ADD | Uptravi selexipag

UPTRAVI Initiation and Titration Guide

A guide for Healthcare Professionals

Prescribing information can be found at the back of this booklet.

Overview

Indication

- 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 monotherapy in patients who are not candidates for these therapies.[1]

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.[1]

Treatment with UPTRAVI should only be initiated and monitored by a healthcare provider experienced in the treatment of PAH. Use this guide to help your patients take UPTRAVI correctly.

Updated recommended funding information

ENGLAND[2] (from 1st April 2019)

Combination therapy in patients with PAH, WHO FC III on a PDE5i plus an ERA, after failure to respond, or a sub-optimal response, to a PDE5i plus an ERA.

SCOTLAND[3*]

Combination therapy in sub-population of patients with PAH, specifically those in WHO FC III who are insufficiently controlled with an ERA and a PDE5i and who would otherwise be considered for treatment with inhaled iloprost.

WALES[4]

Triple combination therapy in patients with PAH, with WHO FC III who are insufficiently controlled with an ERA and a PDE5i.

*The Northern Ireland Health and Social Care Board has adopted the policy applied by the Scottish Medicines Consortium.[16]

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Low risk status is the goal of PAH treatment

- ESC/ERS PH guidelines advocate regular, multi-parameter, risk assessment of patients with the overall treatment goal of achieving a low risk status[5*]
- Achieving low-risk status and/or an increased number of low-risk criteria increases the likelihood that patients will have a better prognosis[6-8]

Risk assessment in PAH[5]

Determinants of prognosis		Risk level		
		Low <5%	Intermediate 5–10%	High >10%
Clinical signs of right heart failure		Absent	Absent	Present
Progression of symptoms		No	Slow	Rapid
Syncope		No	Occasional	Repeated
WHO FC		I, II	III	IV
6MWD		>440m	165–440m	<165m
CPET	Peak VO_2 (ml/min/kg) (% predicted)	>15m (>65%)	11-15 (35%–65%)	11 (<35%)
	VE/VCO_2 slope	<36	36–44.9	≥45
NT-proBNP plasma levels	BNP (ng/L)	<50	50–300	>300
	NT-proBNP (ng/L)	<300	300–1,400	>1,400
Imaging (echocardiography, CMR imaging)	RA area (cm^2)	<18	18–26	>26
	Pericardial effusion	Absent	Absent or minimal	Present
Haemodynamics	RAP (mmHg)	<8	8–14	>14
	CI ($L/min/m^2$)	≥2.5	2.0–2.4	<2.0
	SvO_2 (%)	>65	60–65	<60

- Patients at intermediate risk have been reported to have a 5 year mortality of up to 56% in the SPAHR registry[7]

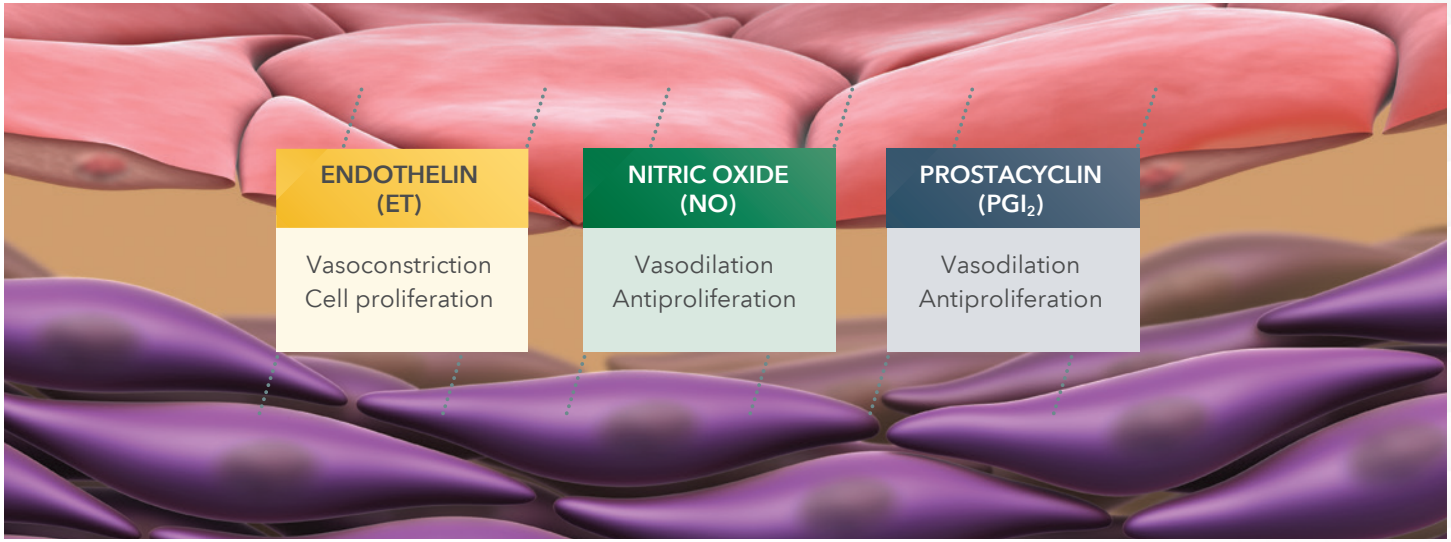
"In the case of inadequate clinical response with sequential double combination therapy, triple combination therapy should be attempted (ECS/ERS guidelines)"[5]

* Of mortality at 12 months.

