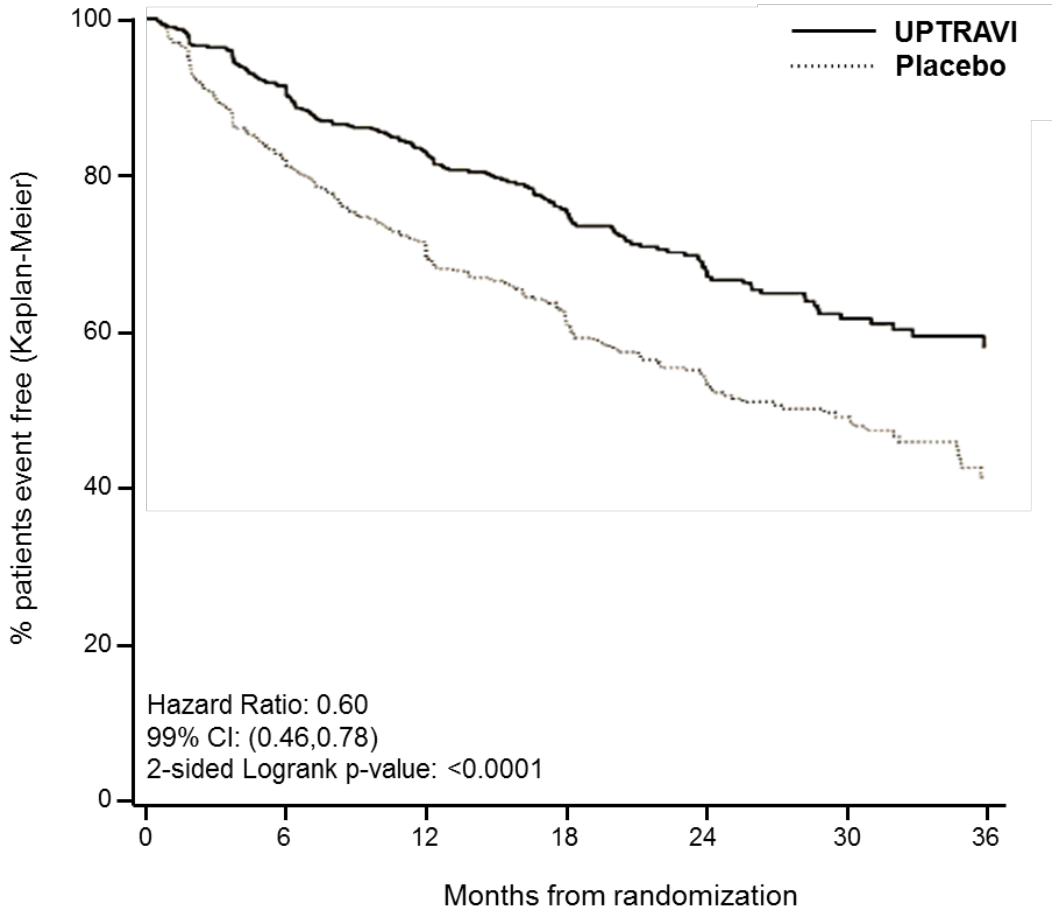
Patients on selexipag achieved doses within the following groups: 200–400 micrograms (23%), 600–1000 micrograms (31%) and 1200–1600 micrograms (43%).

The overall median double-blind treatment duration was 63.7 weeks for 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 (99% confidence interval [CI] 22 to 54%; two-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 (Table 7).

