

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Uptravi 100 microgram film-coated tablets
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 100 microgram film-coated tablets

Each film-coated tablet contains 100 micrograms of selexipag.

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 1 000 microgram film-coated tablets

Each film-coated tablet contains 1 000 micrograms of selexipag.

Uptravi 1 200 microgram film-coated tablets

Each film-coated tablet contains 1 200 micrograms of selexipag.

Uptravi 1 400 microgram film-coated tablets

Each film-coated tablet contains 1 400 micrograms of selexipag.

Uptravi 1 600 microgram film-coated tablets

Each film-coated tablet contains 1 600 micrograms of selexipag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Uptravi 100 microgram film-coated tablets

Round, 3.0 mm diameter, light-yellow, film-coated tablets, with “1” debossed on one side.

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) 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 section 5.1).

4.2 Posology and method of administration

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

Posology

Individualised dose titration

Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 micrograms given twice daily to 1 600 micrograms given twice daily (individualised maintenance dose).

The recommended starting dose 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. 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 some adverse reactions, reflecting the mode of action of selexipag (such as headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing), may occur. They are usually transient or manageable with symptomatic treatment (see section 4.8). However, if a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level.

In patients in whom up-titration was limited by reasons other than adverse reactions reflecting the mode of action of selexipag, a second attempt to continue up-titration to the highest individually tolerated dose up to a maximum dose of 1 600 micrograms twice daily may be considered.

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 and/or a dose reduction to the next lower dose should be considered.

Interruptions and discontinuations

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

If treatment is missed for 3 days or more, Upravi should be restarted at a lower dose and then up-titrated.

There is limited experience with abrupt discontinuation of selexipag in patients with PAH. No evidence for acute rebound has been observed.

However, if the decision to withdraw Upravi is taken, it should be done gradually while an alternative therapy is introduced.

Dose adjustment with co-administration of moderate CYP2C8 inhibitors

When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), the total daily dose of Upravi should be reduced to half by administering half of each dose twice daily. Alternatively, a once daily dosing frequency to achieve half of the daily dose of Upravi may be continued in patients already well controlled on a once daily dosing regimen or may be applied in patients for whom the appropriate dose strength(s) supporting twice daily dosing with half the dose is not available. If the therapy is not tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. When co-administration of a moderate CYP2C8 inhibitor is stopped, the total daily dose of Upravi should be increased, as applicable. The maximum dose of 1 600 micrograms twice daily should not be exceeded (see section 4.5).

Special populations

Elderly (≥ 65 years)

No adjustment to the dose regimen is needed in elderly people (see section 5.2). There is limited clinical experience in patients over the age of 75 years, therefore Upravi should be used with caution in this population (see section 4.4).

Hepatic impairment

Selexipag should not be administered in patients with severe liver impairment (Child-Pugh class C; see section 4.4). For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of treatment should be 100 micrograms twice daily and increased at weekly intervals by increments of 100 micrograms twice daily until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced. In these patients the maximum dose is 800 micrograms given twice daily. Alternatively, a once daily dosing frequency to achieve half of the daily dose of Uptravi may be continued in patients already well controlled on a once daily dosing regimen or may be applied in patients for whom the appropriate dose strength(s) supporting twice daily dosing with half the dose is not available. No adjustment to the dose regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

Renal impairment

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 [eGFR] < 30 mL/min/1.73 m²); dose titration should be done with caution in these patients (see section 4.4).

Paediatric 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 paediatric 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).

Method of administration

Oral use.

The film-coated tablets are to be taken orally in the morning and in the evening. To improve tolerability, it is recommended to take Uptravi with food and, at the beginning of each up-titration phase, to take the first increased dose in the evening.

The film-coated tablets are to be swallowed with water. The tablets should not be split or crushed because the tablet coating protects the active substance from light.

Patients who have poor vision or are blind must be instructed to get assistance from another person when taking Uptravi during the titration period.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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; see section 4.5).

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 (e.g., patients on antihypertensive therapy or with

resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction) (see section 4.8).

Hyperthyroidism

Hyperthyroidism has been observed with Upravi. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism (see section 4.8).

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when Upravi is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, treatment is to be discontinued.

Elderly (≥ 65 years)

There is limited clinical experience with selexipag in patients over the age of 75 years, therefore, Upravi should be used with caution in this population (see section 4.2).

Hepatic impairment

There is no clinical experience with selexipag in patients with severe liver impairment (Child-Pugh class C), therefore treatment should not be administered in these patients. The exposure to selexipag and its active metabolite is increased in subjects with moderate hepatic impairment (Child-Pugh class B; see section 5.2). In patients with moderate hepatic impairment, the total daily dose of Upravi should be reduced (see section 4.2).

Renal impairment

In patients with severe renal impairment ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), caution should be exercised during dose titration. There is no experience with Upravi in patients undergoing dialysis (see section 5.2), therefore Upravi should not be used in these patients.

Women of childbearing potential

Women of childbearing potential should practise effective contraception while taking selexipag (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on selexipag

Selexipag is hydrolysed to its active metabolite by carboxylesterases (see section 5.2). 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 weak substrate of the P-gp efflux pump. The active metabolite is a weak substrate of the breast cancer resistance protein (BCRP).

The pharmacokinetics of selexipag and its active metabolite are not affected by warfarin.

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, the major contributor to efficacy, increased approximately 11-fold. Concomitant administration of Upravi with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated (see section 4.3).

Concomitant administration of Uptravi with clopidogrel (loading dose of 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 but increased the exposure to the active metabolite approximately 2.2 and 2.7-fold following loading dose and maintenance dose, respectively. The total daily dose of Uptravi should be decreased by reducing each dose to half when co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide). Alternatively, a once daily dosing frequency to achieve half of the daily dose of Uptravi may be continued in patients already well controlled on a once daily dosing regimen or may be applied in patients for whom the appropriate dose strength(s) supporting twice daily dosing with half the dose is not available. When co-administration of a moderate CYP2C8 inhibitor is stopped increase the total daily dose of Uptravi, as applicable. The maximum dose of 1 600 micrograms twice daily should not be exceeded (see section 4.2).

Inducers of CYP2C8

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 selexipag may be required with concomitant administration of inducers of CYP2C8 (e.g., rifampicin, carbamazepine, phenytoin).

Inhibitors of UGT1A3 and UGT2B7

The effect of strong inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole) on the exposure to selexipag and its active metabolite has not been studied. Caution is required when administering these medicinal products concomitantly with Uptravi. A potential pharmacokinetic interaction with strong inhibitors of UGT1A3 and UGT2B7 cannot be excluded.

Inhibitors and inducers of CYP3A4

In the presence of 400 mg/100 mg lopinavir/ritonavir twice daily, a strong CYP3A4 inhibitor, exposure to selexipag increased approximately 2-fold, whereas the exposure to the active metabolite of selexipag did not change. Given the 37-fold higher potency of the active metabolite, this effect is not clinically relevant. Since a strong inhibitor of CYP3A4 did not affect the pharmacokinetics of the active metabolite, indicating that the CYP3A4 pathway is not important in the elimination of the active metabolite, no effect of inducers of CYP3A4 on the pharmacokinetics of the active metabolite is expected.

PAH-specific therapies

In the phase 3 placebo-controlled trial in patients with PAH, the use of selexipag in combination with both an ERA and a PDE-5 inhibitor resulted in a 30% lower exposure to the active metabolite.

Transporter inhibitors (lopinavir/ritonavir)

In the presence of 400 mg/100 mg lopinavir/ritonavir twice daily, a strong 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. Given that the majority of the pharmacological effect is driven by the active metabolite, this effect is not clinically relevant.

Effect of selexipag on other medicinal products

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

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 daily) 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.

Midazolam

At steady state after up-titration to 1 600 micrograms selexipag twice a day, no clinically relevant 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.

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 to the CYP2C9 substrate S-warfarin, reduced efficacy of hormonal contraceptives is not expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should practise 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 prostacyclin (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.

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 ability to drive and use machines

Uptravi has 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, see section 4.8) should be kept in mind when considering the patient's ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing. These reactions are more frequent during the up-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 1 156 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.

Tabulated list of adverse reactions

Adverse reactions obtained from the pivotal clinical study and post-marketing surveillance are tabulated below. The adverse reactions are ranked by frequency within each system organ class (SOC) and presented in order of decreasing seriousness. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1\ 000$ to $<1/100$); rare ($\geq 1/10\ 000$ to $<1/1\ 000$); very rare ($<1/10\ 000$).

System organ class	Very common	Common	Uncommon
Blood and lymphatic disorders		Anaemia* Haemoglobin decreased*	
Endocrine disorders		Hyperthyroidism* Thyroid-stimulating Hormone decreased	
Metabolism and nutrition disorders		Decreased appetite Weight decrease	
Nervous system disorders	Headache*		
Cardiac disorders			Sinus tachycardia*
Vascular disorders	Flushing*	Hypotension*	
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis (of non-infectious origin)	Nasal congestion	
Gastro-intestinal disorders	Diarrhoea* Vomiting* Nausea*	Abdominal pain Dyspepsia*	
Skin and subcutaneous tissue disorders		Rash Urticaria Erythema Angioedema [†]	
Musculoskeletal and connective tissue disorders	Jaw pain* Myalgia* Arthralgia* Pain in extremity*		
General disorders and administration site conditions		Pain	

* See section Description of selected adverse reactions.

[†] Cases of angioedema have been reported in post-marketing experience with a latency that can exceed 30 days of treatment.

Description of selected adverse reactions

Pharmacological effects associated with titration and maintenance treatment

Adverse reactions associated with the mode of action of selexipag have been observed frequently, in particular during the phase of individualised dose titration, and are tabulated below:

Prostacyclin-like associated adverse reactions	Titration		Maintenance	
	Selexipag	Placebo	Selexipag	Placebo
Headache	64%	28%	40%	20%
Diarrhoea	36%	12%	30%	13%
Nausea	29%	13%	20%	10%

Pain in jaw	26%	4%	21%	4%
Myalgia	15%	5%	9%	3%
Pain in extremity	14%	5%	13%	6%
Vomiting	14%	4%	8%	6%
Flushing	11%	4%	10%	3%
Arthralgia	7%	5%	9%	5%

These effects are usually transient or manageable with symptomatic treatment. 7.5% of patients on selexipag discontinued treatment due to these adverse reactions. The approximate rate of adverse reactions that were serious was 2.3% in the selexipag group and 0.5% in the placebo group. In clinical practice, gastro-intestinal events have been observed to respond to anti-diarrhoeal, anti-emetic, and anti-nauseant medicinal products and/or medicinal products for functional gastro-intestinal disorders. Pain-associated events have frequently been treated with analgesics (such as paracetamol).

