HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use UPTRAVI® safely and effectively. See full prescribing information for UPTRAVI®.

UPTRAVI® (selexipag) tablets, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Contraindications 07/2017

----------INDICATIONS AND USAGE----------

UPTRAVI® is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Starting dose: 200 mcg twice daily. (2.1)
- Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily. (2.1)
- Maintenance dose is determined by tolerability. (2.1)
- Moderate hepatic impairment: Starting dose 200 mcg once daily, increase the dose by 200 mcg once daily at weekly intervals to the highest tolerated dose up to 1600 mcg. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg. (3)

----------CONTRAINDICATIONS----------

Concomitant use with strong CYP2C8 inhibitors. (4, 7.1, 12.3)

----------WARNINGS AND PRECAUTIONS----------

Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment. (5.1)

----------ADVERSE REACTIONS----------

Adverse reactions occurring more frequently (≥5%) on UPTRAVI compared to placebo are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Moderate CYP2C8 inhibitors (e.g., deferasirox and teriflunomide) may increase exposure to the active metabolite of UPTRAVI (7.1)
- CYP2C8 inducers (e.g., rifampin) decrease exposure to the active metabolite. Increase up to twice the dose of UPTRAVI (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: discontinue UPTRAVI or breastfeeding. (8.2)
- Severe hepatic impairment: Avoid use. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

UPTRAVI 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 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%), PAH associated with congenital heart disease with repaired shunts (10%) *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dose of UPTRAVI is 200 micrograms (mcg) given twice daily. Tolerability may be improved when taken with food *[see Clinical Pharmacology (12.3)]*.

Increase the dose in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.

Do not split, crush, or chew tablets.

2.2 Interruptions and Discontinuations

If a dose of medication is missed, patients should take a 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.

2.3 Dosage Adjustment in Patients with Hepatic Impairment

No dose adjustment of UPTRAVI is necessary for patients with mild hepatic impairment (Child-Pugh class A).

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of UPTRAVI is 200 mcg once daily. Increase in increments of 200 mcg once daily at weekly intervals, as tolerated *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

3 DOSAGE FORMS AND STRENGTHS

UPTRAVI is available in the following strengths:

- 200 mcg [Light yellow tablet debossed with 2]
- 400 mcg [Red tablet debossed with 4]
- 600 mcg [Light violet tablet debossed with 6]
- 800 mcg [Green tablet debossed with 8]
- 1000 mcg [Orange tablet debossed with 10]
- 1200 mcg [Dark violet tablet debossed with 12]
- 1400 mcg [Dark yellow tablet debossed with 14]
- 1600 mcg [Brown tablet debossed with 16]

4 CONTRAINDICATIONS

Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Veno-Occlusive Disease (PVOD)

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of UPTRAVI has been evaluated in a long-term, placebo-controlled study enrolling 1156 patients with symptomatic PAH (GRIPHON study) *[see Clinical Studies (14)]*. The exposure to UPTRAVI in this trial was up to 4.2 years with median duration of exposure of 1.4 years.

Table 1 presents adverse reactions more frequent on UPTRAVI than on placebo by ≥3%.

Table 1 Adverse Reactions

	UPTRAVI	**Placebo**
Adverse Reaction	**N=575**	**N=577**
Headache	65%	32%
Diarrhea	42%	18%
Jaw pain	26%	6%
Nausea	33%	18%
Myalgia	16%	6%
Vomiting	18%	9%
Pain in extremity	17%	8%
Flushing	12%	5%
Arthralgia	11%	8%
Anemia	8%	5%
Decreased appetite	6%	3%
Rash	11%	8%

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

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

Laboratory Test Abnormalities

Hemoglobin

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin 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 in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Uptravi. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Symptomatic hypotension

7 DRUG INTERACTIONS

7.1 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 administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Although not studied, use of UPTRAVI with moderate CYP2C8 inhibitors (e.g., teriflunomide and deferasirox) can be expected to increase exposure to the active metabolite of selexipag. Consider a less frequent dosing regimen, e.g., once-daily, when initiating UPTRAVI in patients on a moderate CYP2C8 inhibitor. Reduce UPTRAVI when a moderate CYP2C8 inhibitor is initiated.

7.2 CYP2C8 Inducers

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase dose up to twice of UPTRAVI when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with UPTRAVI in pregnant women. Animal reproduction studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival. A slight reduction in maternal as well as in fetal body weight was observed when pregnant rats were administered selexipag during organogenesis at a dose producing an exposure approximately 47 times that in humans at the maximum recommended human dose. No adverse developmental outcomes were observed with oral administration of selexipag to pregnant rabbits during organogenesis at exposures up to 50 times the human exposure at the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day (up to 47 times the exposure at the maximum recommended human dose of 1600 mcg twice daily on an area under the curve [AUC] basis) during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg (up to 50 times the exposure to the active metabolite at the maximum recommended human dose of 1600 mcg twice daily on an AUC basis) during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

8.2 Lactation

It is not known if UPTRAVI is present in human milk. Selexipag or its metabolites were present in the milk of rats. Because many drugs are present in the human milk and because of the potential for serious adverse reactions in nursing infants, discontinue nursing or discontinue UPTRAVI.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1368 subjects in clinical studies of UPTRAVI 248 subjects were 65 years of age and older, while 19 were 75 and older. No overall differences were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity cannot be ruled out.