Why delay targeting the prostacyclin pathway?

- Adding UPTRAVI to double combination therapy (with a phosphodiesterase-type 5 inhibitor [PDE5i] and an endothelin receptor antagonist [ERA]) provides the opportunity to target the 3 main signalling pathways in PAH using oral therapy*

Key signalling pathways in PAH pathophysiology [9,10]



How can you help your PAH patients stay ahead of disease progression?

* Under the current clinical classification, PAH consists of different aetiologies leading to precapillary pulmonary hypertension (PH), which is defined by an end-expiratory mean pulmonary artery pressure (PAP) ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and PVR >3 Wood units at rest.[10]

What is **UPTRAVI?**

UPTRAVI is the only oral therapy targeting the prostacyclin pathway in the UK:[1]

- Indicated in FC II and III
- Indicated for the long term treatment of PAH
- For monotherapy and in combination with other therapies
- Backed by Class 1 outcomes evidence in triple combination therapy with a PDE5i and ERA[5]

Proven to reduce the risk of morbidity-mortality events in combination with an ERA, a PDE5i, or both an ERA and a PDE5i[11,12*]

UPTRAVI - Helping patients with PAH stay ahead of progression[11§]

*As measured by a composite primary endpoint. The results were driven by a decrease in hospitalisation and other disease progression events (the results were not driven by mortality).

§ Progression or worsening of PAH, as defined by the occurrence of the following events: hospitalisation for worsening of PAH, initiation of chronic oxygen/parenteral prostanoids for worsening of PAH, the need for lung transplantation or atrial septostomy for worsening of PAH, other progression events, or death.

For patients at intermediate risk, consider adding UPTRAVI

SIGNS OF INTERMEDIATE RISK

RISK PROGRESSION

ERA

+/-

PDE5i

ADD Uptravi selexipag

If patients remain at intermediate risk or progress to high risk, substitution with SC or IV prostacyclin analogues should be considered[13]

> **“For patients on intermediate-risk status on double combination therapy with an ERA and a PDE5i or riociguat, the addition of selexipag should be considered[13]”**

- Galie N, et al. Eur Respir J. 2018.

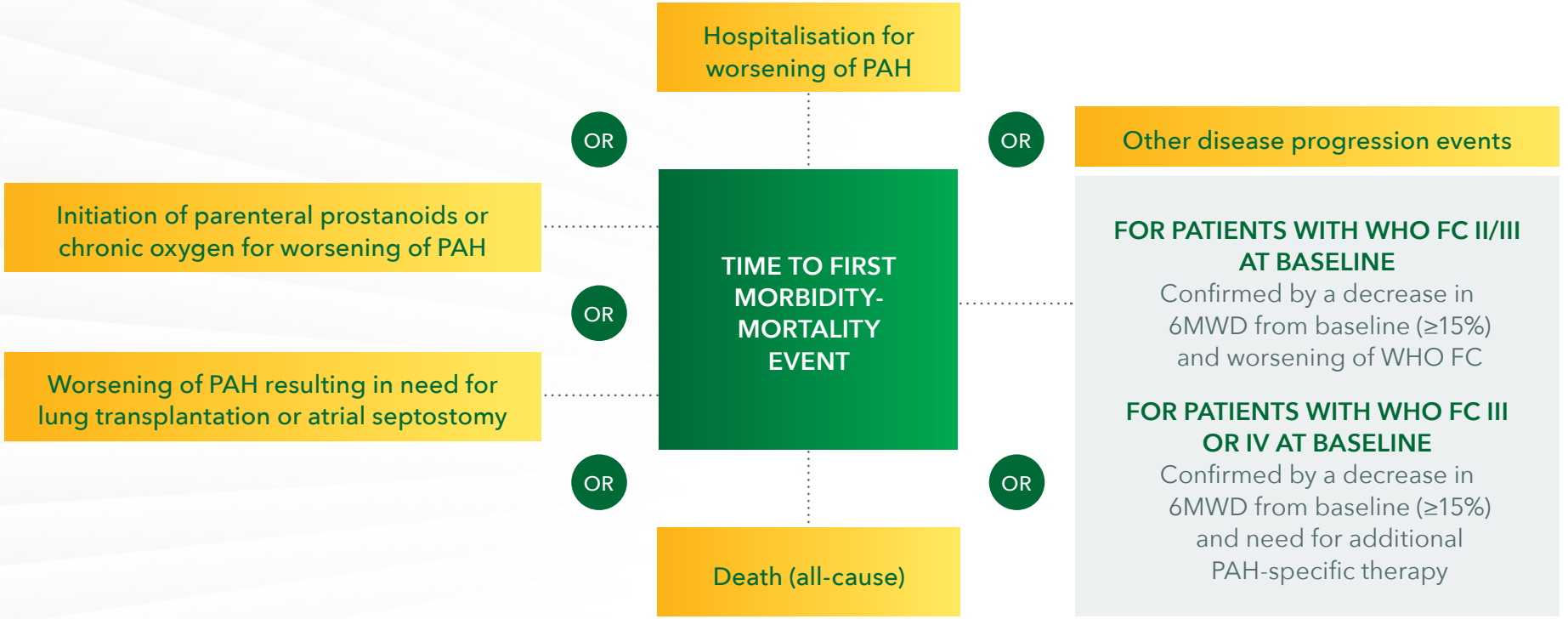
> **“Therapies targeting the prostacyclin pathway should be added for patients receiving dual combination therapy who do not achieve a low-risk status[14]”**