Haemoglobin decrease

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 selexipag-treated patients and 5.0% of placebo-treated patients.

In a phase 3 placebo-controlled study in patients newly diagnosed with PAH, mean absolute changes in haemoglobin at regular visits compared to baseline ranged from –1.77 to –1.26 g/dL in the triple therapy group (selexipag, macitentan, tadalafil) compared to –1.61 to –1.28 g/dL in the double therapy group (placebo, macitentan and tadalafil). A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 19.0% of patients in the triple therapy group and 14.5% in the double therapy group. Anaemia was reported with very common frequency (13.4%) in the triple therapy group compared to common frequency (8.3%) in the double therapy group.

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 thyroid-stimulating hormone 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.

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. Electrocardiogram investigations showed sinus tachycardia in 11.3% of patients in the selexipag group compared to 8.8% in the placebo group (see section 5.1).

Hypotension

In the phase 3 placebo-controlled study in patients with PAH, hypotension was reported for 5.8% of patients in the selexipag group compared to 3.8% in the placebo group. Mean absolute changes in systolic blood pressure at regular visits compared to baseline ranged from –2.0 to –1.5 mmHg in the selexipag group compared to –1.3 to 0.0 mmHg in the placebo group and in diastolic blood pressure ranged from –1.6 to –0.1 mmHg in the selexipag group compared to –1.1 to 0.3 mmHg in the placebo group. Systolic blood pressure decrease below 90 mmHg was recorded for 9.7% of patients in the selexipag group compared 6.7% in the placebo group.

Dyspepsia

In a phase 3 placebo-controlled study in patients newly diagnosed with PAH, dyspepsia was reported with very common frequency (16.8%) in patients receiving triple therapy (selexipag, macitentan,

tadalafil) compared to common frequency (8.3%) in patients receiving double therapy (placebo, macitentan and tadalafil).

Long-term safety

Of the 1 156 patients who participated in the pivotal study, 709 patients entered a long-term open-label extension study (330 patients who continued on selexipag from the GRIPHON study and 379 patients who received placebo in GRIPHON and crossed over to selexipag). Long-term follow up of patients treated with selexipag for a median treatment duration of 30.5 months and for a maximum of up to 103 months showed a safety profile that was similar to that observed in the pivotal clinical study described above.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Isolated cases of overdose up to 3 200 micrograms 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin, ATC code: B01AC27

Mechanism of action

Selexipag is a selective IP receptor agonist 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 (EP₁–EP₄, DP, FP, and TP). Selectivity against EP₁, EP₃, FP, and TP is important because these are well-described contractile receptors in the gastro-intestinal tract and blood vessels. Selectivity against EP₂, EP₄, and DP₁ 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 prevents cardiac and pulmonary remodelling in a rat model of PAH and causes proportional decreases in pulmonary and peripheral pressures, indicating that peripheral vasodilation reflects pulmonary pharmacodynamic efficacy. Selexipag does not cause IP receptor desensitisation *in vitro* nor tachyphylaxis in a rat model.

Pharmacodynamic effects

Cardiac electrophysiology

In a thorough QT study in healthy subjects, repeated doses of 800 and 1 600 micrograms of selexipag twice daily did not show an effect on cardiac repolarisation (QT_c interval) or conduction (PR and QRS intervals) and had a mild accelerating effect on heart rate (the placebo-corrected, baseline-adjusted increase in heart rate reached 6–7 bpm at 1.5 to 3 h after dosing with 800 micrograms selexipag and 9–10 bpm at the same timepoints after 1 600 micrograms selexipag).

Coagulation factors

In phase 1 and 2 studies a slight decrease in plasma levels of von Willebrand factor (vWF) was observed with selexipag; the vWF values remained above the lower limit of the normal range.

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 ERAs and/or 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/m² (95% CI: 0.13, 0.83) compared to placebo (N = 10).

Clinical efficacy and safety

Efficacy in patients with PAH

The effect of selexipag on progression of PAH was demonstrated in a multi-centre, long-term (maximum duration of exposure approximately 4.2 years), double-blind, placebo-controlled, parallel-group, event-driven phase 3 study (GRIPHON) in 1 156 patients with symptomatic (WHO FC I–IV) PAH. Patients were randomised to either placebo (N = 582) or selexipag (N = 574) twice daily. The dose was increased at weekly intervals by increments of 200 micrograms given twice daily to determine the individualised maintenance dose (200–1 600 micrograms twice daily).

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 WHO FC II or III at baseline) confirmed by a decrease in 6-minute walk distance (6MWD) from baseline ($\geq 15\%$) and worsening of WHO FC or (patients in WHO FC III or IV at baseline) confirmed by a decrease in 6MWD from baseline ($\geq 15\%$) 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%). 17.9% of patients were ≥ 65 and 1.1% ≥ 75 years of age. 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 simple corrected congenital heart disease (10%), and PAH associated with other aetiologies (drugs and toxins [2%] and HIV [1%]).

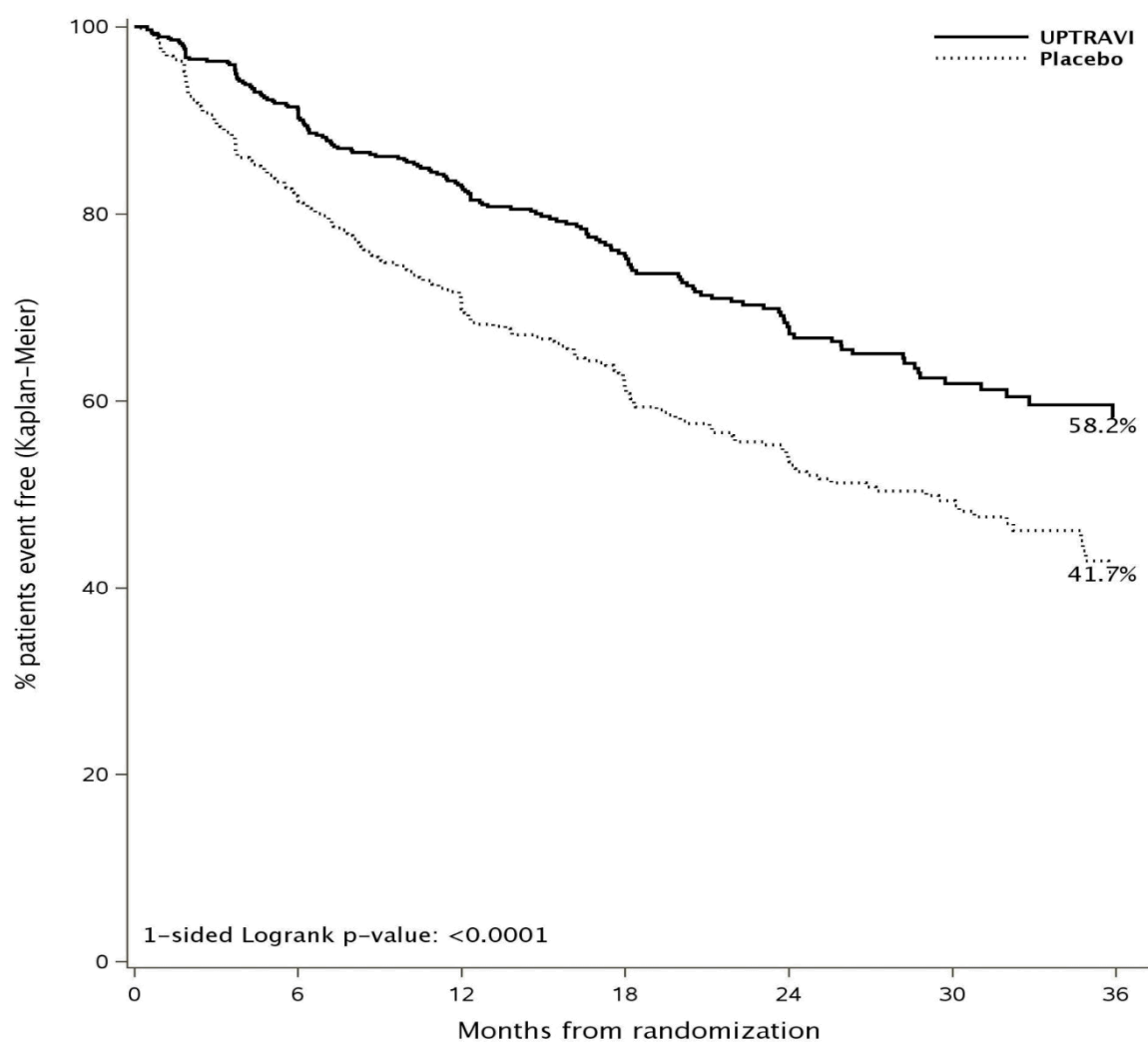
At baseline, the majority of enrolled patients (80%) were being treated with a stable dose of a specific therapy for PAH, either an ERA (15%) or a PDE-5 inhibitor (32%) or both an ERA and a PDE-5 inhibitor (33%).

The overall median double-blind treatment duration was 63.7 weeks for the placebo group and 70.7 weeks for the selexipag group. 23% of patients on selexipag achieved maintenance doses in the range of 200–400 micrograms, 31% achieved doses in the range of 600–1 000 micrograms, and 43% achieved doses in the range of 1 200–1 600 micrograms.

Treatment with selexipag 200–1 600 micrograms twice daily 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 (Table 1).

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



UPTRAVI patients:

at risk	574	455	361	246	171	101	40
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Placebo patients:

at risk	582	433	347	220	149	88	28
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Table 1 Summary of outcome events

Endpoints & statistics	Patients with an event		Treatment comparison: selexipag vs placebo			
	Placebo (N=582)	Selexipag (N=574)	Absolute risk reduction	Relative risk reduction (99% CI)	HR (99% CI)	p-value
Morbidity-mortality event^a	58.3%	41.8%	16.5%	40% (22%; 54%)	0.60 (0.46; 0.78)	< 0.0001
Hospitalisation due to PAH^b n (%)	109 (18.7%)	78 (13.6%)	5.1%	33% (2%; 54%)	0.67 (0.46; 0.98)	0.04
Disease progression^b n (%)	100 (17.2%)	38 (6.6%)	10.6%	64% (41%; 78%)	0.36 (0.22; 0.59)	< 0.0001
i.v./s.c. Prostanoid initiation or oxygen therapy^{b,c} n (%)	15 (2.6%)	11 (1.9%)	0.7%	32% (–90%; 76%)	0.68 (0.24; 1.90)	0.53
Death up to EOT + 7 days^d n (%)	37 (6.4%)	46 (8.0%)	–1.7%	–17% (–107%; 34%)	1.17 (0.66; 2.07)	0.77
Death up to study closure^d n (%)	105 (18.0%)	100 (17.4%)	0.6%	3% (–39%; 32%)	0.97 (0.68; 1.39)	0.42

CI = confidence interval; EOT = end of treatment; HR = hazard ratio; i.v. = intravenous; PAH = pulmonary arterial hypertension; s.c. = subcutaneous.

