Uptravi selexipag tablets 200-1600 mcg

Helping Your Patients Titrate on UPTRAVI® and Receive Support

Use this guide to better understand how you can help prepare your patients for their UPTRAVI® (selexipag) prescriptions.

- **Familiarize** yourself with the titration process
- **Consider** the adverse events they may experience so you are ready to help
- **Know** what options are available for support to educate your patients about their disease and their medication

INDICATION

UPTRAVI® (selexipag) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness of UPTRAVI® Tablets was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Concomitant use of strong inhibitors of CYP2C8 (eg, gemfibrozil) with UPTRAVI® is contraindicated.

Hypersensitivity to the active substance or to any of the excipients is contraindicated.

Please see additional Important Safety Information throughout and on pages 10 and 11, and full Prescribing Information for UPTRAVI®.

Understanding Dose Adjustment With UPTRAVI® (selexipag)[1]

Uptravi selexipag tablets | 200-1600 mcg

Your patient's recommended starting dose is **200 mcg twice daily**. UPTRAVI® dosing is **unique to each patient** based on how their body **responds and adjusts to treatment.** The dose adjustment phase is how you find **your patient's personal maintenance dose.**

STARTING DOSE

200 mcg
(twice daily*)

TITRATE UP

usually at weekly intervals to reach your patient's personal maintenance dose (as tolerated)

TITRATE DOWN

if the current dose cannot be tolerated

Tablet not shown at actual size.

MAINTENANCE DOSE

Your patient's personal maintenance dose
(twice daily*)

Titrations usually occur weekly. However, slower titration may be considered to help manage some common side effects.[1,2]

Once your patient has started taking UPTRAVI® at their recommended starting dose, their dose will be **increased by 200 mcg twice daily** to the highest tolerated dose up to **1600 mcg twice daily.** When your patient is no longer able to tolerate their dose, the treating healthcare provider (HCP) will **reduce to the previous tolerated dose.** Tolerability may be improved when taken with food.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Pulmonary Edema with Pulmonary Veno-Occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI®.

ADVERSE REACTIONS

Adverse reactions more frequent compared to placebo (≥3%) seen with UPTRAVI® Tablets are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI® Tablets and in none of the patients on placebo.

Please see additional Important Safety Information throughout and on pages 10 and 11, and full Prescribing Information for UPTRAVI®.

*Once daily for patients with moderate hepatic impairment and co-administration with moderate CYP2C8 inhibitors (eg, clopidogrel, deferasirox, and teriflunomide). Increase in increments of 200 mcg once daily at weekly intervals.

What Does Dose Adjustment Look Like?[1]

Uptravi selexipag tablets | 200-1600 mcg

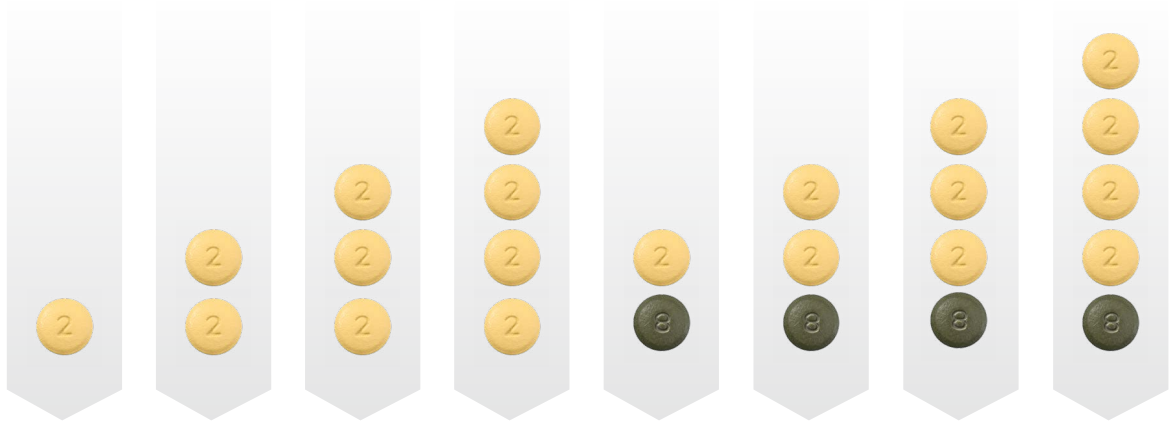
Simple steps to meet your patient's individual needs