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



UPTRAVI patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

Table 7 Primary Endpoint and Related Components in GRIPHON

	UPTRAVI N=574		Placebo N=582		Hazard Ratio (99% CI)	p-value
	n	%	n	%		
Primary endpoint events up to the end of treatment						
All primary endpoint events	155	27.0	242	41.6	0.60 [0.46,0.78]	<0.0001
As first event:						
• Hospitalisation for PAH	78	13.6	109	18.7		
• Other disease Progression (Decrease in 6MWD plus worsening functional class or need for other therapy)	38	6.6	100	17.2		
• Death	28	4.9	18	3.1		
• Parenteral prostanoid or chronic oxygen therapy	10	1.7	13	2.2		
• PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	1	0.2	2	0.3		

The observed benefit of selexipag was similar regardless of the dose achieved when patients are titrated to their highest tolerated dose (see Dosage and Administration). This was shown by the hazard ratio for the 3 pre-defined categories (0.60 for 200–400 micrograms twice daily, 0.53 for 600–1000 micrograms twice daily, and 0.64 for 1200–1600 micrograms twice daily), which was consistent with the overall treatment effect (0.60).

The numerical increase in deaths up to end of treatment + 7 days but not up to study closure was further investigated by mathematical modelling, showing that the most likely explanation for this phenomenon is a reduction of non-fatal events by selexipag and a neutral effect on PAH mortality.

Figures 2A, B and C show time to first event analyses for primary endpoint components of hospitalisation for PAH (A), other disease progression (B), and death (C)—all censored 7 days after any primary end point event (because many patients on placebo transitioned to open-label UPTRAVI at this point).