^a % of patients with an event at 36 months = $100 \times (1 - \text{Kaplan-Meier estimate})$; hazard ratio estimated using Cox's proportional hazard model; unstratified one-sided log-rank p-value

^b % of patients with an event as part of the primary endpoint up to EOT + 7 days; hazard ratio estimated using Aalen Johansen method; 2-sided p-value using Gray's test

^c Includes 'Need for lung transplantation or atrial septostomy' (1 patient on selexipag and 2 on placebo)

^d % of patients with an event up to EOT + 7 days or up to study closure; hazard ratio estimated using Cox's proportional hazard model; unstratified one-sided log-rank p-value

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 imbalance in deaths is consistent with the assumption of a neutral effect on PAH mortality and reduction of non-fatal events.

The observed effect of selexipag versus placebo on the primary endpoint was consistent across individualised maintenance dose as shown by the hazard ratio for the three pre-defined categories (0.60 for 200–400 micrograms twice daily, 0.53 for 600–1 000 micrograms twice daily, and 0.64 for 1 200–1 600 micrograms twice daily), which was consistent with the overall treatment effect (0.60).

The efficacy of selexipag on the primary endpoint was consistent across subgroups of age, sex, race, aetiology, geographical region, WHO FC, and as monotherapy or in combination with an ERA or a PDE-5 inhibitor or triple combination with both an ERA and a PDE-5 inhibitor.

Time to PAH-related death or hospitalisation for PAH was assessed as a secondary endpoint. The risk of an event for this endpoint was reduced by 30% in patients receiving selexipag compared to placebo (HR 0.70, 99% CI: 0.50, 0.98; one-sided log-rank $p = 0.0031$). The percentages of patients with an event at Month 36 were 28.9% and 41.3% in the selexipag and placebo groups, respectively, with an absolute risk reduction of 12.4%.

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 (15.0%) patients on selexipag and 123 (21.1%) patients on placebo. Selexipag reduced the risk of hospitalisation for PAH as a 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 selexipag 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 selexipag group and 83 (14.3%) for the placebo group.

Symptomatic endpoints

Exercise capacity was evaluated as a secondary endpoint. Median 6MWD at baseline was 376 m (range: 90–482 m) and 369 m (range: 50–515 m) in selexipag patients and placebo patients, respectively. Treatment with selexipag resulted in a placebo-corrected median effect on 6MWD measured at trough (i.e., approximately 12 h post-dose) of 12 m at Week 26 (99% CI: 1, 24 m; one-sided p value = 0.0027). In patients without concurrent PAH-specific therapy, the placebo-corrected treatment effect measured at trough was 34 m (99% CI: 10, 63 m).

Quality of life was assessed in a subset of patients in the GRIPHON study using the Cambridge Pulmonary Hypertension Outcome Review (CAMPBOR) questionnaire. There was no significant treatment effect from baseline to Week 26.

Long-term data in 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 selexipag in the GRIPHON study; of these, 330 patients continued selexipag treatment in the open-label extension study. The median follow-up duration was 4.5 years and the median exposure to selexipag was 3 years. During the follow-up, at least one other PAH medicinal product was added to selexipag in 28.4% of the patients. However, most of the treatment exposure (86.3%) in all of the 574 patients was accumulated without addition of any new PAH medicinal product. Kaplan-Meier estimates of survival of these 574 patients across the GRIPHON and the long-term extension study at 1, 2, 5 and 7 years were 92%, 85%, 71%, and 63%, respectively. Survival at 1, 2, 5, and 7 years for 273 patients of WHO FC II at baseline of the pivotal study were 97%, 91%, 80% and 70%, respectively, and for 294 patients of WHO FC III at baseline were 88%, 80%, 62% and 56%, respectively. Given that additional PAH treatment was initiated in a small proportion of patients and that there was no control group in the extension study, the survival benefit of selexipag cannot be confirmed from these data.

Initial triple combination treatment with selexipag, macitentan and tadalafil in newly diagnosed PAH patients

In a double blind, placebo-controlled study, a total of 247 newly diagnosed PAH patients were randomised to evaluate the treatment effect of initial triple (selexipag, macitentan and tadalafil) (N = 123) versus initial double (placebo, macitentan and tadalafil) (N = 124) therapy. The primary endpoint, change from baseline in pulmonary vascular resistance (PVR) at Week 26, did not show a statistically significant difference between the groups, while showing an improvement from baseline in both treatment groups (relative reduction by 54% in the initial triple therapy group vs 52% in the initial double therapy group). Over a median follow-up of 2 years, 4 (3.4%) patients in the triple therapy group and 12 (9.4%) patients in the double therapy group died.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Uptravi in one or more subsets of the paediatric population for treatment of pulmonary hypertension, (see section 4.2 for information on paediatric use).

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 the 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 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 in humans is approximately 49%. This is most probably due to a first-pass effect of selexipag, as plasma concentrations of the active metabolite are similar after the same oral and intravenous dose administration.

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 exceed 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 6.2–13.5 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.

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.

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 (eGFR < 30 mL/min/1.73 m²).

Hepatic impairment

In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, 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 modelling and simulation data from a study in subjects with hepatic impairment, the exposure to selexipag at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once-daily regimen is predicted to be approximately 2-fold higher than that in healthy subjects during a twice-daily regimen. The exposure to the active metabolite at steady state in these patients during a once-daily regimen is predicted to be similar to that in healthy subjects during a twice-daily regimen. Subjects with severe hepatic impairment (Child-Pugh class C) showed similar predicted exposure at steady state as subjects with moderate hepatic impairment during a once-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. A delay in the closure of the femoral and/or tibial epiphyseal growth plate was observed in juvenile dogs. A no-observed-adverse-effect level was not established. In juvenile dogs, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. Safety margins adapted for IP receptor potency for the active metabolite were 2-fold (based on total exposure) in relation to human therapeutic exposure. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific sensitivity of dogs to develop intussusception, 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. 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. Additional histopathological findings of selexipag were observed only at exposures sufficiently in excess of the maximum human exposure, indicating little relevance to humans.

In a fertility study performed in rats, a prolongation of oestrus cycles resulting in increases in days until copulation was observed at exposures 173-fold above therapeutic exposures (based on total

exposures), the no-observed-effect level being 30-fold above therapeutic exposures. Otherwise, fertility parameters were not affected.

Selexipag was not teratogenic in rats and rabbits (exposure margins above therapeutic exposure of 13-fold for selexipag and 43-fold for the active metabolite, based on total exposure). Safety margins for potential IP receptor-related effects on reproduction were 20 for fertility and 5 and 1 (based on free exposure) for embryo-foetal development in rats and rabbits, respectively, when adapted for differences in receptor potency. In the rat pre-/post-natal development study, selexipag induced no effects on maternal and pup reproductive function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)

Maize starch

Low-substituted hydroxypropylcellulose

Hydroxypropylcellulose

Magnesium stearate

Film coating

Uptravi 100 microgram film-coated tablet

Hypromellose (E464)

Propylene glycol (E1520)

Titanium dioxide (E171)

Iron oxide yellow (E172)

Iron oxide black (E172)

Carnauba wax

Talc

Uptravi 200 microgram film-coated tablet

Hypromellose (E464)

Propylene glycol (E1520)

Titanium dioxide (E171)

Iron oxide yellow (E172)

Carnauba wax

Uptravi 400 microgram film-coated tablet

Hypromellose (E464)

Propylene glycol (E1520)

Titanium dioxide (E171)

Iron oxide red (E172)

Carnauba wax

Uptravi 600 microgram film-coated tablet

Hypromellose (E464)

Propylene glycol (E1520)

Titanium dioxide (E171)

Iron oxide red (E172)

Iron oxide black (E172)

Carnauba wax

Uptravi 800 microgram film-coated tablet

Hypromellose (E464)

Propylene glycol (E1520)

Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide black (E172)
Carnauba wax

Uptravi 1 000 microgram film-coated tablet

Hypromellose (E464)
Propylene glycol (E1520)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Carnauba wax

Uptravi 1 200 microgram film-coated tablet

Hypromellose (E464)
Propylene glycol (E1520)
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide red (E172)
Carnauba wax

Uptravi 1 400 microgram film-coated tablet

Hypromellose (E464)
Propylene glycol (E1520)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Carnauba wax

Uptravi 1 600 microgram film-coated tablet

Hypromellose (E464)
Propylene glycol (E1520)
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

Blister: 4 years.
Bottle: 18 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Uptravi 100 microgram film-coated tablets

High density polyethylene (HDPE) bottle with twist-off child-resistant closure, containing 1 g silica desiccant capsule in the cap, and a heat seal liner.

Cartons of 60 film-coated tablets (bottles).
Cartons of 140 film-coated tablets (titration pack, bottles).

Uptravi 200 microgram film-coated tablets

Polyamide / aluminium / HDPE / PE with an embedded desiccant agent / HDPE blister sealed with an aluminium foil.

Each blister strip contains 10 film-coated tablets.

Cartons of 10 or 60 film-coated tablets. (1 or 6 blister strips)

Cartons of 60 or 140 film-coated tablets (titration packs, 6 or 14 blister strips).

Uptravi 400 microgram, 600 microgram, 800 microgram, 1 000 microgram, 1 200 microgram, 1 400 microgram, and 1 600 microgram film-coated tablets

Polyamide / aluminium / HDPE / PE with an embedded desiccant agent / HDPE blister sealed with an aluminium foil.

Each blister strip contains 10 film-coated tablets

Cartons of 60 film-coated tablets (6 blister strips).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1083/001
EU/1/15/1083/002
EU/1/15/1083/003
EU/1/15/1083/004
EU/1/15/1083/005
EU/1/15/1083/006
EU/1/15/1083/007
EU/1/15/1083/008
EU/1/15/1083/009
EU/1/15/1083/010
EU/1/15/1083/011
EU/1/15/1083/012
EU/1/15/1083/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 2016

Date of latest renewal: 14 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

Prior to the launch of Uptravi in each Member State, the MAH must agree on the content and format of the Controlled Access System with the National Competent Authority.