1 The Dose Adjustment Phase

Patients will receive a starting supply of **200-mcg and 800-mcg tablets.** With each dose adjustment during this phase, the treating HCP can simply **add or remove a single 200-mcg tablet** to increase or decrease your patient's dose as needed. **See the adjacent table for the different tablet combinations at each dose.**

2 The Maintenance Phase

Once the patient's personal maintenance dose is achieved, a single-tablet equivalent will be dispensed BID. There are **8 different single-tablet strengths of UPTRAVI®**, each a unique color.



UPTRAVI® is available in the following

(Tablets are not actual size.)

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

CYP2C8 Inhibitors

Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant use of UPTRAVI® with strong inhibitors of CYP2C8 is contraindicated.

Concomitant administration of UPTRAVI® with clopidogrel, a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.7-fold. Reduce the dosing of UPTRAVI® to once daily in patients on a moderate CYP2C8 inhibitor.

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BID=twice daily.

Dose Adjustment Was Established in GRIPHON[1,3,4]

The largest outcomes trial conducted in PAH (N=1156)

The safety and efficacy of UPTRAVI® (selexipag) were demonstrated in a multicenter, double-blind, placebo-controlled, parallel-group, event-driven study in patients with symptomatic PAH (>98% WHO FC II or III). The primary endpoint was the time to first disease progression event.*

Treatment with UPTRAVI® resulted in a **40% risk reduction**† (99% CI: 22% to 54%; *P*<0.0001; HR 0.60) in disease progression compared with placebo (27% [155/574] vs 41.6% [242/582], respectively).

Adverse reactions occurring more frequently (≥5%) on UPTRAVI® compared with placebo are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing.

See the **full GRIPHON study design**

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS (continued)

CYP2C8 Inducers
Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase UPTRAVI® dose, up to twice, when co-administered with rifampin. Reduce UPTRAVI® when rifampin is stopped.

DOSAGE AND ADMINISTRATION

Recommended Dosage
Recommended starting dose is 200 mcg twice daily for UPTRAVI® Tablets. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

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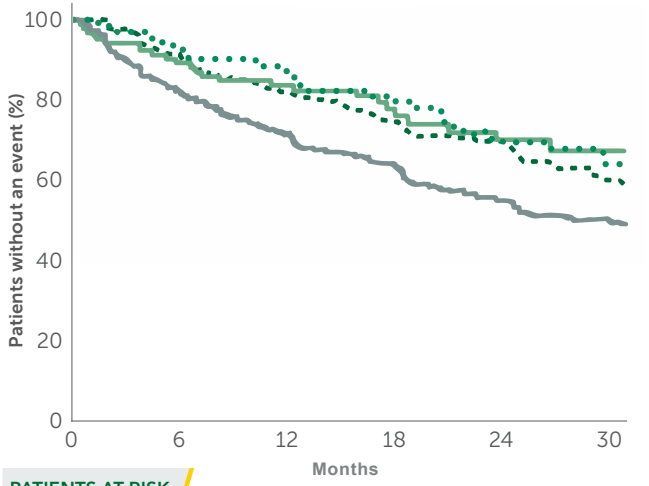
*The primary endpoint was the time to first PAH disease progression event: a) death, b) hospitalization for PAH, c) need for lung transplantation or balloon atrial septostomy for worsening of PAH, d) parenteral prostanoid or chronic oxygen therapy, or e) other disease progression (decrease in 6MWD plus worsening of FC or need of other therapy).
†Hazard ratio based on primary endpoint events up to the end of treatment.
6MWD=6-minute walk distance; CI=confidence interval; FC=Functional Class; GRIPHON=Prostacyclin (PGI_2) **R**eceptor Agonist **I**n **P**ulmonary Arterial **H**ypertensi**ON**; HR=hazard ratio; PAH=pulmonary arterial hypertension; WHO=World Health Organization.