Figure 2A Hospitalisation for PAH as the First Endpoint in GRIPHON

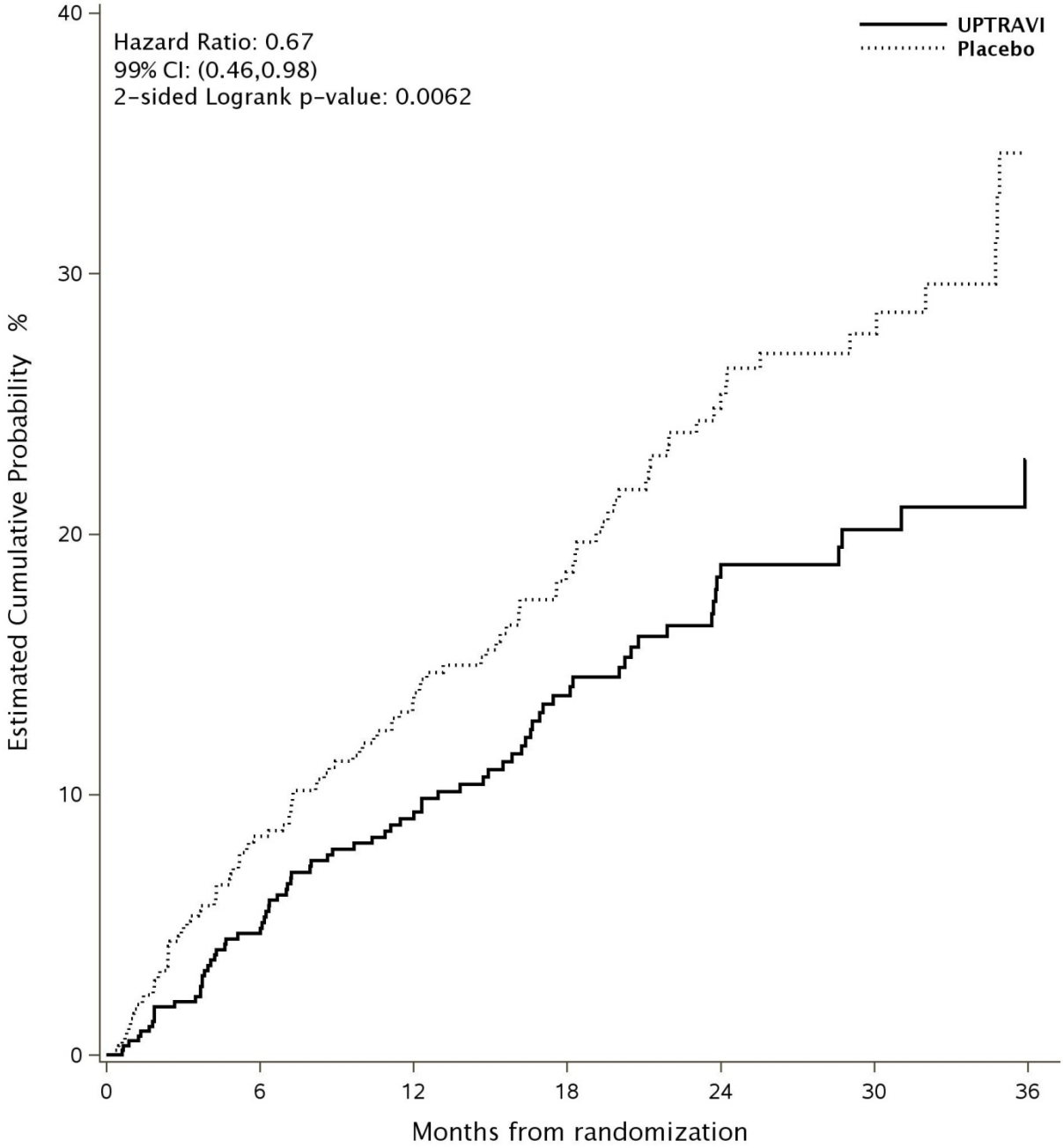