- Gaine S, et al. Eur Respir Rev. 2017.

UPTRAVI clinical evidence

GRIPHON - Assessing the effect of UPTRAVI on long-term outcomes[11*]

- Primary endpoint consistent with recommendations from the 4th and 5th World Symposiums on Pulmonary Hypertension

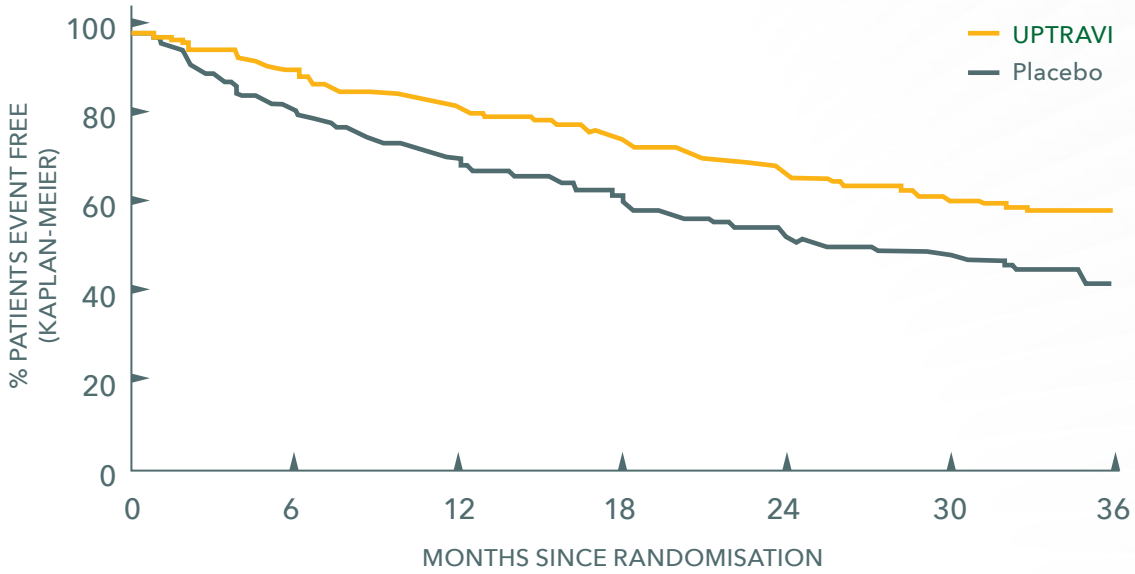


All events were adjudicated by a blinded critical events committee (CEC).[11]
6MWD = 6 minute walk distance.

* Secondary endpoints included time to PAH-related death or hospitalisation for PAH and excercise capacity as measured by placebo-corrected median increase in 6MWD.

UPTRAVI - The only oral therapy targeting the prostacyclin pathway indicated to improve long-term outcomes[11]

Time to first morbidity-mortality event in GRIPHON (overall study population)[11*]



Adapted from Sitbon O, *et al. N Engl J Med.* 2015.

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

Overall study population

40%
RISK REDUCTION
(HR 0.60, 99% CI: 0.46–0.78)
16.5% ARR[1†]

Subgroup analysis

Triple combination therapy
(PDE5i + ERA + UPTRAVI)

37%
REDUCTION OF MORBIDITY-MORTALITY (HR 0.63, 95% CI: 0.44–0.90) ARR 13%[12,15‡]

ARR = absolute risk reduction; CI = confidence interval; HR = hazard ratio
Median treatment duration for the UPTRAVI group was 70.7 weeks[11] (overall study population) and 63.1 weeks in the triple combination subgroup.[12]

*As measured by a composite primary endpoint. Results were driven by a decrease in hospitalisation and other disease progression events and not by mortality on its own.

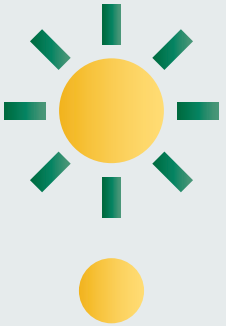
†ARR at 36 months. ‡The subgroup analysis of the primary endpoint in all patients receiving double combination therapy with an ERA and a PDE5i at baseline was pre-specified; ARR at 30 months.[11]

Getting patients started with **UPTRAVI**[1]

How to take UPTRAVI

Starting dose: 200 mcg twice daily. Patients should take their first and second doses about 12 hours apart (eg, 8:00pm and 8:00am). At the beginning of treatment and each time the patient is ready to step up, it is recommended they take the **first dose of each step in the evening.** This could help patients by making adverse reactions less noticeable.