8.6 Patients with Hepatic Impairment

No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C). Avoid use of UPTRAVI in patients with severe hepatic impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No adjustment to the dosing regimen is needed in patients with estimated glomerular filtration rate > 15 mL/min/1.73 m^2.

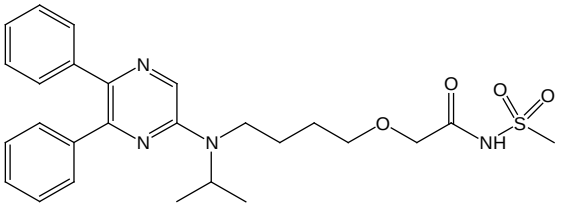
There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with glomerular filtration rates < 15 mL/min/1.73 m^2 *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Isolated cases of overdose up to 3200 mcg 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.

11 DESCRIPTION

UPTRAVI (selexipag) is a selective non-prostanoid IP prostacyclin receptor agonist. The chemical name of selexipag is 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-*N*-(methylsulfonyl) acetamide. It has a molecular formula of $C_{26}H_{32}N_4O_4S$ and a molecular weight of 496.62. Selexipag has the following structural formula:



Selexipag is a pale yellow crystalline powder that is practically insoluble in water. In the solid state selexipag is very stable, is not hygroscopic, and is not light sensitive.

Depending on the dose strength, each round film-coated tablet for oral administration contains 200, 400, 600, 800, 1000, 1200, 1400, or 1600 mcg of selexipag. The tablets include the following inactive ingredients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, and magnesium stearate. The tablets are film coated with a coating material containing hypromellose, propylene glycol, titanium dioxide, carnauba wax along with mixtures of iron oxide red, iron oxide yellow or iron oxide black.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selexipag is an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. Selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP_{1-4}, DP, FP, and TP).

12.2 Pharmacodynamics

Cardiac electrophysiology:

At the maximum tolerated dose of 1600 mcg twice daily, selexipag does not prolong the QT interval to any clinically relevant extent.

Platelet aggregation:

Both selexipag and its active metabolite caused concentration-dependent inhibition of platelet aggregation *in vitro* with an IC_{50} of 5.5 µM and 0.21 µM, respectively. However, at clinically relevant concentrations, there was no effect on platelet aggregation test parameters as seen following multiple-dose administrations of selexipag in healthy subjects from 400 mcg up to 1800 mcg twice daily.

Pulmonary hemodynamics:

A Phase 2 clinical study assessed hemodynamic variables after 17 weeks of treatment in patients with PAH WHO Functional Class II–III and concomitantly receiving endothelin receptor antagonists (ERAs) and/or phosphodiesterase type 5 (PDE-5) inhibitors. Patients titrating selexipag to an individually tolerated dose (200 mcg twice daily increments up to 800 mcg 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%) and an increase in cardiac index (median treatment effect) of 0.41 L/min/m^2 (95% CI 0.10, 0.71) compared to placebo (N=10).

Drug interaction:

In a study in healthy subjects, selexipag (400 mcg twice a day) did not influence the pharmacodynamic effect of warfarin on the international normalized ratio.

12.3 Pharmacokinetics

The pharmacokinetics of selexipag and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of selexipag and the active metabolite, after both single- and multiple-dose administration, were dose-proportional up to a single dose of 800 mcg and multiple doses of up to 1800 mcg twice daily.

In healthy subjects, inter-subject variability in exposure (area under the curve over a dosing interval, AUC) 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.

Exposures to selexipag and the active metabolite at steady-state in PAH patients and healthy subjects were 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.

Both in healthy subjects and PAH patients, after oral administration, exposure at steady-state to the active metabolite is approximately 3- to 4-fold that of selexipag. Exposure to the active metabolite is approximately 30% higher after oral administration compared to the same intravenous dose in healthy subjects.

Absorption

The absolute bioavailability of selexipag is approximately 49%. Upon oral administration, maximum observed plasma concentrations of selexipag and its active metabolite are reached within about 1–3 hours and 3–4 hours, respectively.

In the presence of food, the absorption of selexipag was prolonged resulting in a delayed time to peak concentration (T_{max}) and ~30% lower peak plasma concentration (C_{max}). The exposure to selexipag and the active metabolite (AUC) did not significantly change in the presence of food.

Distribution

The volume of distribution of selexipag at steady state is 11.7 L.

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).

Metabolism

Selexipag is hydrolyzed to its active metabolite, (free carboxylic acid) in the liver and intestine by carboxylesterases. Oxidative metabolism, catalyzed mainly by CYP2C8 and to a smaller extent by CYP3A4, leads to the formation of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceeds 3% of the total drug-related material.