The Controlled Access System is aimed to facilitate the identification of prescribers, to approach them with the appropriate information on the safe and effective use of Uptravi, and to provide them with risk minimisation tools, especially regarding the potential risk of medication error. The Controlled Access System should include 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 minimise the risks of medication error in particular;

- Tracking of the receipt of the kits by prescribers.

The MAH shall ensure that in each Member State where Uptravi is marketed, all healthcare professionals who are expected to prescribe and/or dispense Uptravi are provided with a Prescriber Kit containing the following:

- The Summary of Product Characteristics for Uptravi;
- Cover letter to the healthcare professional;
- Healthcare professional A4 laminated titration guide(s);
- Patient titration guide(s);
- Patient Leaflet.

The cover letter to the healthcare professional should 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, and it should provide a list of the contents of the Prescriber Kit.

The healthcare professional A4 laminated titration guides for selexipag starting doses of 100 micrograms and 200 micrograms are intended to reduce the risk of medication error due to the titration phase at treatment initiation with Uptravi and it should contain the following key elements:

- The dosing and titration concept;
- The move to the maintenance dose (titration phase);
- Expectations and management of adverse reactions during the titration phase;
- Encouragement and guidance for healthcare professionals 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 healthcare professional and the patient (need for contact and to schedule telephone calls).

Patient titration guides for selexipag starting doses of 100 micrograms and 200 micrograms are available. The patient titration guide to be used by the healthcare professionals during discussions with the patient should contain the following key elements:

- Lay language version of the healthcare professional A4 laminated titration guide;
- Diary to facilitate Uptravi use and serve as a reminder for the patients (e.g., to contact her/his doctor), and a place to record intake of tablets;
- Information about the safe and effective use of Uptravi in lay language.

The patient titration guide corresponding to the patient's selexipag starting dose of 100 micrograms or 200 micrograms along with the Patient Information Leaflet should be given to the patient after the demonstration. Patients will receive a titration guide and Patient Leaflet in their titration packs of Uptravi.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON - TITRATION PACK****1. NAME OF THE MEDICINAL PRODUCT**

Uptravi 100 microgram film-coated tablets
selexipag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 micrograms of selexipag

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

Titration pack
140 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split or crush.
Read the package leaflet and titration guide before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/15/1083/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Uptravi 100 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Uptravi 100 microgram film-coated tablets
selexipag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 micrograms of selexipag

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split or crush.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/15/1083/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Uptravi 100 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Uptravi 100 microgram film-coated tablets
selexipag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 micrograms of selexipag

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

60 film-coated tablets

140 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split or crush.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1083/012
EU/1/15/1083/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON - TITRATION PACK****1. NAME OF THE MEDICINAL PRODUCT**

Uptravi 200 microgram film-coated tablets
selexipag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 micrograms of selexipag

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

Titration pack
60 film-coated tablets
140 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split or crush.
Read the package leaflet and titration guide before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1083/003
EU/1/15/1083/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Uptravi 200 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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
selexipag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 micrograms of selexipag
Each film-coated tablet contains 400 micrograms of selexipag
Each film-coated tablet contains 600 micrograms of selexipag
Each film-coated tablet contains 800 micrograms of selexipag
Each film-coated tablet contains 1 000 micrograms of selexipag
Each film-coated tablet contains 1 200 micrograms of selexipag
Each film-coated tablet contains 1 400 micrograms of selexipag
Each film-coated tablet contains 1 600 micrograms of selexipag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split or crush.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1083/001
EU/1/15/1083/002
EU/1/15/1083/004
EU/1/15/1083/005
EU/1/15/1083/006
EU/1/15/1083/007
EU/1/15/1083/008
EU/1/15/1083/009
EU/1/15/1083/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Uptravi 200 microgram
Uptravi 400 microgram
Uptravi 600 microgram
Uptravi 800 microgram
Uptravi 1 000 microgram
Uptravi 1 200 microgram
Uptravi 1 400 microgram
Uptravi 1 600 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Uptravi 200 microgram tablets
Uptravi 400 microgram tablets
Uptravi 600 microgram tablets
Uptravi 800 microgram tablets
Uptravi 1 000 microgram tablets
Uptravi 1 200 microgram tablets
Uptravi 1 400 microgram tablets
Uptravi 1 600 microgram tablets
selexipag

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Janssen-Cilag Int

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Uptravi 100 microgram film-coated tablets
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
selexipag

Read all of this leaflet carefully before taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet

1. What Uptravi is and what it is used for
2. What you need to know before you take Uptravi
3. How to take Uptravi
4. Possible side effects
5. How to store Uptravi
6. Contents of the package and other information

1. What Uptravi is and what it is used for

Uptravi is a medicine that contains the active substance selexipag. It acts on blood vessels in a similar way to the natural substance prostacyclin, making them relax and widen.

Uptravi is used for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients insufficiently controlled with other types of medicines for PAH known as endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. Uptravi can be used on its own if the patient is not a candidate for these medicines.

PAH is high blood pressure in the blood vessels that carry blood from the heart to the lungs (the pulmonary arteries). In people with PAH, these arteries narrow, so the heart has to work harder to pump blood through them. This may cause people to feel tired, dizzy, short of breath, or experience other symptoms.

By acting in a similar way to the natural substance prostacyclin, this medicine widens the pulmonary arteries and reduces their hardening. This makes it easier for the heart to pump blood through the pulmonary arteries. Uptravi lowers the pressure in the pulmonary arteries, it relieves the symptoms of PAH and slows down progression of PAH disease.

2. What you need to know before you take Uptravi

Do not take Uptravi

- if you are allergic to selexipag or any of the other ingredients of this medicine (listed in section 6).
- if you have a heart problem, such as:
 - poor blood flow to the heart muscles (severe coronary heart disease or unstable angina); symptoms can include chest pain
 - heart attack within the last 6 months
 - weak heart (decompensated cardiac failure) that is not under close medical observation
 - severe irregular heartbeat
 - defect of the heart valves (inborn or acquired) that causes the heart to work poorly (not related to pulmonary hypertension)
- if you have had a stroke within the last 3 months, or any other occurrence that reduced the blood supply to the brain (e.g., transient ischaemic attack)
- if you are taking gemfibrozil (medicine used to lower the level of fats [lipids] in the blood)

Warnings and precautions

Talk to your PAH doctor or nurse before taking Uptravi if you

- are taking medicines for high blood pressure
- have low blood pressure associated with symptoms such as dizziness
- have recently experienced significant blood loss or fluid loss such as severe diarrhoea or vomiting
- have problems with your thyroid gland
- have severe problems with your kidneys or are undergoing dialysis
- have or have had severe problems with your liver not working properly

If you notice any of the above signs or your condition changes, **tell your doctor immediately.**

Children and adolescents

Do not give this medicine to children under 18 years of age, because Uptravi has not been tested in children.

Elderly patients

There is limited experience with Uptravi in patients older than 75 years. Uptravi should be used with caution in this age group.

Other medicines and Uptravi

Tell your doctor if you are taking, have recently taken, or might take any other medicines. Taking other medicines may affect how Uptravi works.

Talk to your PAH doctor or nurse if you are taking any of the following medicines:

- Gemfibrozil (medicine used to lower the level of fats [lipids] in the blood)
- Clopidogrel (medicine used to inhibit blood clots in coronary artery disease)
- Deferasirox (medicine used to remove iron from the blood stream)
- Teriflunomide (medicine used to treat relapsing-remitting multiple sclerosis)
- Carbamazepine (medicine used to treat some forms of epilepsy, nerve pain or to help control serious mood disorders when some other medicines do not work)
- Phenytoin (medicine used to treat epilepsy)
- Valproic acid (medicine used to treat epilepsy)
- Probenecid (medicine used to treat gout)
- Fluconazole, rifampicin or rifapentine (antibiotics used to treat infections)

Pregnancy and breast-feeding

Uptravi is not recommended during pregnancy and breast-feeding. If you are a woman who can have children, you should use an effective contraceptive method while taking Uptravi. If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines

Uptravi can cause side effects such as headaches and low blood pressure (see section 4), which may affect your ability to drive; the symptoms of your condition can also make you less fit to drive.

3. How to take Uptravi

Uptravi should only be prescribed by a doctor experienced in the treatment of PAH. Always take this medicine exactly as your doctor has told you. Check with your doctor if you are in doubt or have any questions.

Tell your doctor if you experience side effects, as your doctor may recommend that you change your Uptravi dose.

Tell your doctor if you have problems with your liver not working properly or are taking other medicines as your doctor may recommend that you take a lower dose of Uptravi twice daily or take it only once daily.

If you have poor vision or experience any type of blindness, get help from another person when taking Uptravi during the titration period (process of gradually increasing your dose).

Finding the right dose for you

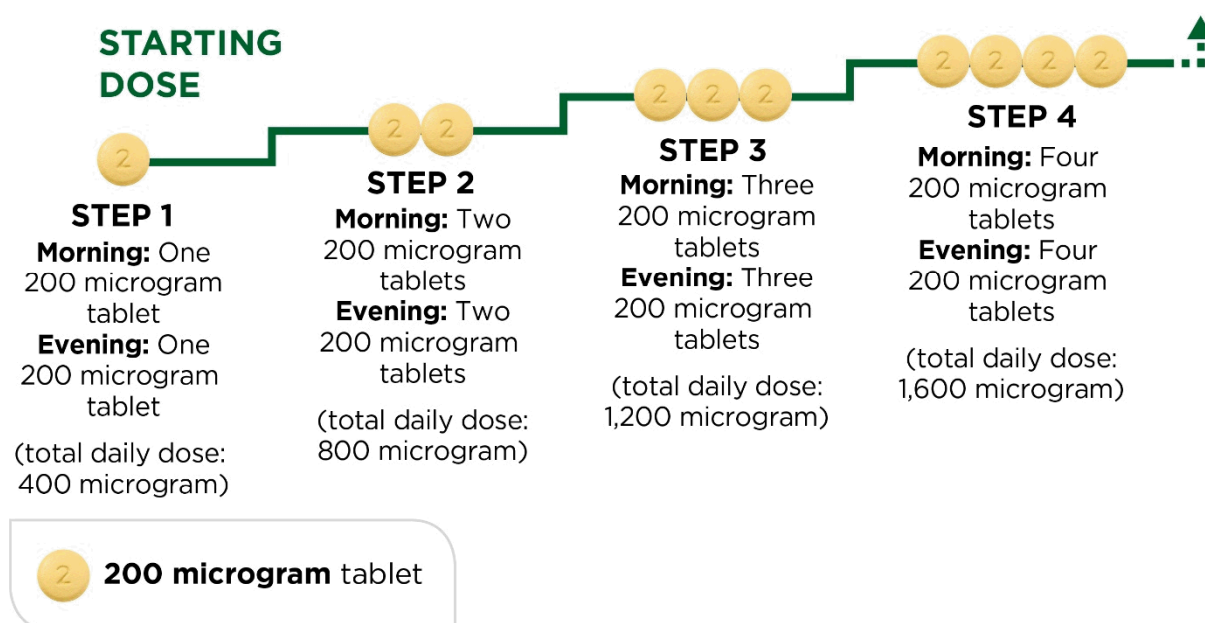
If your doctor prescribes 200-microgram tablets

At the start of treatment, most patients will take **a 200-microgram tablet in the morning and another 200-microgram tablet in the evening, about 12 hours apart**. It is recommended to initiate treatment in the evening. Your doctor will instruct you to gradually increase your dose. This is called titration. It lets your body adjust to the new medicine. The goal of titration is to reach the most appropriate dose. This will be the highest dose you can tolerate, which may reach the maximum dose of 1 600 micrograms in the morning and in the evening.