EVENING DOSE



MORNING DOSE

Tablets must be swallowed whole with a glass of water. The tablets should never be split, crushed, or chewed.

TO HELP IMPROVE TOLERABILITY:

It is recommended to take UPTRAVI with food.

It is recommended to take the first dose of each step in the evening.

In the event of a missed dose:

If a dose of UPTRAVI is missed, patients should take the missed dose as soon as possible unless the next dose is within the next 6 hours.
If treatment is missed for 3 days or more, restart UPTRAVI at a lower dose and then retitrate.

Ensure your patients understand that they should never take 2 full doses of UPTRAVI to make up for missing a dose.

UPTRAVI has two phases of treatment[1]

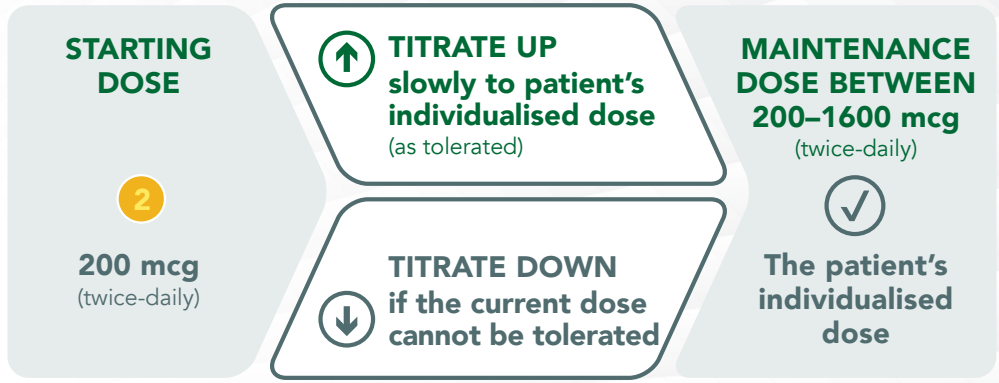
The number on the tablet relates to the dosage strength. It does not tell you how many tablets to take.

1 PHASE 1: TITRATION

The goal of titration is to reach the individually appropriate dose for each patient. Each dosing step lasts about a week. Gradually increase the dose by 200 mcg twice daily until adverse reactions that cannot be tolerated and medically managed are experienced.

2 PHASE 2: MAINTENANCE*

The patient's highest tolerated dose, or a maximum dose of 1600 mcg twice daily, becomes their individualised maintenance dose. Patients usually reach their individualised maintenance dose within 8 weeks. Once a maintenance dose is achieved, an equivalent single-tablet strength for the individualised maintenance dose can be prescribed. The maintenance dose may need to be adjusted over time.



(Tablets are not actual size)

Contact your patients regularly during the titration period to discuss their treatment experience and help them manage their adverse reactions.

* If prostacyclin-associated adverse reactions are not a factor, a second attempt to continue up-titration to the highest individually tolerated dose up to a maximum of 1600 mcg twice daily may be considered.

What your patients will receive[1]

TO START TITRATION (STAGES 1-4)

Patients will receive a Titration Pack containing:

- 140 UPTRAVI 200 mcg film-coated tablets for titration.
  This pack contains enough tablets for the first 4 titration stages.
- A Titration Guide that includes an explanation of the titration process along with diary pages where patients can fill in the number of tablets they take in the evening and morning.
- A Patient Information Leaflet

>800 mcg (2)

<800 mcg (8) + (2)

Until maintenance dose has been established, four 200 mcg tablets are taken in case patients need to step back down to a lower dose.

!

Reducing the tablet burden

TO TITRATE PAST 800 MCG (STEPS 5-8)