Elimination

Elimination of selexipag is predominately via metabolism with a mean terminal half-life of 0.8-2.5 hours. The terminal half-life of the active metabolite is 6.2-13.5 hours. There is minimal accumulation of the active metabolite upon twice daily repeat administration suggesting that the effective half-life is in the range of 3-4 hours. The total body clearance of selexipag is 17.9 L/hour.

Excretion

In a study in healthy subjects with radiolabeled selexipag, approximately 93% of radioactive drug material was eliminated in feces and only 12% in urine. Neither selexipag nor its active metabolite were found in urine.

Specific 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.

Age:

The pharmacokinetic variables (C_{max} and AUC) were similar in adult and elderly subjects up to 75 years of age. There was no effect of age on the pharmacokinetics of selexipag and the active metabolite in PAH patients.

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 that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment *[see Use in Specific Populations (8.6)]*.

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, the exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in these patients during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice-daily regimen.

Renal Impairment:

A 40-70% 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 (estimated glomerular filtration rate ≥ 15 mL/min/1.73 m^2 and < 30 mL/min/1.73 m^2) *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies:

In vitro studies

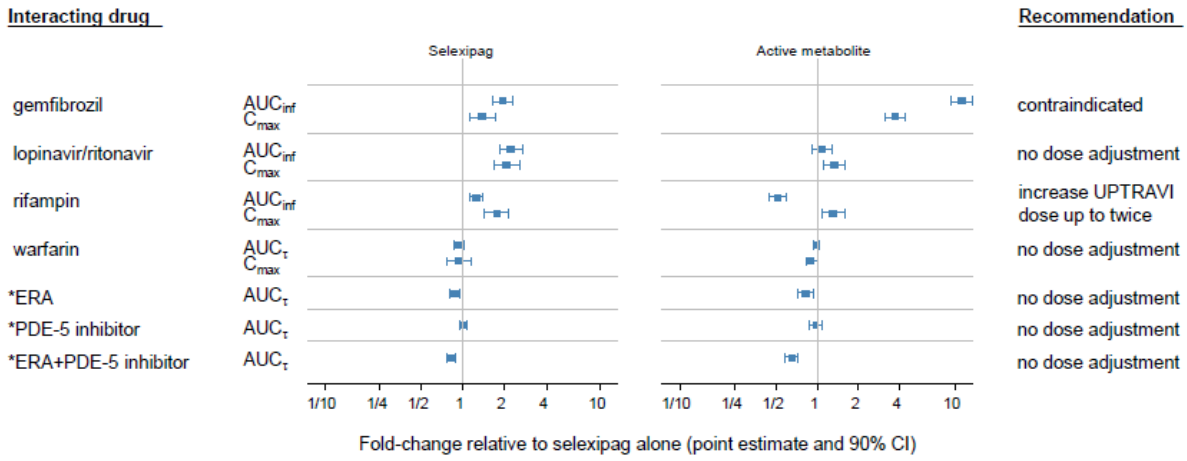
Selexipag is hydrolyzed to its active metabolite by carboxylesterases. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP).

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

The effect of moderate inhibitors of CYP2C8 on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration with moderate inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite*[see Drug Interactions (7.1)]*.

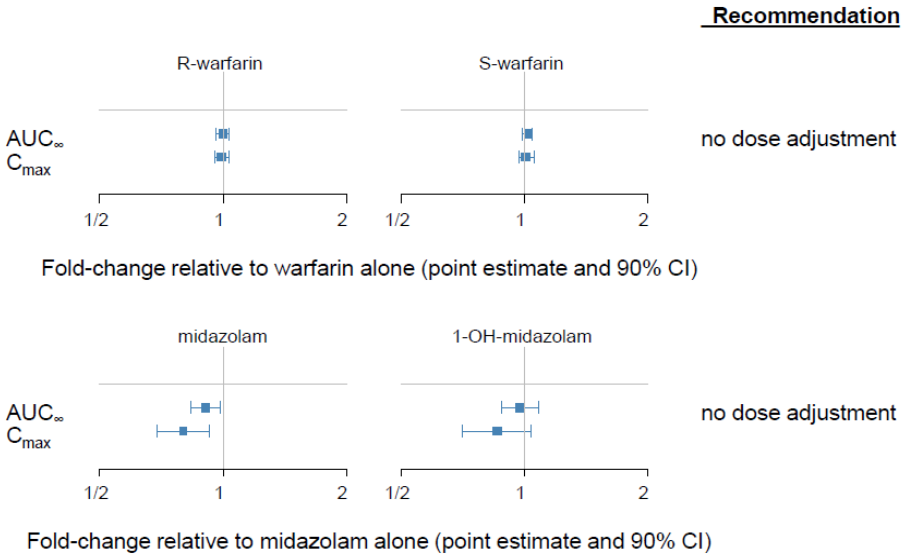
The results on in vivo drug interaction studies are presented in Figure 1 and 2.

Figure 1 Effect of Other Drugs on UPTRAVI and its Active Metabolite



*ERA and PDE-5 inhibitor data from GRIPHON.