Treatment Effect of UPTRAVI® Was Similar, Regardless of the Personal Maintenance Dose Achieved[1,4,5]

Time to first disease progression event in GRIPHON by dose group



PATIENTS AT RISK

133	84	68	41	29	19	UPTRAVI® low-dose group
180	152	116	84	52	28	UPTRAVI® medium-dose group
246	219	177	121	90	54	UPTRAVI® high-dose group
582	433	347	220	149	88	Placebo

Efficacy by dose group*:

40% RISK REDUCTION
(low dose: 200 mcg to 400 mcg)
HR 0.60 (95% CI: 0.41, 0.88)

47% RISK REDUCTION
(medium dose: 600 mcg to 1000 mcg)
HR 0.53 (95% CI: 0.38, 0.72)

36% RISK REDUCTION
(high dose: 1200 mcg to 1600 mcg)
HR 0.64 (95% CI: 0.49, 0.82)

UPTRAVI® doses were achieved across the 3 prespecified groups in the GRIPHON trial†:

- 200 mcg to 400 mcg BID (low dose): **23% of patients (n=133)**
- 600 mcg to 1000 mcg BID (medium dose): **31% of patients (n=179)**
- 1200 mcg to 1600 mcg BID (high dose): **43% of patients (n=246)**

UPTRAVI® dose adjustment support tools are available to help your patients start and stay on therapy–learn more on pages 8 and 9

IMPORTANT SAFETY INFORMATION (continued)

DOSAGE AND ADMINISTRATION (continued)

Patients With Hepatic Impairment
For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of UPTRAVI® Tablets is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI® in patients with severe hepatic impairment (Child-Pugh class C).

Co-administration With Moderate CYP2C8 Inhibitors
When co-administered with moderate CYP2C8 inhibitors (eg, clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI® to once daily.

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*Not adjusted for multiplicity.
†In the UPTRAVI® group, 14 patients discontinued the 200 mcg twice-daily dosage during the dose adjustment phase and 1 patient received doses different from the per-protocol dosing; all 15 were assigned to 0 mcg and are not reported here.

Titrate to Achieve the Right Personal Maintenance Dose for Your Patient

Uptravi selexipag tablets | 200-1600 mcg

Every patient is different. The goal is to reach the dose that's **right for each patient**, not necessarily to reach 1600 mcg BID.[1]

JANE*

Aged: 52 years

Diagnosed with PAH-CTD

Background therapy: PDE-5i + ERA

Maintenance dose of UPTRAVI®: 400 mcg BID

JUAN*

Aged: 46 years

Diagnosed with IPAH

Background therapy: PDE-5i

Maintenance dose of UPTRAVI®: 800 mcg BID

LISA*

Aged: 60 years

Diagnosed with HPAH

Background therapy: ERA

Maintenance dose of UPTRAVI®: 1400 mcg BID

TITRATING DOWN

When a patient is no longer able to tolerate their dose of UPTRAVI® during the dose adjustment phase, the treating HCP may decide to reduce the patient's dose (titrate down).[1] **Set expectations with your patient about the possible duration of common adverse reactions.**

ROADMAP TO MAINTENANCE

An **open dialogue** between you and your patients can help **set their expectations** during the dose adjustment phase and beyond. It can help them to understand, before starting treatment, that dose adjustment is necessary and temporary, and to find strategies to help manage common side effects.[1,2]

IMPORTANT SAFETY INFORMATION (continued)

DOSAGE AND ADMINISTRATION (continued)

Dosage Strengths
UPTRAVI® tablet strengths:
200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

Additional Important Safety Information for UPTRAVI® IV
Use UPTRAVI® for injection in patients who are temporarily unable to take oral therapy.

Administer UPTRAVI® for injection twice daily by intravenous infusion at a dose that corresponds to the patient's current dose of UPTRAVI® Tablets (see Table 1 in full Prescribing Information). Administer UPTRAVI® for injection as an 80-minute intravenous infusion.

Adverse Reactions: Infusion-site reactions (infusion-site erythema/redness, pain and swelling) were reported with UPTRAVI® for injection.

Please see additional Important Safety Information throughout and on pages 10 and 11, and full Prescribing Information for UPTRAVI®.