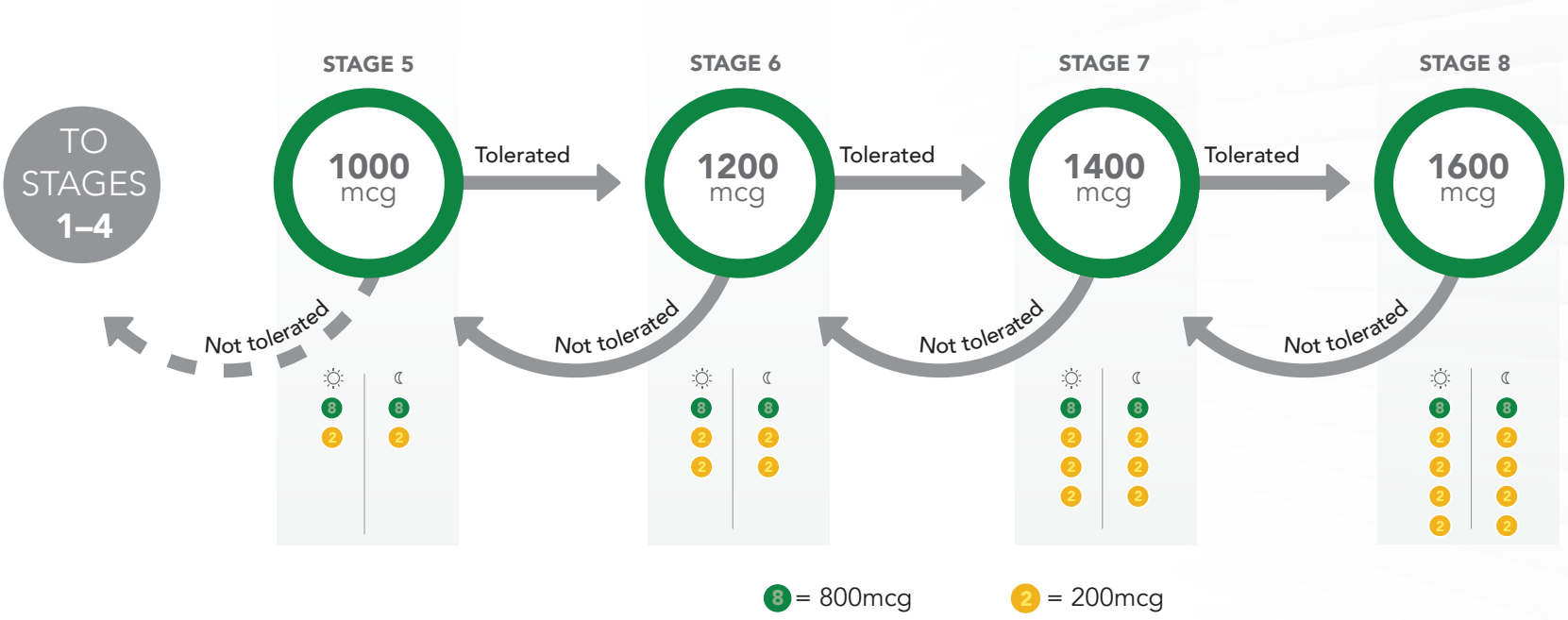
Patients will receive a second Titration Pack plus a pack of 800 mcg tablets

- If a patient requires a dose higher than 800 mcg, the addition of the 800 mcg pack reduces the amount of tablets he/she must take every dose during the titration phase

Prescribe Titration pack of 140 UPTRAVI 200 mcg tablets

\+

1 pack of 60 UPTRAVI 800 mcg tablets



In clinical practice, adverse reactions were manageable[1]

Prostacyclin-associated adverse reactions are expected and reflect the mode of action of UPTRAVI.
They may range from mild to severe, and some may subside in a few days or weeks, while others are more persistent.

During titration, it is recommended to continue treatment even in the event of expected prostacyclin-associated adverse reactions.
In clinical trials they were usually transient, mild to moderate, and manageable with symptomatic treatment.

The PH specialist team may advise patients to buy OTC anti-diarrheals and analgesics, or to ask you for a prescription for an anti-emetic.

Frequently reported adverse events associated with titration and maintenance with UPTRAVI include:

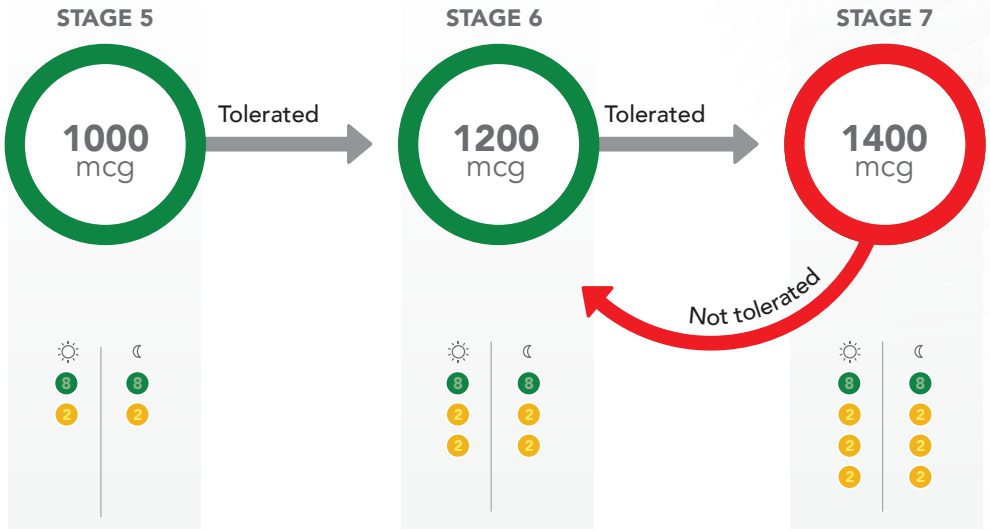
Pain	Gastrointestinal (GI) effects	Skin effects
Headache	Nausea	Flushing
Jaw pain	Vomiting	
Myalgia	Diarrhoea	
Arthralgia		
Pain in extremity		

- GI events have been observed to respond to anti-diarrhoeal, anti-emetic, and anti-nauseant medicinal products and/or medicinal products for functional GI disorders.
- Pain-associated events have frequently been treated with analgesics.
- When adverse reactions cannot be tolerated and medically managed, reduce the dose to the previous level.
  Each patient's highest tolerated dose, or a maximum dose of 1600 mcg twice daily, becomes their individualised maintenance dose.