Figure 2 Effect of UPTRAVI on Other Drugs



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In the 2-year carcinogenicity studies, chronic oral administration of selexipag revealed no evidence of carcinogenic potential in rats at 100 mg/kg/day and mice at 500 mg/kg/day. The exposures were more than 25-fold human exposure.

Mutagenesis: Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.

Fertility: The no effect dose for effects on fertility was 60 mg/kg/day in a study in which rats were administered selexipag orally. This dose corresponded to an exposure of 175-times (active metabolite) the human therapeutic exposure.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension

The effect of selexipag on progression of PAH was demonstrated in a multi-center, double-blind, placebo-controlled, parallel group, event-driven study (GRIPHON) in 1156 patients with symptomatic (WHO Functional Class I [0.8%], II [46%], III [53%], and IV [1%]) PAH. Patients were randomized to either placebo (N = 582), or UPTRAVI (N = 574). The dose was increased in weekly intervals by increments of 200 mcg twice a day to the highest tolerated dose up to 1600 mcg twice a day.

The primary study endpoint was the time to first occurrence up to end-of-treatment of: a) death, b) hospitalization for PAH, c) PAH worsening resulting in need for lung transplantation, or balloon atrial septostomy, d) initiation of parenteral prostanoid therapy or chronic oxygen therapy, or e) other disease progression based on a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy.

The mean age was 48 years, the majority of patients were white (65%) and female (80%). Nearly all patients were in WHO Functional Class II and III at baseline.

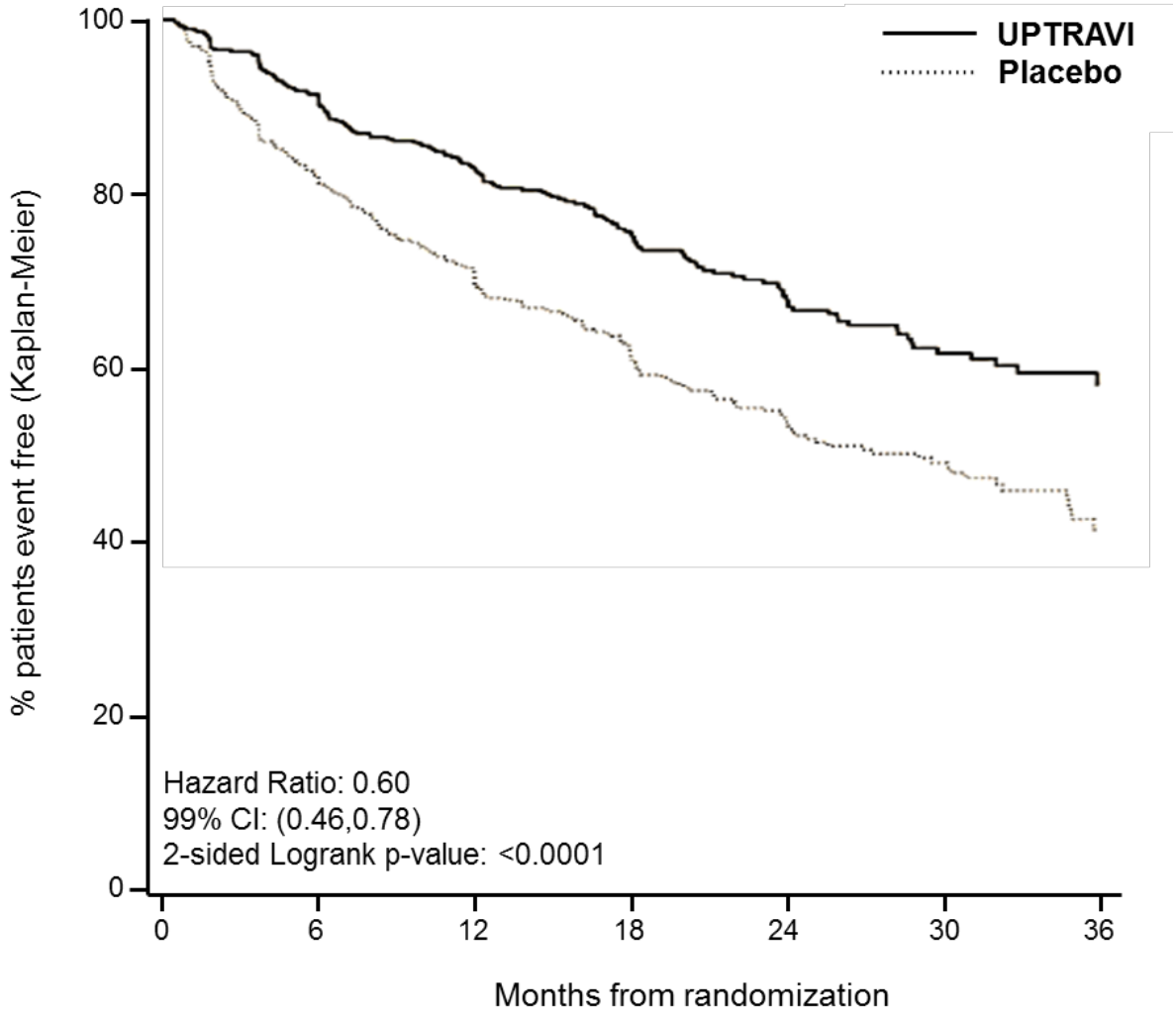
Idiopathic or heritable PAH was the most common etiology in the study population (58%) followed by PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%), drugs and toxins (2%), and HIV (1%).