Figure 2B Disease Progression as the First Endpoint in GRIPHON

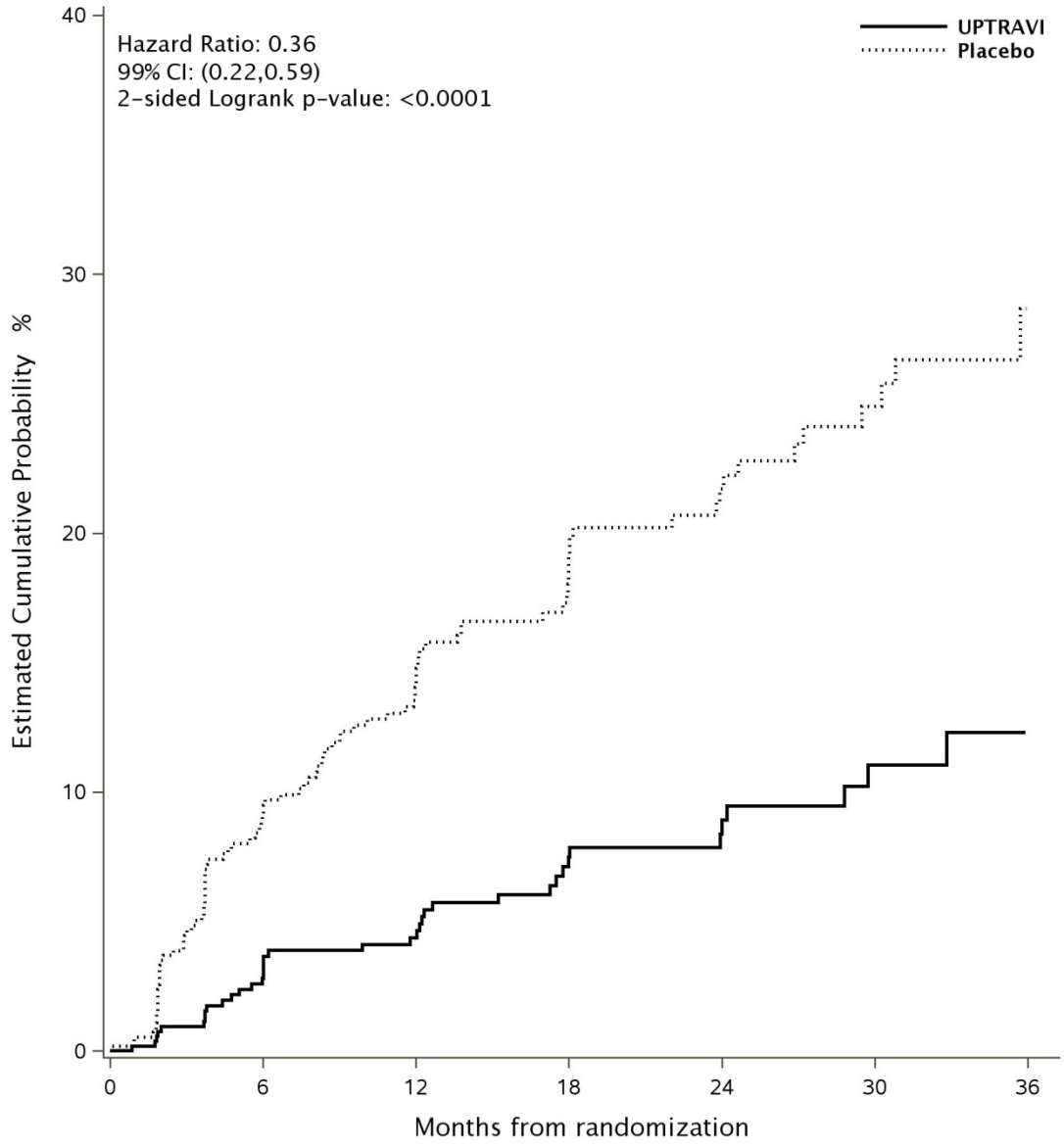