Side effects are more frequent during the titration phase. Most side effects are transient and may improve or stop once the patient has reached their individual maintenance dose. Healthcare professionals may want to ensure that patients have access to symptomatic treatments to help manage any adverse events they may experience.

Titration: Stepping back[1]

Patients should expect to experience adverse reactions during titration. If a patient reaches a dose that cannot be tolerated and medically managed due to adverse reactions, reduce the dose by one 200 mcg tablet once in the morning and once in the evening to the previous dose level.



>800 mcg (2)

<800 mcg (8) + (2)

Until maintenance dose has been established, four 200 mcg tablets are taken in case patients need to step back down to a lower dose.

Transitioning to the maintenance phase[1]

Each patient's highest tolerated dose, or maximum dose of 1600 mcg twice daily, becomes his/her individualised maintenance dose. Patients should take this dose twice daily.

Example of titration to the maintenance dose:

1 tablet twice daily, once maintenance is achieved

Once a maintenance dose is achieved, an equivalent single-tablet strength for the individualised maintenance dose can be prescribed.

The goal of titration is not to reach the 1600 mcg dose, but rather to reach the maximum tolerable dose for each patient.

Maintenance doses

TO TRANSITION TO MAINTENANCE

Once patients reach their maintenance dose, they will receive a pack of 60 tablets at that dose.

The colour of the tablet may not match the colour of the box.

The following are the available maintenance doses:

200 mcg

400 mcg

600 mcg

800 mcg

1000 mcg

1200 mcg

1400 mcg

1600 mcg

UPTRAVI - Use in special populations[1]

PREGNANCY AND FEEDING

- There are no data on the use of UPTRAVI in pregnant women. UPTRAVI is not recommended during pregnancy or for women of child-bearing potential not using contraception

USE IN CHILDREN

- The safety and efficacy of UPTRAVI in children has not been established. No data are available

HYPOTENSION

- UPTRAVI has vasodilatory properties that may result in lowering of blood pressure. Before prescribing UPTRAVI, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects

HEPATIC IMPAIRMENT

- UPTRAVI should not be administered in patients with severe liver impairment (Child-Pugh class C)
- In patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of UPTRAVI should be 200 mcg once daily, increased at weekly intervals up to the patient's individualised maintenance dose

RENAL IMPAIRMENT

- No adjustment to the dosing regimen is needed in patients with mild or moderate renal impairment
- No change to the starting dose is required in patients with severe renal impairment, but dose titration should be done with caution in these patients
- UPTRAVI should not be used in patients undergoing dialysis

FERTILITY

- There are no clinical data available. In animal studies, UPTRAVI at high doses caused transient disturbances in oestrus cycles, which did not affect fertility. The relevance for humans is not known

UPTRAVI has the following contraindications: severe coronary heart disease or unstable angina; myocardial infarction within the last 6 months; decompensated cardiac failure if not under close medical supervision; severe arrhythmias; cerebrovascular events (eg, transient 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 with strong inhibitors of CYP2C8 (eg, gemfibrozil).

UPTRAVI - DDIs with drugs concomitantly used in PAH[1]

ERA and PDE5i	• In a phase 3 placebo-controlled study, the use of UPTRAVI in combination with both an ERA and a PDE5i resulted in a 30% lower exposure to the active metabolite[1] but the efficacy in patients receiving the triple combination was similar to that seen in the overall study population[12]
Warfarin	• No effect on exposure to UPTRAVI nor warfarin (phase 1 study)*
Transporters and CYP3A4 inhibitors	• No clinically relevant increase of exposure to UPTRAVI (phase 1 study with lopinavir/ritonavir)†
CYP3A4 substrates	• Concomitant administration of UPTRAVI with CYP3A4 substrates does not require dose adjustment‡
Hormonal contraceptives	• No DDIs expected based on metabolic pathways§

DDI = drug-drug interaction

* In a study in healthy subjects, UPTRAVI (400 mcg 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. UPTRAVI did not influence the pharmacodynamic effect of warfarin on the international normalised ratio.

† In the presence of 400/100 mg lopinavir/ritonavir twice daily, a strong inhibitor of CYP3A4, OATP (OATP1B1 and OATP1B3), and P-gp, exposure to UPTRAVI increased approximately 2-fold, whereas exposure to the active metabolite of UPTRAVI did not change. Given that the majority of the pharmacological effect is driven by the active metabolite, this effect is not clinically relevant.

‡ In a DDI study, at steady state after up-titration of UPTRAVI to 1600 mcg twice daily, no clinically relevant change in exposure to midazolam (a sensitive CYP3A4 substrate) or its metabolite was observed.