The first pack of tablets you receive will contain the light-yellow 200-microgram tablets. Your doctor will tell you to increase your dose in steps, usually every week but the interval between increases could be longer.

With each step, you will add one 200-microgram tablet to your morning dose and another 200-microgram tablet to your evening dose. **The first intake of the increased dose is recommended to be in the evening.** The diagram below shows the number of tablets to take **every morning and every evening** for the first 4 steps.

Each dosing step lasts about 1 week.

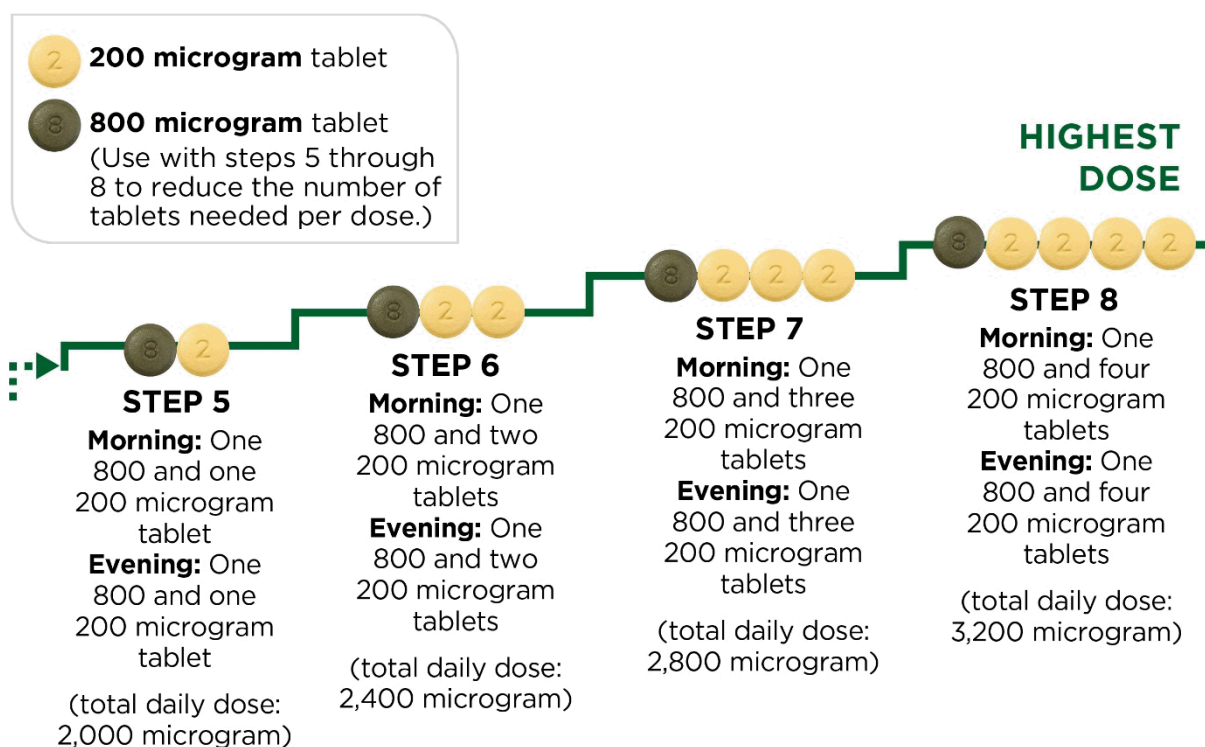


If your doctor tells you to increase your dose further, you will add one 200-microgram tablet to your morning dose and one 200-microgram tablet to your evening dose with each new step. The first intake of the increased dose is recommended to be in the evening.

If your doctor instructs you to further increase your dose and move to step 5, this may be done by taking one green 800-microgram tablet and one light-yellow 200-microgram tablet in the morning and one 800-microgram tablet and one 200-microgram tablet in the evening.

The maximum dose of Upravi is 1 600 micrograms in the morning and 1 600 micrograms in the evening. However, not every patient will reach this dose, because different patients require different doses.

The diagram below shows the number of tablets to take every morning and every evening at each step, starting with step 5.



If your doctor prescribes 100-microgram tablets

If your liver is not working properly or you are taking certain medicines, your doctor may prescribe 100-microgram tablets as your starting dose.

At the start of treatment, you will take **one 100-microgram tablet in the morning and another 100-microgram tablet in the evening, about 12 hours apart**. It is recommended to initiate treatment in the evening. Your doctor will instruct you to gradually increase your dose. This is called titration. It lets your body adjust to the new medicine. The goal of titration is to reach the most appropriate dose. This will be the highest dose you can tolerate, which may reach the maximum dose of 800 micrograms in the morning and in the evening.

Your doctor will tell you to increase your dose in steps, usually every week but the interval between increases could be longer.

With each step, you will add one 100-microgram tablet to your morning dose and another 100-microgram tablet to your evening dose. **The first intake of the increased dose is recommended to be in the evening.** Please refer to the Patient titration guide included in the titration pack, for instructions on how to step up your dose.

Tell your doctor if you stop taking or might stop taking any medicines, as your dose of selexipag may need to be adjusted.

If your doctor tells you to increase your dose further, you will add one 100-microgram tablet to your morning dose and one 100-microgram tablet to your evening dose with each new step. The first intake of the increased dose is recommended to be in the evening.

If your doctor instructs you to further increase your dose above 400 micrograms, this may be done by taking one red 400-microgram tablet and one light-yellow 100-microgram tablet in the morning and one 400-micrograms tablet and one 100-microgram tablet in the evening. Please refer to the patient titration guide included in the titration pack, for instructions on how to step up your dose.

When uptitrating with the 100-micrograms tablets, the maximum dose of Uptravi is 800 micrograms in the morning and 800 micrograms in the evening. However, not every patient will reach this dose, because different patients require different doses.

Using the titration guide during titration

You will receive the titration pack which contains a titration guide and patient leaflet. The titration guide is providing information on the titration process and is allowing you to record the number of tablets you take every day.

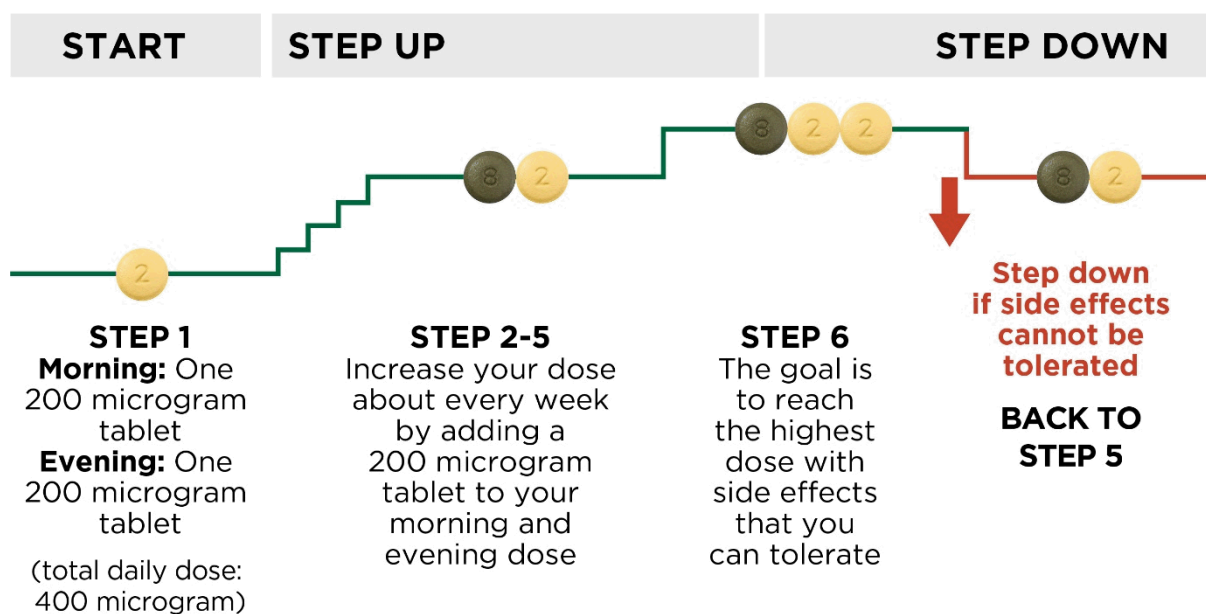
Remember to record the number of tablets you take every day in your titration diary. The titration steps usually last about 1 week. If your doctor instructs you to prolong each titration step longer than 1 week, there are additional diary pages to allow you to track this. **Remember to talk to your PAH doctor or nurse regularly during titration.**

Stepping down to a lower dose due to side effects

During titration, you may experience side effects such as headache, diarrhoea, feeling sick (nausea), being sick (vomiting), jaw pain, muscle pain, leg pain, joint pain, or reddening of the face (see section 4). If these side effects are difficult for you to tolerate, talk to your doctor about how to manage or treat them. There are treatments available that can help relieve the side effects. For example, painkillers such as paracetamol may help treat pain and headache.

If the side effects cannot be treated or do not gradually get better on the dose you are taking, your doctor may adjust your dose by reducing the number of light-yellow tablets you take by one in the morning and by one in the evening. The diagram below shows stepping down to a lower dose. Do this only if instructed to do so by your doctor.

Titration with 200-microgram tablets



If you are titrating with 100-microgram tablets, please refer to the patient titration guide included in the titration pack for instructions for stepping down.