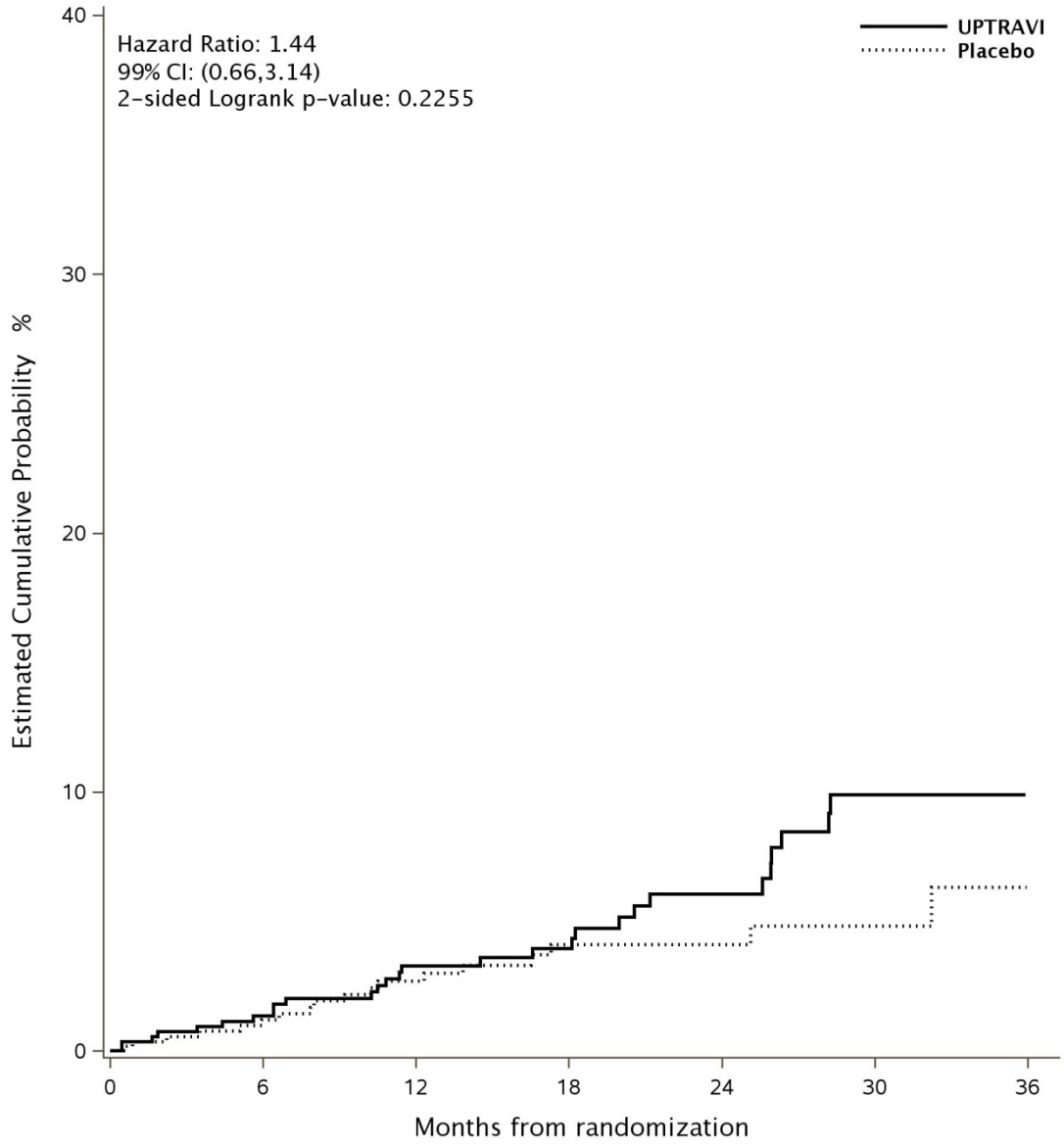
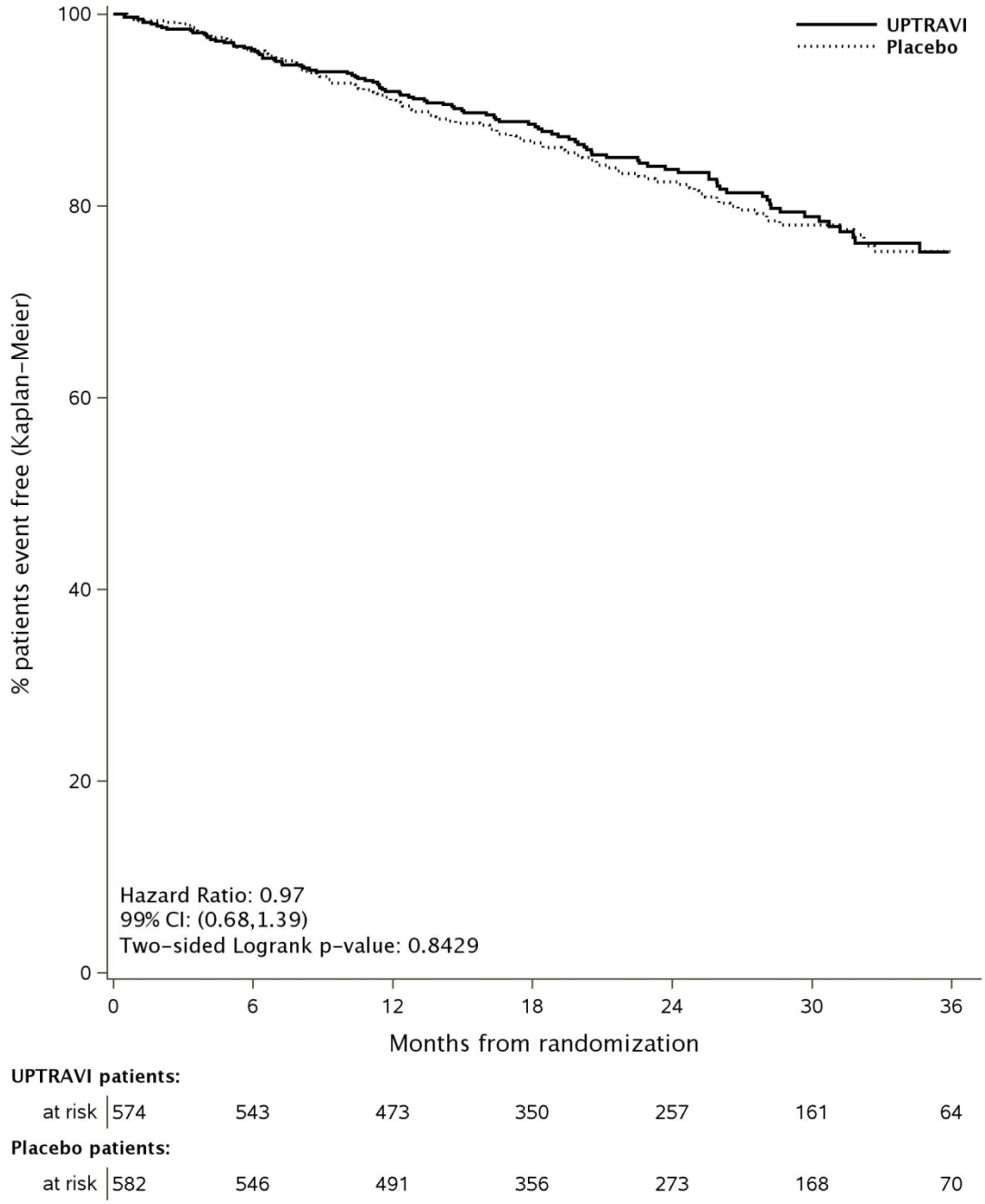