§ Specific DDI studies with hormonal contraceptives have not been conducted. Since UPTRAVI 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.

UPTRAVI is contraindicated for concomitant use with strong inhibitors of CYP2C8 (eg, gemfibrozil). When co-administered with moderate CYP2C8 inhibitors, reduce the dosing of UPTRAVI to once daily. Revert to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped. For complete information about potential drug-drug interactions, please consult the Summary of Product Characteristics.

Patient resources

The following materials were designed to help your patients feel confident about their treatment.

UPTRAVI Patient Brochure provides:

- Information about PAH
- Information about treatment with UPTRAVI
- Explanation of dosing and titration

UPTRAVI Patient Dosage Guide provides:

- An explanation that individual patients will require different doses of UPTRAVI, and that a greater dose is not necessarily more effective
- Supporting information on how IP receptor density influences the dose of UPTRAVI that is required

For patients interested in learning more about PAH, ways to manage their condition, and available treatment options, suggest visiting the website:

www.phauk.org

Helpful tips

- **Help patients understand their treatment plan with UPTRAVI.**
  Consider whether some of the UPTRAVI materials can further support your efforts to educate your patients

- **Talk to patients and set expectations about the goal of titration.**
  Explain that they will reach the highest possible dose that they can tolerate, and that you will recommend or prescribe medications that may help minimise the impact of adverse reactions

- **Explain the titration schedule.**
  Provide an overview of how quickly you expect they will step forward their doses. For instance, in the GRIPHON study, each stage lasted about one week

- During every interaction, it's important to ask about adverse reactions, prescription adherence, mental and emotional state, and lifestyle modifications

For complete information about the safety, tolerability, and potential drug-drug interactions of UPTRAVI, please consult the Summary of Product Characteristics.

UPTRAVI® ▼ **200-1600 µg film-coated tablets**
PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): selexipag
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.
INDICATION(s): Long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO FC II-III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase type 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.
DOSAGE & ADMINISTRATION: Individualised dose titration: Only a PAH experienced physician should initiate and monitor treatment. Up-titrate patients to the highest individually tolerated dose, which can range from 200 to 1600 microgram (µg) given twice daily (BD).
The recommended starting dose is 200 µg BD approximately 12 hours apart. Increase dose in increments of 200 µg BD, usually at weekly intervals, based on tolerability. During titration some adverse reactions reflecting the mode of action of Uptravi may occur, these are usually transient or manageable with symptomatic treatment. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level. **Individualised maintenance dose**: Maintain the highest tolerated dose a patient can take with tolerable adverse events. If it is necessary to stop treatment withdraw gradually. **Administration:** Take each tablet orally, morning and evening with food to improve tolerability. During the uptitration phase take the first increased dose in the evening.
Interruptions and discontinuations: Missed doses should be taken as soon as possible, unless the next dose is scheduled within 6 hrs. If treatment is missed for 3 days or more, restart at a lower dose and then uptitrate. There is limited experience with abrupt discontinuation. No evidence for acute rebound has been observed. **Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors**: When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of Uptravi to once daily. 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.
Elderly (≥65 yrs): No dose adjustment required. There is limited clinical experience in patients over 75 yrs, therefore Uptravi should be used with caution in this population.
Paediatric population (< 18 years): No data are available. Not recommended to use selexipag in paediatric population.
Hepatic impairment: Do not treat patients with severe liver impairment (Child-Pugh class C). Moderate hepatic impairment (ChildPugh class B): the starting dose of Uptravi 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. Mild hepatic impairment (ChildPugh class A): No dose adjustment required.
Renal impairment: Mild/moderate: No dose adjustment required. Severe: Caution should be exercised during dose titration.
CONTRAINDICATIONS: Hypersensitivity to active substance/excipients, severe coronary heart disease, unstable angina, myocardial infarction within 6 months, decompensated cardiac failure, severe arrhythmias, cerebrovascular events within 3 months, congenital or acquired valvular defects, concomitant use with strong CYP2C8 inhibitors (e.g. gemfibrozil).
SPECIAL WARNINGS & PRECAUTIONS: Hypotension: Vasodilatory properties may reduce blood pressure. Before prescribing Uptravi, carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects. Hyperthyroidism: has been observed, monitor thyroid function if clinically indicated. Pulmonary venoocclusive disease: If signs of pulmonary oedema occur consider possibility of pulmonary veno-occlusive disease which has been reported with vasodilators (mainly prostacyclins), if confirmed discontinue treatment.
SIDE EFFECTS: Very common: Headache, flushing, nasopharyngitis, diarrhoea, vomiting, nausea, jaw pain, myalgia, arthralgia & pain in extremity. **Common:** Anaemia, decreased haemoglobin, hyperthyroidism, decreased thyroid-stimulating hormone, decreased appetite, weight decrease, hypotension, nasal congestion, abdominal pain, rash, urticaria, erythema, pain.
Refer to SmPC for other side effects.
PREGNANCY: There are no data from the use of selexipag in pregnant women. Women of childbearing potential should practise effective contraception. Uptravi is not recommended during pregnancy and in women of childbearing potential not using contraception.
LACTATION: It is unknown if selexipag or its metabolites are excreted in human milk. Uptravi should not be used during breast-feeding.
INTERACTIONS: Consider adjustment of selexipag dose in case of co-administration with CYP2C8 inducers (rifampicin, carbamazepine, phenytoin). Use caution with concomitant use of Uptravi with strong inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, fluconazole).
Dosing frequency of Uptravi should be reduced to once daily when co-administered with moderate CYP2C8 inhibitors (e.g. clopidogrel, deferasirox, teriflunomide) . Dosing frequency of Uptravi should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped.
Refer to SmPC for full details of interactions.
Ability to drive and use machines: Uptravi has a minor influence on the ability to drive and use machines.
LEGAL CATEGORY: POM
PRESENTATIONS, PACK SIZES, MARKETING AUTHORISATION NUMBER(S) & BASIC NHS COSTS