At baseline, the majority of enrolled patients (80%) were being treated with a stable dose of an endothelin receptor antagonist (15%), a PDE-5 inhibitor (32%), or both (33%).

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

Treatment with UPTRAVI resulted in a 40% reduction (99% CI: 22 to 54%; two-sided log-rank *p*-value < 0.0001) of the occurrence of primary endpoint events compared to placebo (Table 2; Figure 3). The beneficial effect of UPTRAVI was primarily attributable to a reduction in hospitalization for PAH and a reduction in other disease progression events (Table 2). The observed benefit of UPTRAVI was similar regardless of the dose achieved when patients were titrated to their highest tolerated dose *[see Dosage and Administration (2.1)]*.

Figure 3 Kaplan-Meier Estimates of the First Morbidity-Mortality Event in GRIPHON



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

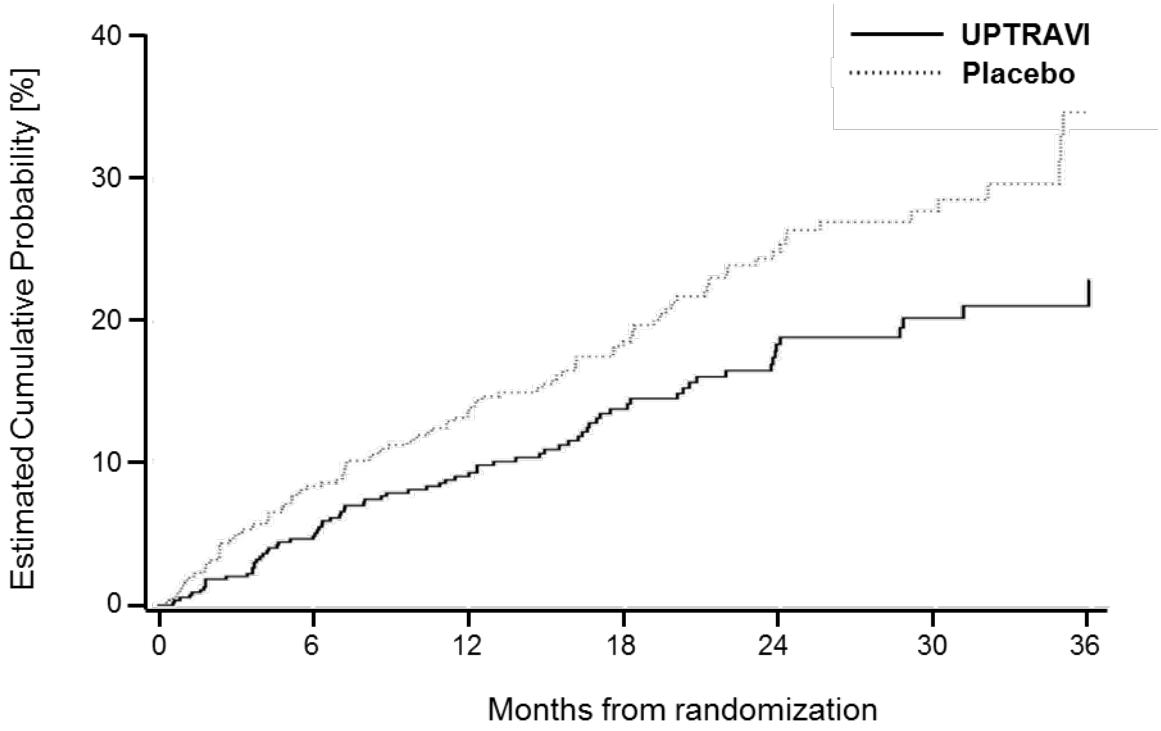
Table 2 Primary Endpoints and Related Components in GRIPHON

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

It is not known if the excess number of deaths in the selexipag group is drug-related because there were so few deaths and the imbalance was not observed until 18 months into GRIPHON.