*These are hypothetical patients. No identification with actual persons is intended or should be inferred.
ERA=endothelin receptor antagonist; HPAH=heritable PAH; IPAH=idiopathic PAH; PAH-CTD=PAH associated with connective tissue disease; PDE-5i=phosphodiesterase type-5 inhibitor.

Work With Your Patients to Manage Common Side Effects of Prostacyclin Pathway Agents[2]

Adapted from Kingman et al, 2017. The information provided in the table below was not compiled by Janssen. The recommendations in the table are based on the authors' experiences with PAH and other disease states. While similarities in adverse reaction management in multiple PH centers reinforce the recommendations, there is no direct evidence to support them. Accordingly, healthcare providers can consider the following recommendations, but should rely on their clinical judgment. A clear understanding of the individual patient's needs, additional medications, and other relevant clinical factors should inform management decisions.

Pain Management	Non-pharmacologic: heating pad, massage, acupuncture, acupressure, relaxation techniques; pharmacologic: acetaminophen, ibuprofen (if not contraindicated), gabapentin, pregabalin; lowering the dose of prostacyclin or switching to a different prostacyclin therapy; refractory pain should be referred to pain management or palliative care
Leg Pain	Screen for iron deficiency; gabapentin may be a more successful analgesic for leg pain
Jaw Pain	Usually no interventions needed; reassure patient that this will get better with time; take slow bites or sips of water, suck on saltine crackers or hard candy, chew gum before eating
Headache	Pretreat before oral or inhaled doses or prior to up-titration of parenteral prostacyclin; mild/moderate headache: acetaminophen, ibuprofen, assess volume status; severe headache: referral to neurology (if titration becomes limited or headaches become chronic), evaluate for secondary cause (ie, check INR, brain imaging, referral to specialist)
Nausea/Vomiting	Take with food, eat small frequent meals, ginger-based foods (ginger ale); antiemetics: ondansetron; for inhaled therapies, swish and spit after each treatment session, temporarily decrease by one breath 4 times a day; rule out pregnancy; refer to gastroenterologist; slow titration or decrease dose
Loss of Appetite/ Weight Loss	Dietary consult; increase caloric content, small frequent meals, nutritional supplement; evaluate for other metabolic causes of weight loss
Diarrhea	Diphenoxylate/atropine; loperamide; slow up-titration or decrease dose; dietary changes: increase fiber, gluten free, low fat, BRAT diet; probiotic; decrease diuretic; rule out other causes, such as *C. diff*; refer to GI
Flushing/Rash	Reassurance; slow down up-titration only if absolutely needed; cold packs, compress at back of neck; inhaled therapies: if severe, can decrease by one breath 4 times a day and then increase again when symptom improves

Tell your patients to ask their treating HCP about additional strategies to manage common side effects.

BRAT=bananas, rice, applesauce, toast; *C. diff=Clostridioides difficile*; GI=gastrointestinal; INR=prothrombin time international normalized ratio; PH=pulmonary hypertension.

UPTRAVI® Specialty Pharmacy (SP) Titration Education Support Program (sponsored by Janssen)

After the treating HCP has made the decision to prescribe UPTRAVI® (selexipag), **the patient may choose to receive nurse educational support as they start therapy.**

For patients to receive this service, "yes" must be checked on the enrollment form to opt in to the nurse support and titration education program.

Within 48 hours of your patient's receipt of their first UPTRAVI® shipment, an SP Nurse can have an interaction with your patient.

During these visits with your patient, the nurse can:

EDUCATE
the patient on what to expect as they start therapy with UPTRAVI®

HELP
to address potential patient misconceptions about UPTRAVI® dosing

ENSURE
the patient's understanding of reaching their personal dose

PROVIDE
the patient and/or their caregiver with recommendations on when to call their HCP

The information provided is educational in nature and not intended to provide medical advice, replace a treatment plan from the patient's doctor or nurse, provide case management services, or serve as a reason to prescribe.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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WARNINGS AND PRECAUTIONS

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Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI®.

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Janssen Offers One-on-One Educational Support

PAH Companion withMe

Once a decision has been made to prescribe a Janssen PAH medication, PAH Companion withMe is a suite of patient support resources customized for your patients' specific questions, needs, and interests. One-on-one educational conversations with a dedicated PAH Companion—coupled with access to current PAH tools and resources—help your patients take a more active role in their care.