PRESENTATIONS	PACK SIZES	MARKETING AUTHORISATION NUMBER(S)	BASIC NHS COSTS
200 µg tablets (Titration pack)	140 tablets	EU/1/15/1083/003	£ 7000
200 µg tablets	60 tablets	EU/1/15/1083/002	£ 3000
400 µg tablets	60 tablets	EU/1/15/1083/004	£ 3000
600 µg tablets	60 tablets	EU/1/15/1083/005	£ 3000
800 µg tablets	60 tablets	EU/1/15/1083/006	£ 3000
1000 µg tablets	60 tablets	EU/1/15/1083/007	£ 3000
1200 µg tablets	60 tablets	EU/1/15/1083/008	£ 3000
1400 µg tablets	60 tablets	EU/1/15/1083/009	£ 3000
1600 µg tablets	60 tablets	EU/1/15/1083/010	£ 3000

MARKETING AUTHORISATION HOLDER: Janssen-Cilag International NV, Turnhoutseweg 30, B 2340 Beerse, Belgium.
FURTHER INFORMATION IS AVAILABLE FROM: Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK.
Prescribing information last revised: April 2020

Adverse events should be reported. ▼ **This medicinal product is subject to additional monitoring and it is therefore important to report any suspected adverse events related to this medicinal product. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.**

Adverse events should also be reported to Janssen-Cilag Limited on 01494 567447 or at dsafety@its.jnj.com.

References: 1. Uptravi Summary of Product Characteristics. **2.** Clinical Commissioning Policy: Selexipag for treating pulmonary arterial hypertension (adults). Reference: NHS England Reference 170104P December 2018. Available at: https://www.england.nhs.uk/commissioning/publication/selexipag-for-treating-pulmonary-arterial-hypertension-adults/. Accessed April 2020. **3.** Scottish Medicines Consortium. Selexipag 200-1600 microgram filmcoated tablets (UPTRAVI). SMC no. 1235/17. May 2018. Available at: https://www.scottishmedicines.org.uk/media/3416/selexipag-uptravi-resubmission-final-april-2018-amended-270418-for-website.pdf. Accessed April 2020. **4.** All Wales Medicines Strategy Group. Selexipag 200-1600 microgram film-coated tablets (UPTRAVI). Advice no. 0918. June 2018. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/700. Accessed April 2020. **5.** Galie N, *et al.* The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Heart J.* 2016. 2016; 37: 67-119. **6.** Boucly A, *et al.* Risk Assessment, prognosis and guideline implementation in pulmonary arterial hypertension *Eur Respir J.* 2017;50:2. **7.** Kylhammar D, Kjellstrom B, Hjalmarsson C, *et al;* on behalf of SveFPH and SPAHR. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension [published June 1, 2017]. *Eur Heart J.* doi:10.1093/eurheartj/ehx257. **8.** Hoeper MM, *et al.* Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J.* 2017;50(2):1700740. doi:10.1183/13993003.00740-2017. **9.** Lau EMT, Giannoulatoue E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertensions. *Nat Rev Cardiol.* 2017;14:603-614. **10.** Humbert M, Lau EM, Montani D, Jais X, Sitbon O, Simmoneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation.* 2014;130(24):2189-2208. **11.** Sitbon O, Channick R, Chin KM, *et al.* GRIPHON Investigators. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med.* 2015;373(26):2522-2533. **12.** Coghlan JG. Targeting the Prostacyclin Pathway with Selexipag in Patients with Pulmonary Arterial Hypertension Receiving Double Combination Therapy: Insights from the Randomized Controlled GRIPHON Study. *Am J Cardiovasc Drugs.* 2018; 18: 37-47. **13.** Galie N, *et al.* Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J.* 2019;53(1). **14.** Gaine S and McLaughlin V. Pulmonary arterial hypertension: tailoring treatment to risk in the current era. *Eur Respir Rev.* 2017;26:170095. **15.** Actelion Pharmaceuticals Ltd. Data on File, SEL 18/0150, May 2018. **16.** Northern Ireland Health and Social Care Board. Available at: http://www.hscboard.hscni.net/. Accessed April 2020.

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