Figure 2C Death as the First Endpoint in GRIPHON



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) (Figure 3).

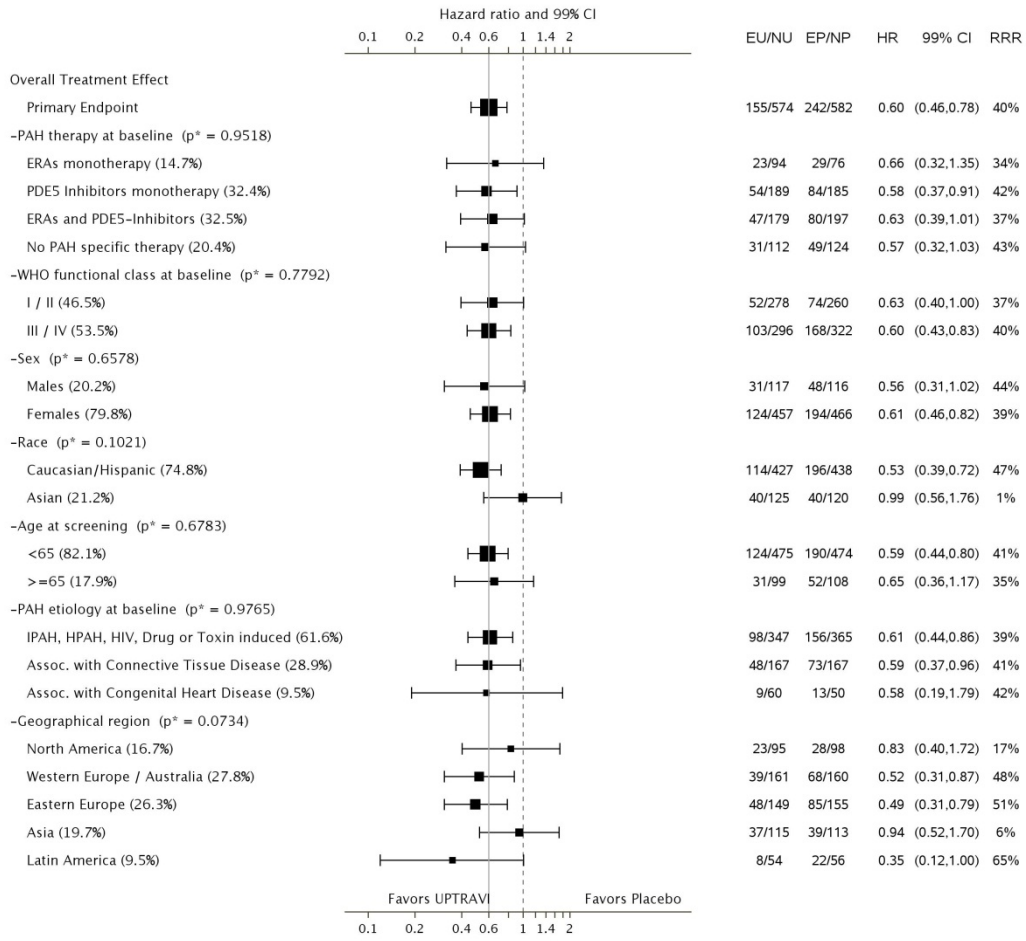
Figure 3 Kaplan-Meier estimates of the occurrence of death up to study closure