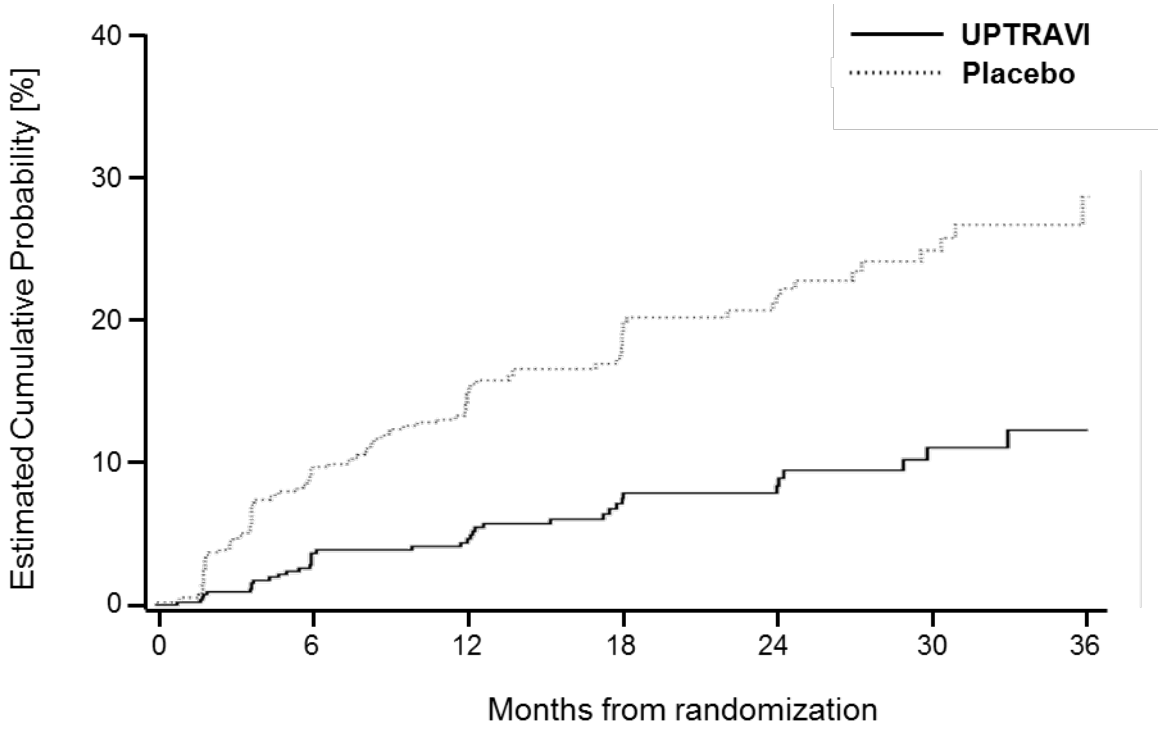
Figures 4A, B, and C show time to first event analyses for primary endpoint components of hospitalization for PAH (A), other disease progression (B), and death (C)—all censored 7 days after any primary end point event (because many patients on placebo transitioned to open-label UPTRAVI at this point).

Figure 4 A Hospitalization for PAH as the First Endpoint in GRIPHON



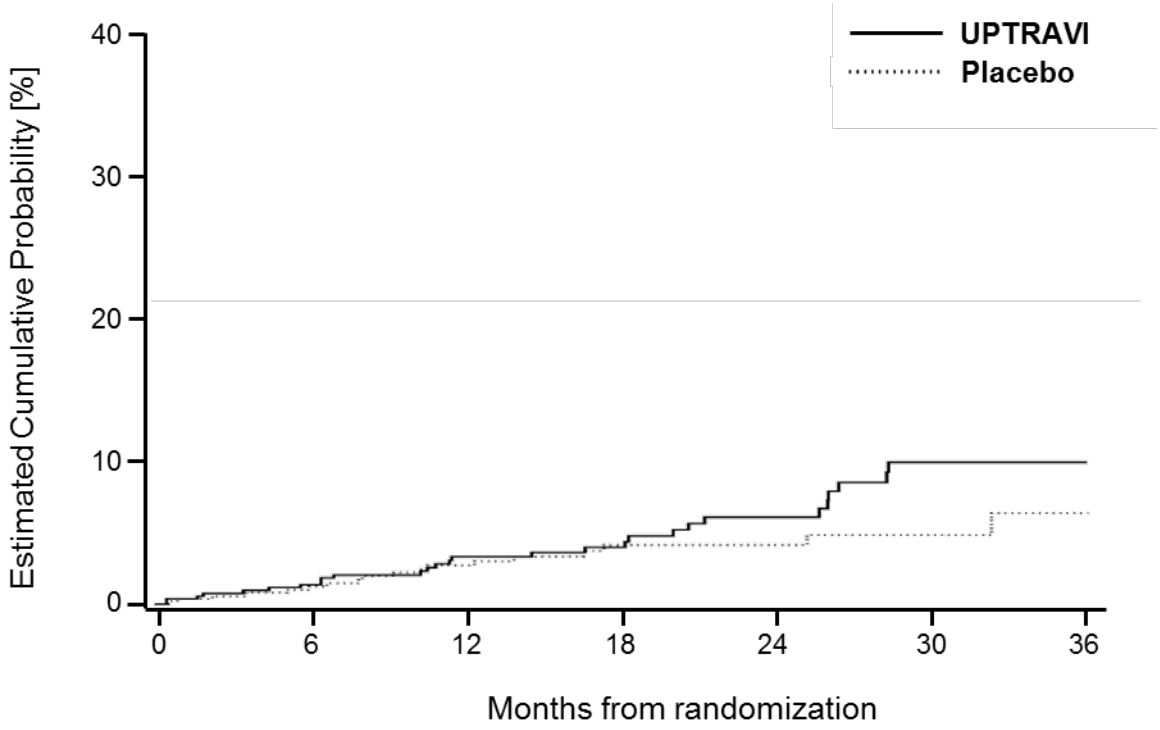
UPTRAVI patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