If your side effects are manageable after stepping down your dose, your doctor may decide that you should stay on that dose. Please see section Maintenance dose below for more information.

Maintenance dose

The highest dose that you can tolerate during titration will become your maintenance dose. Your maintenance dose is the dose you should continue to take on a regular basis.

Your doctor will prescribe suitable tablet strength(s) for your maintenance dose. **This may allow you to take one tablet in the morning and one in the evening, instead of multiple tablets each time.**

For a full description of Uptravi tablets, including colours and marking, please see section 6 of this leaflet.

Over time, your doctor may adjust your maintenance dose as needed.

If, at any time, after taking the same dose for a long time, you experience side effects that you cannot tolerate or side effects that have an impact on your normal daily activities, contact your doctor as your dose may need to be reduced. The doctor may then prescribe you a lower dose. Please remember to dispose of unused tablets (see section 5).

Take Uptravi once in the morning and once in the evening, about 12 hours apart.

Take the tablets with meals as you might tolerate your medicine better. The tablet coating provides protection. Swallow the tablets whole with a glass of water. Do not split or crush the tablets.

If you take more Uptravi than you should

If you have taken more tablets than you have been told to take, ask your doctor for advice.

If you forget to take Uptravi

If you forget to take Uptravi, take a dose as soon as you remember, then continue to take your tablets at the usual times. If it is nearly time for your next dose (within 6 hours before you would normally take it), you should skip the missed dose and continue to take your medicine at the usual time. **Do not take a double dose to make up for a forgotten tablet.**

If you stop taking Uptravi

Suddenly stopping your treatment with Uptravi might lead to your symptoms getting worse. Do not stop taking Uptravi unless your doctor tells you to. Your doctor may tell you to reduce the dose gradually before stopping completely.

If, for any reason, you stop taking Uptravi for more than 3 consecutive days (if you missed 3 morning and 3 evening doses, or 6 doses in a row or more), **contact your doctor immediately as your dose may need to be adjusted to avoid side effects.** Your doctor may decide to restart your treatment on a lower dose, gradually increasing to your previous maintenance dose.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. You may experience side effects not only during the titration period when your dose is being increased, but also later after taking the same dose for a long time.

If you experience swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing (angioedema), you should contact your doctor immediately.

If you experience any of these side effects: headache, diarrhoea, feeling sick (nausea), being sick (vomiting), jaw pain, muscle pain, leg pain, joint pain, or reddening of the face, that you cannot tolerate or that cannot be treated, you should contact your doctor as the dose you are taking may be too high for you and may need to be reduced.

Very common side effects (may affect more than 1 in 10 people)

- Headache
- Flushing (reddening of the face)
- Nausea and vomiting (feeling sick and being sick)
- Diarrhoea
- Jaw pain, muscle pain, joint pain, leg pain
- Nasopharyngitis (stuffy nose)

Common side effects (may affect up to 1 in 10 people)

- Anaemia (low red blood cell levels)
- Hyperthyroidism (overactive thyroid gland)
- Reduced appetite
- Weight loss
- Hypotension (low blood pressure)
- Stomach pain, including indigestion
- Pain
- Changes in some blood test results including those measuring blood cell counts or your thyroid function
- Rashes, including hives, may cause a burning or stinging sensation and skin redness
- Angioedema and its symptoms as described at the beginning of this section

Uncommon side effects (may affect up to 1 in 100 people)

- Increased heart rate

Reporting of side effects

If you have any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V..](#) By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Uptravi

Keep this medicine out of the sight and reach of children.

Do not use Uptravi after the expiry date, which is stated on the carton and on the blister or bottle label after “EXP.” The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Uptravi contains

The active substance is selexipag.

Uptravi 100 microgram film-coated tablets contain 100 micrograms of selexipag
Uptravi 200 microgram film-coated tablets contain 200 micrograms of selexipag
Uptravi 400 microgram film-coated tablets contain 400 micrograms of selexipag
Uptravi 600 microgram film-coated tablets contain 600 micrograms of selexipag
Uptravi 800 microgram film-coated tablets contain 800 micrograms of selexipag
Uptravi 1 000 microgram film-coated tablets contain 1 000 micrograms of selexipag
Uptravi 1 200 microgram film-coated tablets contain 1 200 micrograms of selexipag
Uptravi 1 400 microgram film-coated tablets contain 1 400 micrograms of selexipag
Uptravi 1 600 microgram film-coated tablets contain 1 600 micrograms of selexipag

The other ingredients are:

Tablet core

Mannitol (E421)

Maize starch

Low-substituted hydroxypropylcellulose

Hydroxypropylcellulose

Magnesium stearate

Film coating

Hypromellose (E464)

Propylene glycol (E1520)

Titanium dioxide (E171)

Iron oxides (E172)

Carnauba wax

Uptravi 100 microgram film-coated tablets contain iron oxide yellow, iron oxide black (E172) and talc.

Uptravi 200 microgram film-coated tablets contain iron oxide yellow (E172).

Uptravi 400 microgram film-coated tablets contain iron oxide red (E172).

Uptravi 600 microgram film-coated tablets contain iron oxide red and iron oxide black (E172).

Uptravi 800 microgram film-coated tablets contain iron oxide yellow and iron oxide black (E172).

Uptravi 1 000 microgram film-coated tablets contain iron oxide red and iron oxide yellow (E172).

Uptravi 1 200 microgram film-coated tablets contain iron oxide black and iron oxide red (E172).

Uptravi 1 400 microgram film-coated tablets contain iron oxide yellow (E172).

Uptravi 1 600 microgram film-coated tablets contain iron oxide black, iron oxide red and iron oxide yellow (E172).

What Uptravi looks like and contents of the pack

Uptravi 100 microgram film-coated tablets: Round, 3.0 mm diameter, light-yellow, film-coated tablets with “1” marked on one side.

Uptravi 200 microgram film-coated tablets: Round, 7.3 mm diameter, light-yellow, film-coated tablets with “2” marked on one side.

Uptravi 400 microgram film-coated tablets: Round, 7.3 mm diameter, red, film-coated tablets with “4” marked on one side.

Uptravi 600 microgram film-coated tablets: Round, 7.3 mm diameter, light-violet, film-coated tablets with “6” marked on one side.

Uptravi 800 microgram film-coated tablets: Round, 7.3 mm diameter, green, film-coated tablets with “8” marked on one side.

Uptravi 1 000 microgram film-coated tablets: Round, 7.3 mm diameter, orange, film-coated tablets with “10” marked on one side.

Uptravi 1 200 microgram film-coated tablets: Round, 7.3 mm diameter, dark-violet, film-coated tablets with “12” marked on one side.

Uptravi 1 400 microgram film-coated tablets: Round, 7.3 mm diameter, dark-yellow, film-coated tablets with “14” marked on one side.

Uptravi 1 600 microgram film-coated tablets: Round, 7.3 mm diameter, brown, film-coated tablets with “16” marked on one side.

Uptravi 100 microgram film-coated tablets are supplied in bottles of 60 tablets and 140 tablets (titration pack).

Uptravi 200 microgram film-coated tablets are supplied in blister packs of 10 or 60 tablets and 60 or 140 tablets (titration packs).

Uptravi 400 microgram, 600 microgram, 800 microgram, 1 000 microgram, 1 200 microgram, 1 400 microgram, and 1 600 microgram film-coated tablets are supplied in blister packs of 60 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

Janssen Pharmaceutica NV
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Lietuva

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

TITRATION GUIDE - TITRATION PACK

Page 1

Uptravi 200 microgram film-coated tablets
selexipag

Titration Guide

Starting Treatment with Uptravi

Please read the accompanying patient information leaflet before starting treatment. Tell your doctor if you experience side effects, as your doctor may recommend that you change your Uptravi dose. Tell your doctor if you are taking other medicines as your doctor may recommend that you take Uptravi only once daily.

Page 2

Contents

How should you take Uptravi?	4
How should you step up your dose?	6
What are the steps?	8
When should you step down?	10
Stepping down	12

Page 3

When you move to your maintenance dose.....	14
If you forget to take Uptravi.....	16
If you stop taking Uptravi.....	17
Titration diary.....	18

Page 4

How should you take Uptravi?

Uptravi is a medicine taken every morning and evening for the treatment of pulmonary arterial hypertension, also called PAH.

The starting dose for Uptravi is 200 micrograms **once in the morning and once in the evening.**

The first intake of Uptravi should be in the evening.

You should take each dose with a glass of water, preferably during a meal.

Page 5

There are 2 phases of treatment with Uptravi:

Titration

In the first several weeks, you will work with your doctor to find the dose of Uptravi that is right for you. Your doctor may have you step up from the starting dose to higher doses of Uptravi. Your doctor may step you down to a lower dose. This process is called titration. It lets your body gradually adjust to the medicine.

Maintenance

Once your doctor has found the dose that is right for you, this will be the dose you take on a regular basis. This is called the maintenance dose.

How should you step up your dose?

You will start at the 200 microgram dose in the morning and in the evening and after discussing with your doctor or nurse step up to the next dose.

The first intake of the increased dose should be in the evening. Each step usually lasts about 1 week. It could take several weeks to find the dose that is right for you.

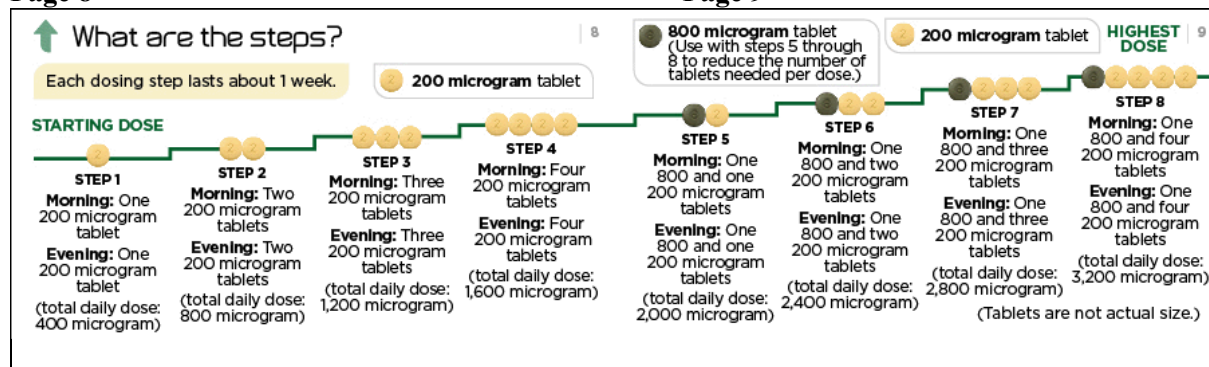
The goal is to reach the dose that is most appropriate to treat you.