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.

Subgroup analyses indicated consistent treatment effect across subgroups of age, sex, race, aetiology, geographical region, WHO Functional Class, and by monotherapy or in combination with ERA, PDE-5 inhibitors or triple combination with both an ERA and a PDE-5 inhibitor (Figure 4).

Figure 4 Sub-group analyses of the primary endpoint in the GRIPHON study



CI = confidence interval; EP = number of placebo patients with events; EU = number of Uptravi patients with events; HR = hazard ratio; NP = number of patients randomised to placebo; NU = number of patients randomised to Uptravi; RRR = relative risk reduction.

The size of the square represents the number of patients in the subgroup.

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all were pre-specified. The 99% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

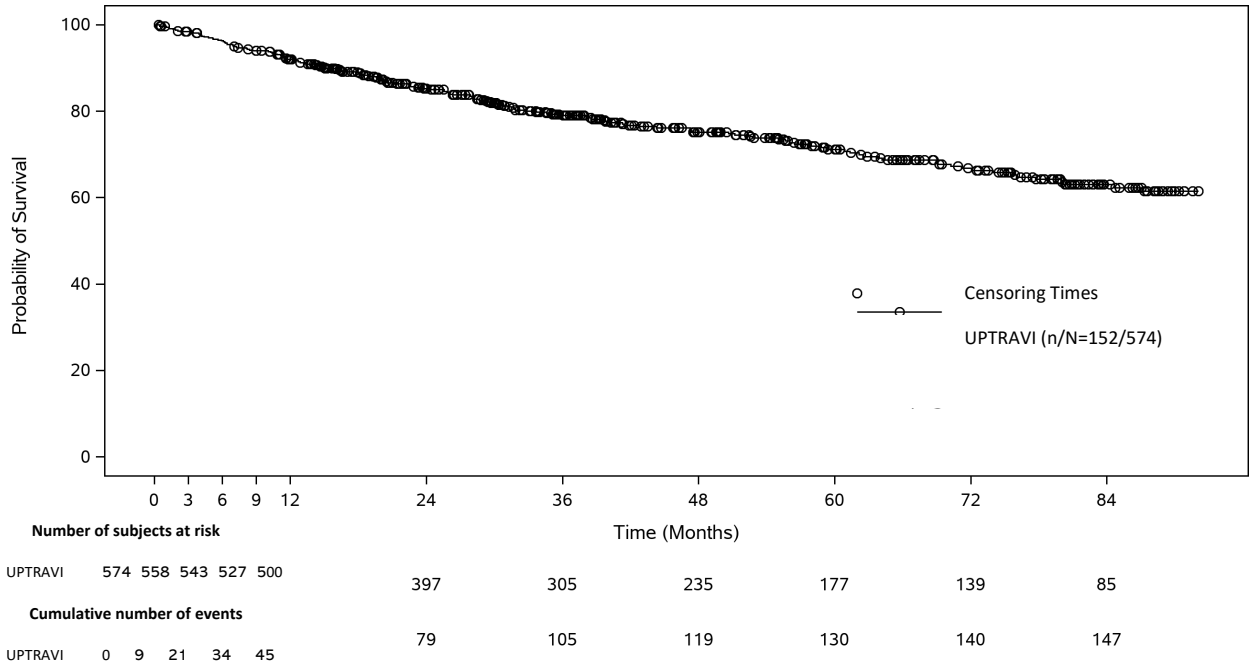
Symptomatic endpoint

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 metres at Week 26 (99% CI: 1 - 24, two-sided p-value: 0.005). In patients without concurrent PAH-specific therapy, the treatment effect measured at trough was 34 metres (99% CI: 10.0 -,63.0 one sided p-value:0.0002).