Figure 4B Disease Progression as the First Endpoint in GRIPHON



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

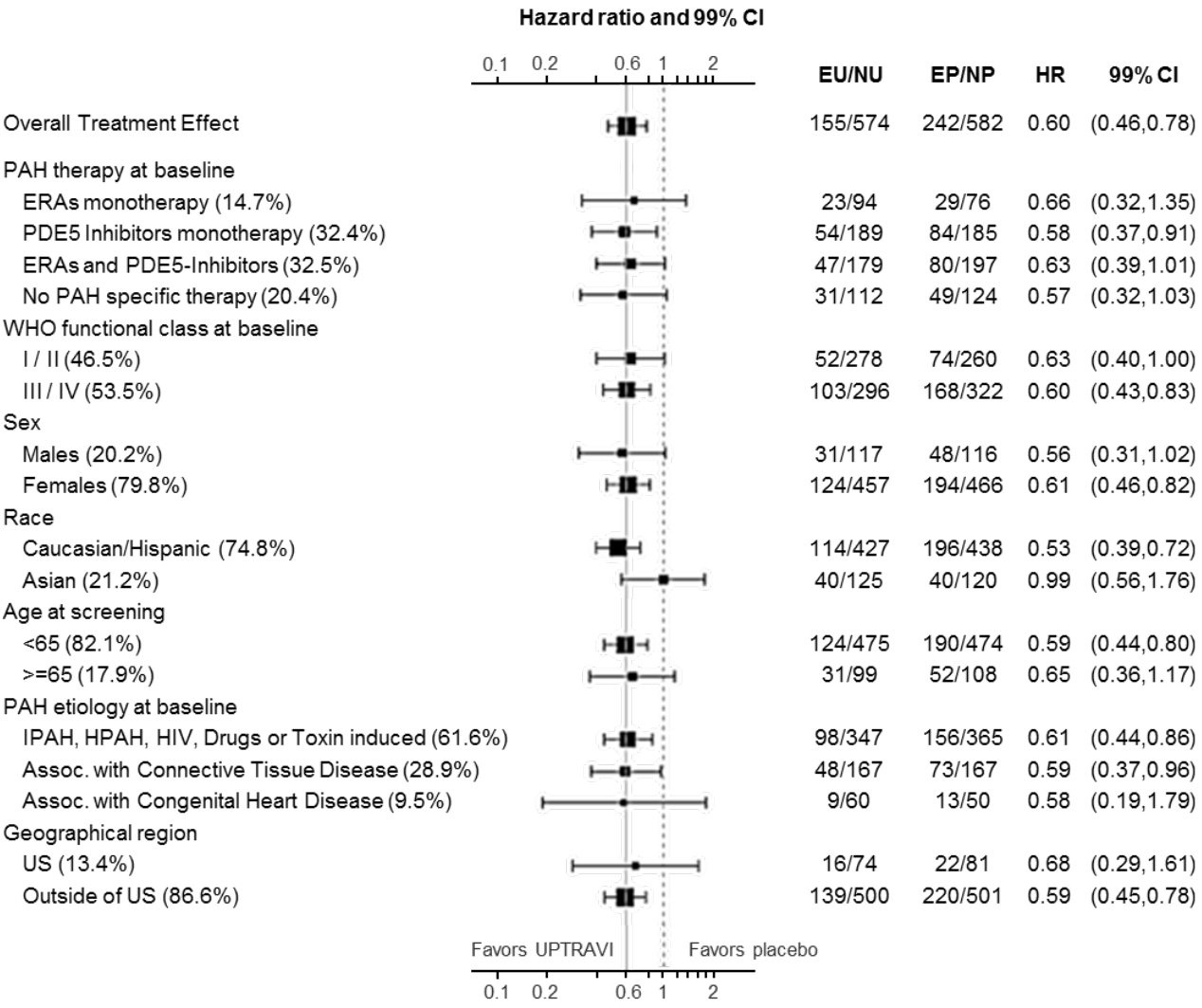
Figure 4C Death as the First Endpoint in GRIPHON



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

The treatment effect of UPTRAVI on time to first primary event was consistent irrespective of background PAH therapy (i.e., in combination with an ERA, PDE-5i, both, or without background therapy) (Figure 5).

Figure 5 Subgroup Analyses of the Primary Endpoint in GRIPHON



Note: Race group “Other” is not displayed in analysis, as the population is less than 30. EU = Number of UPTRAVI patients with events, NU = Number of patients randomized to UPTRAVI, EP = Number of Placebo patients with events, NP = Number of patients randomized to Placebo, HR = Hazard Ratio, CI = Confidence Interval, the size of the squares represent the number of patients in the subgroup.

