PRESCRIBING INFORMATION

Abbreviated summary of product characteristics

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

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 idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. **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 uptitrated 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), usually at weekly intervals. *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, Uptravi should be restarted at a lower dose and then uptitrated. If the decision to withdraw Uptravi 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), reduce the dosing of Uptravi to once daily. 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. Revert to twice daily dosing frequency of Uptravi when co-administration of moderate CYP2C8 inhibitor is stopped. Special populations*: Elderly (≥ 65 years):* No adjustment to the dose regimen is needed in elderly people. *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. *Hepatic impairment:* Selexipag should not be administered in patients with severe liver impairment (ChildPugh class C). For patients with moderate hepatic impairment (ChildPugh class B), the starting dose of treatment should be 200 micrograms once daily and increased at weekly intervals by increments of 200 micrograms given once daily until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced. No adjustment to the dose regimen is needed in patients with mild hepatic impairment (ChildPugh 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 m^2); dose titration should be done with caution in these patients. **Contraindications***:* Selexipag is contraindicated in individuals with hypersensitivity to the drug or its components, severe coronary heart disease, unstable angina, recent myocardial infarction (within 6 months), decompensated cardiac failure (without close medical supervision), severe arrhythmias, recent cerebrovascular events (within 3 months), congenital/acquired valvular defects with relevant myocardial function issues unrelated to pulmonary hypertension, and when used with potent CYP2C8 inhibitors (e.g., gemfibrozil). **Special warnings and precautions for use:** Hypotension: Selexipag has vasodilatory properties that may result in lowering blood pressure. Before prescribing Uptravi, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects. Hyperthyroidism: Hyperthyroidism has been observed with Uptravi. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism. Pulmonary venoocclusive disease: If signs of pulmonary oedema occur when Uptravi is administered in patients with PAH, the possibility of pulmonary venoocclusive 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, Uptravi should be used with caution in this population. Hepatic impairment: There is no clinical experience with selexipag in patients with severe liver impairment (ChildPugh 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 (ChildPugh class B). In patients with moderate hepatic impairment, Uptravi should be dosed once daily. Renal impairment: In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), caution should be exercised during dose titration. Uptravi should not be used in patients undergoing dialysis. Women of childbearing potential: Women of childbearing potential should practise effective contraception while taking selexipag. **Interaction with other medicinal products and other forms of interaction**: Effect of other medicinal products on selexipag: Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a weak substrate of the Pgp 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*: Concomitant administration of Uptravi with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated. *Inducers of CYP2C8:* Dose adjustment of selexipag may be required with concomitant administration of inducers of CYP2C8 (e.g., rifampicin, carbamazepine, phenytoin). *Inhibitors of UGT1A3 and UGT2B7*: Caution is required when administering these medicinal products (valproic acid, probenecid, and fluconazole) concomitantly with Uptravi. because the potential pharmacokinetic interaction with strong inhibitors of UGT1A3 and UGT2B7 cannot be excluded. *Inhibitors and inducers of CYP3A4 and Transporter inhibitors* (lopinavir/ritonavir): It is anticipated that inducers of CYP3A4 will have no impact on the active metabolite's pharmacokinetics. *PAHspecific therapies:* The use of selexipag in combination with both an ERA and a PDE5 inhibitor resulted in a 30% lower exposure to the active metabolite. 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*: No increased risk of bleeding was detected with selexipag compared to placebo, including when selexipag was administered with anticoagulants (heparin, coumarin-type anticoagulants) or inhibitors of platelet aggregation. Selexipag did not influence the pharmacodynamic effect of warfarin on the international normalised ratio. *Midazolam:* No clinically relevant change in exposure to midazolam was observed and no dose adjustment was required. *Hormonal contraceptives:* Nos studies have been conducted. However, reduced efficacy of hormonal contraceptives is not expected. **Fertility, pregnancy and lactation**: Pregnancy: There are no data on the use of selexipag in pregnant women. Uptravi is not recommended during pregnancy and in women of childbearing potential not using contraception. Breastfeeding: A risk to the suckling child cannot be excluded. Uptravi should not be used during breastfeeding. Fertility: There are no clinical data available. **Effects on ability to drive and use machines**: Uptravi has a minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of Selexipag should be kept in mind when considering the patient's ability to drive and use machines. **Undesirable effects**: Very common: headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremities, Nasopharyngitis (of non-infectious origin), arthralgia, and flushing. These reactions are more frequent during the up-titration phase. Common: Anemia, decreased hemoglobin levels, hyperthyroidism, reduced thyroid-stimulating hormone, loss of appetite, weight loss, hypotension, nasal congestion, abdominal pain, rash, urticaria, erythema, and pain. The majority of these reactions are of mild to moderate intensity

Detailed information on this medicinal product is available on the full Summary of Product Characteristics.

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Marketing Authorisation Holder and Manufacturer

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For further information please refer to the locally approved PIL.