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 1800 micrograms twice a day. 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 was 30% and 20% higher, respectively, in PAH patients compared to healthy subjects. 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.

The absolute bioavailability is of selexipag is approximately 49%.

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

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 11.7L.

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 drug-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 6.2-13.5h. 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.

Special populations

No clinically relevant effects of sex, race, age or body weight on the pharmacokinetics of selexipag and its active metabolite have been observed in healthy subjects or PAH patients. In PAH patients, the exposure to selexipag and ACT-333679 decreased 9% and 4%, respectively, with increasing age from 23 to 72 years. PAH patients with body weights of 51 (96) kg showed 30% higher (20% lower) exposure to selexipag and 20% higher (10% lower) exposure to ACT-333679 compared to patients of 70 kg body weight. PAH male patients showed 13% lower exposure to ACT-333679 than female patients. These differences are smaller than the intersubject variability, which is larger than 30%.

Renal impairment

The $AUC_{0-\infty}$ values of selexipag and ACT-333679 were increased 1.73-fold and 1.61-fold, respectively, in subjects with severe renal function impairment (SRFI) compared to healthy subjects, and the $t_{1/2}$ of ACT-333679 was prolonged 1.61-fold in patients with SRFI.

Hepatic impairment

In subjects with mild (Child-Pugh A) or moderate (Child-Pugh 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 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 B) hepatic impairment.
Based on pharmacokinetic modelling of data from a study in subjects with hepatic impairment, the 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 Preclinical 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 1600 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 EP4 receptors in dogs. As human EP4 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 haemodynamics. 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 cores
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 (E171),
Iron oxide yellow (E172),
Carnauba wax.

UPTRAVI 400 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),
Iron oxide red (E172),
Carnauba wax.

UPTRAVI 600 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),
Iron oxide red (E172),
Iron oxide black (E172),
Carnauba wax.

UPTRAVI 800 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),
Iron oxide yellow (E172),
Iron oxide black (E172),
Carnauba wax.

UPTRAVI 1000 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),

Iron oxide red (E172),
Iron oxide yellow (E172),
Carnauba wax.

UPTRAVI 1200 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),
Iron oxide black (E172),
Iron oxide red (E172),
Carnauba wax.

UPTRAVI 1400 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),
Iron oxide yellow (E172),
Carnauba wax.

UPTRAVI 1600 microgram film coated tablet:
Hypromellose,
Propylene glycol,
Titanium dioxide (E171),
Iron oxide black (E172),
Iron oxide red (E172),
Iron oxide yellow (E172),
Carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 30°C. Protect from moisture.

6.5 Nature and contents of container

Uptravi 200 microgram film-coated tablets
Polyamide / aluminium / high-density polyethylene / polyethylene with an embedded desiccant agent / high-density polyethylene blister sealed with an aluminium foil (Alu/Alu blister with desiccant) in cartons of either 60 or 140 (titration pack) film-coated tablets.
Uptravi 400, 600, 800, 1000, 1200, 1400, and 1600 microgram film-coated tablets
Polyamide / aluminium / high-density polyethylene / polyethylene with an embedded desiccant agent / high-density polyethylene blister sealed with an aluminium foil (Alu/Alu blister with desiccant) in cartons of 60 film-coated tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND
Telephone: 0800 800 806
Fax: (09) 588 1398
Email: medinfo@janau.jnj.com

9 DATE OF FIRST APPROVAL

17 March 2016

10 DATE OF REVISION OF THE TEXT

12 December 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Updated website for reporting of suspected adverse reactions
6.3	Updated shelf life