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

6-Minute Walk Distance (6MWD)

Exercise capacity was evaluated as a secondary endpoint. Median absolute change from baseline to week 26 in 6MWD measured at trough (i.e., at approximately 12 hours post-dose) was +4 meters with UPTRAVI and -9 meters in the placebo group. This resulted in a placebo-corrected median treatment effect of 12 meters (99% CI: 1, 24 meters;two-sided p = 0.005).

16 HOW SUPPLIED/STORAGE AND HANDLING

UPTRAVI (selexipag) film-coated, round tablets are supplied in the following configurations:

Strength (mcg)	**Color**	**Debossing**	**NDC-XXX Bottle of 60**	**NDC-XXX Bottle of 140**
200	Light yellow	2	66215-602-06	66215-602-14
400	Red	4	66215-604-06	Not Applicable
600	Light violet	6	66215-606-06	Not Applicable
800	Green	8	66215-608-06	Not Applicable
1000	Orange	10	66215-610-06	Not Applicable
1200	Dark violet	12	66215-612-06	Not Applicable
1400	Dark yellow	14	66215-614-06	Not Applicable
1600	Brown	16	66215-616-06	Not Applicable

UPTRAVI is also supplied in a Titration Pack [NDC 66215-628-20] that includes a 140 count bottle of 200 mcg tablets and a 60 count bottle of 800 mcg tablets.

Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions are permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Package Insert).

Inform patients:

- what to do if they miss a dose
- not to split, crush, or chew tablets.

Manufactured for:

Actelion Pharmaceuticals US, Inc.

5000 Shoreline Court, Ste. 200

South San Francisco, CA 94080, USA

ACT20171016

Patient Information
UPTRAVI (up-TRA-vee)
(selexipag) tablets

Read this Patient Information before you start taking UPTRAVI and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is UPTRAVI?

- UPTRAVI is a prescription medicine used to treat pulmonary arterial hypertension (PAH) which is high blood pressure in the arteries of your lungs.
- UPTRAVI can help slow down the progression of your disease and lower your risk of being hospitalized for PAH.

It is not known if UPTRAVI is safe and effective in children.

Who should not take UPTRAVI?
Do not take UPTRAVI if you

Take gemfibrozil because this medicine may affect how UPTRAVI works and cause side effects.

What should I tell my healthcare provider before taking UPTRAVI?
Before you take UPTRAVI, tell your healthcare provider if you:

- have liver problems.
- have narrowing of the pulmonary veins, a condition called pulmonary veno-occlusive disease.
- are pregnant or plan to become pregnant. It is not known if UPTRAVI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if UPTRAVI passes into your breast milk. You and your healthcare provider should decide if you will take UPTRAVI or breastfeed. You should not do both.
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. UPTRAVI and other medicines may affect each other causing side effects. Do not start any new medicine until you check with your healthcare provider.

How should I take UPTRAVI?

- Take UPTRAVI exactly as your healthcare provider tells you to take it. Do not stop taking UPTRAVI unless your healthcare provider tells you to stop.
- Your healthcare provider will slowly increase your dose to find the dose of UPTRAVI that is right for you.
- If you have side effects, your healthcare provider may tell you to change your dose of UPTRAVI.
- UPTRAVI can be taken with or without food. Taking UPTRAVI with food may help you tolerate UPTRAVI better.
- UPTRAVI is usually taken 2 times each day.
- Swallow UPTRAVI tablets whole. Do not split, crush or chew UPTRAVI tablets.
- 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. Take the next dose at your regular time.
- If you miss 3 or more days of UPTRAVI, call your healthcare provider to see if your dose needs to be changed.
- If you take too much UPTRAVI, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of UPTRAVI?
The most common side effects of UPTRAVI include:

- Headache
- jaw pain
- muscle pain
- pain in arms or legs
- pain in joints
- decreased appetite
- diarrhea
- nausea
- vomiting
- flushing
- low red blood cell count
- rash

These are not all of the possible side effects of UPTRAVI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store UPTRAVI?

- Store UPTRAVI tablets at room temperature between 68°F and 77°F (20°C and 25°C).

Keep UPTRAVI and all medicines out of the reach of children.

General information about the safe and effective use of UPTRAVI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

Do not use UPTRAVI for a condition for which it was not prescribed. Do not give UPTRAVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about UPTRAVI that is written for health professionals.

What are the ingredients in UPTRAVI?

Active ingredient: selexipag

Inactive ingredients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, and magnesium stearate. The tablets are film coated with a coating material containing hypromellose, propylene glycol, titanium dioxide, carnauba wax along with iron oxide red, iron oxide yellow, or iron oxide black.

Manufactured for: Actelion Pharmaceutical US, Inc. 5000 Shoreline Court, Ste. 200 South San Francisco, CA 94080, USA
ACT20171016

For more information, call 1-866-228-3546 or go to www.UPTRAVI.com.

The Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 12/2017