This dose will be your maintenance dose.

Every patient with PAH is different. **Not everyone will end up on the same maintenance dose.**

Some patients may have 200 micrograms in the morning and in the evening as their maintenance dose, while some will reach the highest dose of 1 600 micrograms in the morning and in the evening.

Others may reach a maintenance dose somewhere in between. What is important is that you reach the dose that is most appropriate to treat you.



↓ When should you step down?

As with all medicines, you may experience side effects with Uptravi as you step up to higher doses.

Talk to your doctor or nurse if you have side effects. There are treatments available that can help relieve them.

The most common side effects (may affect more than 1 in 10 people) you may experience while taking Uptravi are:

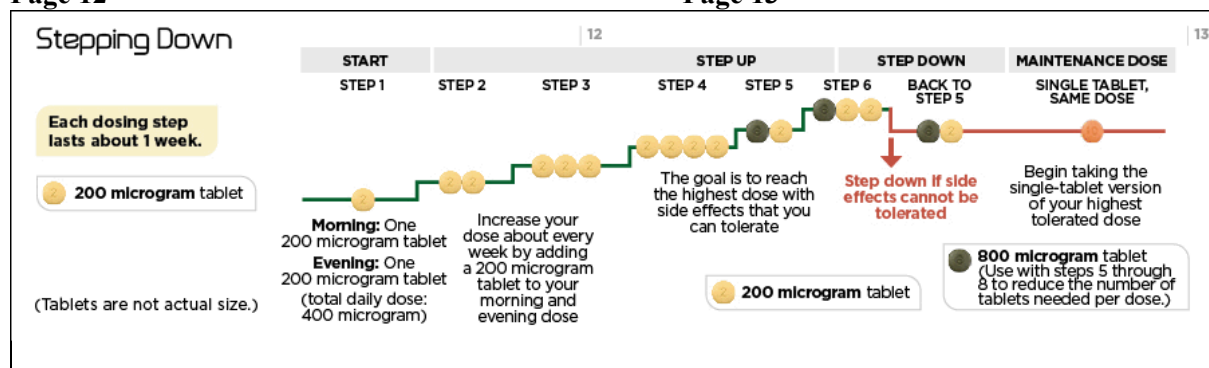
- Headache • Diarrhoea • Nausea • Vomiting
- Jaw pain • Muscle pain • Leg pain • Joint pain
- Facial redness

For a full list of side effects see package leaflet for further information.

If you cannot tolerate the side effects even after your doctor or nurse has tried to treat them, he or she may recommend you step down to a lower dose.

If your doctor or nurse tells you to step down to a lower dose, you should take one less 200 microgram tablet in the morning and one less in the evening.

You should only step down after speaking with your PAH doctor or nurse. This stepping-down process will help you find the dose that is right for you, also called your maintenance dose.

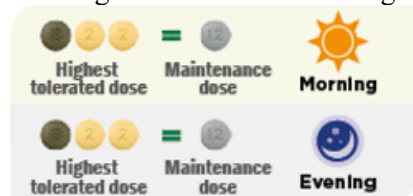


When you move to your maintenance dose

The highest dose that you can tolerate during titration will become your **maintenance dose**. Your maintenance dose is the dose you should continue to take on a regular basis. Your doctor or nurse can prescribe an equivalent **single-tablet strength** for your maintenance dose.

This lets you take just one tablet in the morning and one in the evening, instead of multiple tablets for each dose.

For example, if your highest tolerated dose during titration was 1 200 micrograms once in the morning and once in the evening:



Over time, your doctor or nurse may adjust your maintenance dose as needed.

If you forget to take Upravi

If you miss a dose, take the dose as soon as you remember, then continue to take your tablets at the usual times. If it is within 6 hours of when you would normally take your next dose, you should skip the missed dose and continue to take your medicine at the usual time.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Upravi

Do not stop taking Upravi unless your doctor or nurse tells you to. If, for any reason, you stop taking Upravi for more than 3 consecutive days (if you missed 6 doses in a row), **contact your PAH doctor or nurse immediately as your dose may need to be adjusted to avoid side effects.**

Your doctor or nurse may have you resume treatment at a lower dose, gradually increasing to your previous maintenance dose.

Titration diary

Please read the instructions in the package leaflet carefully.

The following diary pages help you keep track of the number of tablets you need to take in the morning and evening during titration.

Use them to write down the number of tablets you take in the morning and the evening.

Each step usually lasts about 1 week, unless your doctor or nurse instructs you otherwise. If your titration steps last longer than 1 week there are additional diary pages to track this.



Use pages 20 to 27 to track the first weeks of treatment, when you are using 200 microgram tablets only (steps 1–4).



If you have been prescribed both 200 and 800 microgram tablets, use pages 30 to 37 (steps 5–8).

Remember to talk to your PAH doctor or nurse regularly.

Write down your doctor or nurse's instructions:

Doctor's office telephone and e-mail:

Pharmacist's telephone:

Notes:

WEEK	Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							
1	Date: _____							
Morning		0	#	#	#	#	#	#
Evening		#	#	#	#	#	#	#

The first intake of Upravi should be in the evening

WEEK	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							
#	Date: _____							
Morning		#	#	#	#	#	#	#
Evening		#	#	#	#	#	#	#

The first intake of an increased dose of Upravi should be in the evening

WEEK	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							
#	Date: _____							
Morning		#	#	#	#	#	#	#
Evening		#	#	#	#	#	#	#

WEEK	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							
#	Date: _____							
Morning		#	#	#	#	#	#	#
Evening		#	#	#	#	#	#	#

Skip to page 28 if your doctor prescribes 800 microgram tablets

Page 24

WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____							24	WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____							25
Morning	200 micrograms	#	#	#	#	#	#	Morning	200 micrograms	#	#	#	#	#	#		
Evening	200 micrograms	#	#	#	#	#	#	Evening	200 micrograms	#	#	#	#	#	#		
Skip to page 28 if your doctor prescribes 800 microgram tablets								Skip to page 28 if your doctor prescribes 800 microgram tablets									

Page 25

Page 26

WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____							26	WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____							27
Morning	200 micrograms	#	#	#	#	#	#	Morning	200 micrograms	#	#	#	#	#	#		
Evening	200 micrograms	#	#	#	#	#	#	Evening	200 micrograms	#	#	#	#	#	#		
Skip to page 28 if your doctor prescribes 800 microgram tablets								Skip to page 28 if your doctor prescribes 800 microgram tablets									

Page 27

Page 28

Use the following diary pages if your doctor or nurse prescribes 800 microgram tablets in addition to your 200 microgram tablets.

On the diary pages, check off that you have taken **one** 800 microgram tablet every day in the morning and in the evening with your prescribed number of 200 microgram tablets.



Page 29

Remember to talk to your PAH doctor or nurse regularly.

Write down your doctor or nurse's instructions:

Doctor's office telephone and e-mail:

Pharmacist's telephone:

Notes:

Page 30

WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____							30	WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____							31
Morning	200 micrograms	#	#	#	#	#	#	Morning	200 micrograms	#	#	#	#	#	#		
	800 micrograms	1	1	1	1	1	1		800 micrograms	1	1	1	1	1	1		
Evening	200 micrograms	#	#	#	#	#	#	Evening	200 micrograms	#	#	#	#	#	#		
	800 micrograms	1	1	1	1	1	1		800 micrograms	1	1	1	1	1	1		

Page 31

Page 32

WEEK	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YYYY.							32							
#	Date: _____							#							
Morning	200 micrograms	800 micrograms	#	#	#	#	#	Morning	200 micrograms	800 micrograms	#	#	#	#	#
Evening	200 micrograms	800 micrograms	#	#	#	#	#	Evening	200 micrograms	800 micrograms	#	#	#	#	#
			1	1	1	1	1				1	1	1	1	1

Page 33

Page 34

WEEK	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YYYY.							34							
#	Date: _____							#							
Morning	200 micrograms	800 micrograms	#	#	#	#	#	Morning	200 micrograms	800 micrograms	#	#	#	#	#
Evening	200 micrograms	800 micrograms	#	#	#	#	#	Evening	200 micrograms	800 micrograms	#	#	#	#	#
			1	1	1	1	1				1	1	1	1	1

Page 35

Page 36

WEEK	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YYYY.							36							
#	Date: _____							#							
Morning	200 micrograms	800 micrograms	#	#	#	#	#	Morning	200 micrograms	800 micrograms	#	#	#	#	#
Evening	200 micrograms	800 micrograms	#	#	#	#	#	Evening	200 micrograms	800 micrograms	#	#	#	#	#
			1	1	1	1	1				1	1	1	1	1

Page 37

Page 38

Notes	
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Page 39

Page 40

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Page 1

Uptravi 100-microgram film-coated tablets
selexipag

Titration Guide

Starting Treatment with Uptravi

Please read the accompanying patient information leaflet before starting treatment. Tell your doctor if you experience side effects, as your doctor may recommend that you change your Uptravi dose.

Page 2

Contents

How should you take Uptravi?	4
How should you step up your dose?	6
What are the steps?	8
When should you step down?	10
Stepping down	12

Page 3

When you move to your maintenance dose.....	14
If you forget to take Uptravi.....	16
If you stop taking Uptravi.....	17
Titration diary.....	18

Page 4

How should you take Uptravi?

Uptravi is a medicine taken every morning and evening for the treatment of pulmonary arterial hypertension, also called PAH.

The starting dose for Uptravi is 100 micrograms **once in the morning and once in the evening.**

The first intake of Uptravi should be in the evening.

You should take each dose with a glass of water, preferably during a meal.

Page 5

There are 2 phases of treatment with Uptravi:

Titration

In the first several weeks, you will work with your doctor to find the dose of Uptravi that is right for you. Your doctor may have you step up from the starting dose to higher doses of Uptravi. Your doctor may step you down to a lower dose. This process is called titration. It lets your body gradually adjust to the medicine.

Maintenance

Once your doctor has found the dose that is right for you, this will be the dose you take on a regular basis. This is called the maintenance dose.

How should you step up your dose?

You will start at the 100 microgram dose in the morning and in the evening and after discussing with your doctor or nurse step up to the next dose.

The first intake of the increased dose should be in the evening. Each step usually lasts about 1 week. It could take several weeks to find the dose that is right for you.