- Almost 9000 patients actively engaged[6]
- Over 90% of surveyed patients said they would continue the program and recommend it to others[7]
- All communications and materials are available in English and Spanish

A dedicated PAH Companion is ready to answer your patients' questions and help them navigate their treatment experience. Patients who have enrolled can connect with their personal PAH Companion by calling 866-300-1818, Monday–Friday, 8 AM–9 PM ET.

PAH Companion withMe is limited to education for patients about their PAH therapy, its administration, and/or their disease, and is not intended to provide medical advice, replace a treatment plan from the patient's doctor or nurse, or provide case management services.

Patients taking a Janssen PAH medication can enroll in PAH Companion withMe by completing a Janssen Patient Support Program Patient Authorization Form, or by submitting a digital version of the form at PAHconsent.com

Visit **PAHCompanion.com** to learn more

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

Adverse reactions more frequent compared to placebo (≥3%) seen with UPTRAVI® Tablets are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI® Tablets and in none of the patients on placebo.

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Important Safety Information

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INDICATION

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DRUG INTERACTIONS

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Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase UPTRAVI® dose, up to twice, when co-administered with rifampin. Reduce UPTRAVI® when rifampin is stopped.

Important Safety Information (continued)

DOSAGE AND ADMINISTRATION

Recommended Dosage

Recommended starting dose is 200 mcg twice daily for UPTRAVI® Tablets. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

Patients With Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of UPTRAVI® Tablets is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI® in patients with severe hepatic impairment (Child-Pugh class C).

Co-administration With Moderate CYP2C8 Inhibitors

When co-administered with moderate CYP2C8 inhibitors (eg, clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI® to once daily.

Dosage Strengths

UPTRAVI® tablet strengths:
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Additional Important Safety Information for UPTRAVI® IV

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Adverse Reactions: Infusion-site reactions (infusion-site erythema/redness, pain and swelling) were reported with UPTRAVI® for injection.

Please see full Prescribing Information for UPTRAVI®.

cp-126160v5

References: 1. UPTRAVI® (selexipag) full Prescribing Information. Actelion Pharmaceuticals US, Inc. **2.** Kingman M, Archer-Chicko C, Bartlett M, et al. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. *Pulm Circ.* 2017;7(3):598-608. **3.** Coghlan JG, Channick R, Chin K, et al. 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(1):37-47. **4.** Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med.* 2015;373:2522-2533. **5.** Sitbon O, Channick R, Chin KM, et al. Supplemental appendix to: Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med.* 2015;373:2522-2533. **6.** Data on file. Janssen PAH Companion. Weekly Report. January 4, 2023. **7.** Data on file. Janssen PAH Companion. Q2 2022 Business Report. July 2022.

Setting Expectations for Your Patients About Therapy With UPTRAVI® (selexipag)

Getting started

When speaking with your patients about starting therapy with UPTRAVI®, remind them of the following:

Anticipate a call from your specialty pharmacy to alert you of your next shipment of UPTRAVI®

Do not change your dose or stop taking UPTRAVI® unless your doctor tells you to do so[1]

Understand expectations for potential side effects. **Follow up with your doctor** if you have side effects that you cannot tolerate[1]

Try to take UPTRAVI® with food. This may help you tolerate the dose better if you are having side effects with UPTRAVI®[1]

After the dose adjustment phase, you will have found **your personal maintenance dose of UPTRAVI®**. This will be the dose you continue to take on a regular basis, unless your doctor tells you otherwise[1]

What to do about missed doses

It is important that you make your patients aware of what to do if they are unable to stay consistent with their UPTRAVI® dosing. Remind your patients of the following[1]:

- **If you miss a dose of UPTRAVI®**, take it as soon as you remember. If your next scheduled dose is due within 6 hours, skip the missed dose and take the next dose at your regular time
- **If you miss 3 or more days of UPTRAVI®**, call your doctor to see if your dose needs to be changed
- **If you take too much UPTRAVI®**, call your healthcare team or go to the nearest hospital emergency room right away

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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