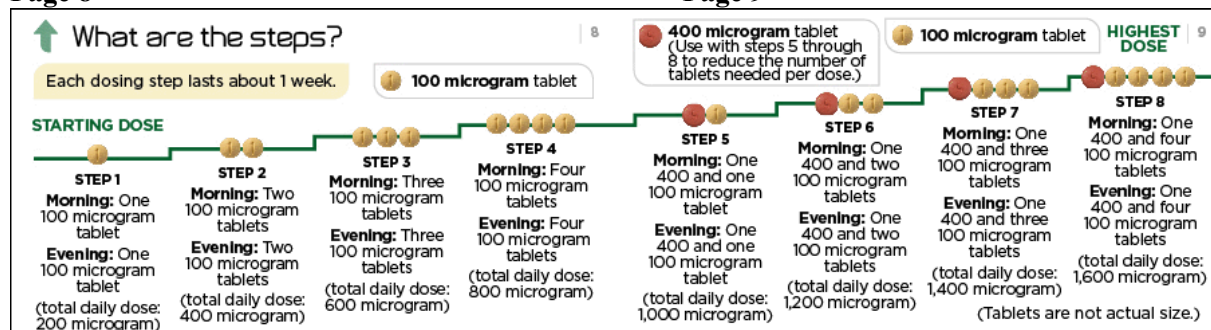
The goal is to reach the dose that is most appropriate to treat you.

This dose will be your maintenance dose.

Every patient with PAH is different. **Not everyone will end up on the same maintenance dose.**

Some patients may have 100 micrograms in the morning and in the evening as their maintenance dose, while some will reach the highest dose of 800 micrograms in the morning and in the evening.

Others may reach a maintenance dose somewhere in between. What is important is that you reach the dose that is most appropriate to treat you.



↓ When should you step down?

As with all medicines, you may experience side effects with Uptravi as you step up to higher doses.

Talk to your doctor or nurse if you have side effects. There are treatments available that can help relieve them.

The most common side effects (may affect more than 1 in 10 people) you may experience while taking Uptravi are:

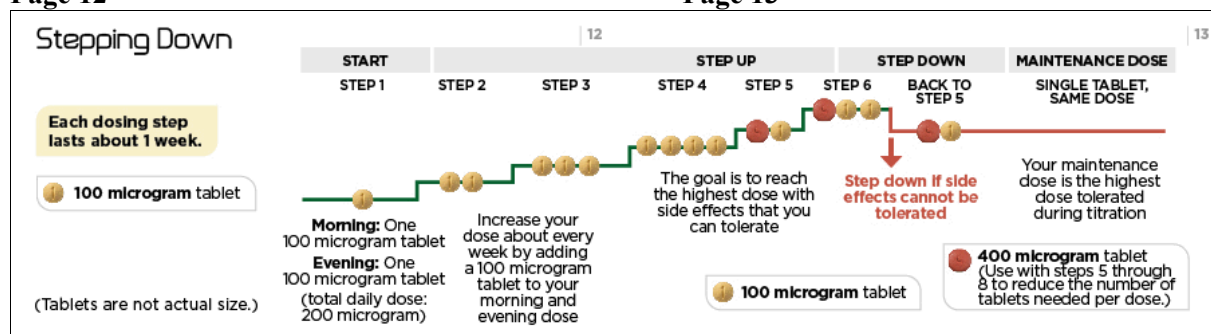
- Headache • Diarrhoea • Nausea • Vomiting
- Jaw pain • Muscle pain • Leg pain • Joint pain
- Facial redness

For a full list of side effects see package leaflet for further information.

If you cannot tolerate the side effects even after your doctor or nurse has tried to treat them, he or she may recommend you step down to a lower dose.

If your doctor or nurse tells you to step down to a lower dose, you should take one less 100 microgram tablet in the morning and one less in the evening.

You should only step down after speaking with your PAH doctor or nurse. This stepping-down process will help you find the dose that is right for you, also called your maintenance dose.

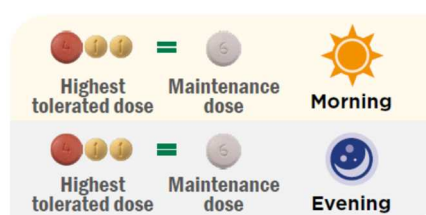


When you move to your maintenance dose

The highest dose that you can tolerate during titration will become your **maintenance dose**. Your maintenance dose is the dose you should continue to take on a regular basis. Your doctor or nurse can prescribe equivalent **single or multiple-tablet strengths** for your maintenance dose.

This may allow you to take one tablet in the morning and one in the evening.

For example, if your highest tolerated dose during titration was 600 micrograms once in the morning and once in the evening:



Over time, your doctor or nurse may adjust your maintenance dose as needed.

If you forget to take Upravi

If you miss a dose, take the dose as soon as you remember, then continue to take your tablets at the usual times. If it is within 6 hours of when you would normally take your next dose, you should skip the missed dose and continue to take your medicine at the usual time.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Upravi

Do not stop taking Upravi unless your doctor or nurse tells you to. If, for any reason, you stop taking Upravi for more than 3 consecutive days (if you missed 6 doses in a row), **contact your PAH doctor or nurse immediately as your dose may need to be adjusted to avoid side effects.**

Your doctor or nurse may have you resume treatment at a lower dose, gradually increasing to your previous maintenance dose.

Titration diary

Please read the instructions in the package leaflet carefully.

The following diary pages help you keep track of the number of tablets you need to take in the morning and evening during titration.

Use them to write down the number of tablets you take in the morning and the evening.

Each step usually lasts about 1 week, unless your doctor or nurse instructs you otherwise. If your titration steps last longer than 1 week there are additional diary pages to track this.



Use pages 20 to 27 to track the first weeks of treatment, when you are using 100 microgram tablets only (steps 1–4).



If you have been prescribed both 100 and 400 microgram tablets, use pages 30 to 37 (steps 5–8).

Remember to talk to your PAH doctor or nurse regularly.

Write down your doctor or nurse's instructions:

Doctor's office telephone and e-mail:

Pharmacist's telephone:

Notes:

WEEK	1	20
	<p>Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.</p> <p>Date: _____</p>	<p>Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.</p> <p>Date: _____</p>
Morning	<p>100 micrograms</p> <p>0</p>	<p>100 micrograms</p> <p></p>
Evening	<p>100 micrograms</p> <p></p>	<p>100 micrograms</p> <p></p>
The first intake of Upravi should be in the evening		The first intake of an increased dose of Upravi should be in the evening

WEEK	22
	<p>Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.</p> <p>Date: _____</p>
Morning	<p>100 micrograms</p> <p></p>
Evening	<p>100 micrograms</p> <p></p>

WEEK	23
	<p>Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.</p> <p>Date: _____</p>
Morning	<p>100 micrograms</p> <p></p>
Evening	<p>100 micrograms</p> <p></p>

Skip to page 28 if your doctor prescribes 400 microgram tablets

Page 24

WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____	24	WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____	25
Morning	100 micrograms	#	Morning	100 micrograms	#
Evening	100 micrograms	#	Evening	100 micrograms	#
Skip to page 28 if your doctor prescribes 400 microgram tablets			Skip to page 28 if your doctor prescribes 400 microgram tablets		

Page 25

Page 26



WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____	26	WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____	27
Morning	100 micrograms	#	Morning	100 micrograms	#
Evening	100 micrograms	#	Evening	100 micrograms	#
Skip to page 28 if your doctor prescribes 400 microgram tablets			Skip to page 28 if your doctor prescribes 400 microgram tablets		

Page 27

Page 28

Use the following diary pages if your doctor or nurse prescribes 400 microgram tablets in addition to your 100 microgram tablets.

On the diary pages, check off that you have taken **one** 400 microgram tablet every day in the morning and in the evening with your prescribed number of 100 microgram tablets.

-  **100 microgram** tablet
-  **400 microgram** tablet
(Use with steps 5 through 8 to reduce the number of tablets needed per dose.)

Page 29

Remember to talk to your PAH doctor or nurse regularly.

Write down your doctor or nurse's instructions:

Doctor's office telephone and e-mail:

Pharmacist's telephone:













Notes:

Page 30

WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____	30	WEEK #	Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY. Date: _____	31
Morning	100 micrograms 400 micrograms	1	Morning	100 micrograms 400 micrograms	1
Evening	100 micrograms 400 micrograms	1	Evening	100 micrograms 400 micrograms	1













Page 31

Page 32

WEEK # _____		Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							32								
Date: _____																	
 Morning	 100 micrograms	#	#	#	#	#	#	#	 Morning	 100 micrograms	#	#	#	#	#	#	#
	 400 micrograms	1	1	1	1	1	1	1		 400 micrograms	1	1	1	1	1	1	1
 Evening	 100 micrograms	#	#	#	#	#	#	#	 Evening	 100 micrograms	#	#	#	#	#	#	#
	 400 micrograms	1	1	1	1	1	1	1		 400 micrograms	1	1	1	1	1	1	1













Page 33

Page 34

WEEK # _____		Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							34								
Date: _____																	
 Morning	 100 micrograms	#	#	#	#	#	#	#	 Morning	 100 micrograms	#	#	#	#	#	#	#
	 400 micrograms	1	1	1	1	1	1	1		 400 micrograms	1	1	1	1	1	1	1
 Evening	 100 micrograms	#	#	#	#	#	#	#	 Evening	 100 micrograms	#	#	#	#	#	#	#
	 400 micrograms	1	1	1	1	1	1	1		 400 micrograms	1	1	1	1	1	1	1

Page 35

Page 36

WEEK # _____		Write down the number of the week of the treatment in the upper left hand corner. Every day write down in the boxes below how many tablets you take in the morning and evening. I spoke with my doctor or nurse on DD/MM/YY.							36								
Date: _____																	
 Morning	 100 micrograms	#	#	#	#	#	#	#	 Morning	 100 micrograms	#	#	#	#	#	#	#
	 400 micrograms	1	1	1	1	1	1	1		 400 micrograms	1	1	1	1	1	1	1
 Evening	 100 micrograms	#	#	#	#	#	#	#	 Evening	 100 micrograms	#	#	#	#	#	#	#
	 400 micrograms	1	1	1	1	1	1	1		 400 micrograms	1	1	1	1	1	1	1

Page 37

Page 38

Notes			
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Page 39

Page 40

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ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for selexipag, the scientific conclusions of PRAC are as follows:

In view of available data on angioedema from clinical trial(s), spontaneous and solicited reports including in some cases a close temporal relationship, with positive de-challenge and/or re-challenge and absence of clear alternative aetiology, a potential plausible mechanism, the PRAC Rapporteur considers a causal relationship between selexipag and angioedema is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing selexipag should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for selexipag the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing selexipag is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.