Patient package insert according to Pharmacists' Regulations (Preparations)- 1986.

This medicine can be sold with a doctor's prescription only

Uptravi® 200 micrograms, Uptravi® 400 micrograms, Uptravi® 600 micrograms, Uptravi® 800 micrograms, Uptravi® 1,000 micrograms, Uptravi® 1,200 micrograms, Uptravi® 1,400 micrograms, Uptravi® 1,600 micrograms

Film-Coated Tablets

The active ingredient and its quantity:
Uptravi 200 micrograms (mcg): each tablet contains selexipag 200 mcg
Uptravi 400 micrograms (mcg): each tablet contains selexipag 400 mcg
Uptravi 600 micrograms (mcg): each tablet contains selexipag 600 mcg
Uptravi 800 micrograms (mcg): each tablet contains selexipag 800 mcg
Uptravi 1,000 micrograms (mcg): each tablet contains selexipag 1,000 mcg
Uptravi 1,200 micrograms (mcg): each tablet contains selexipag 1,200 mcg
Uptravi 1,400 micrograms (mcg): each tablet contains selexipag 1,400 mcg
Uptravi 1,600 micrograms (mcg): each tablet contains selexipag 1,600 mcg

For the list of inactive ingredients, please see section 6.

Read this entire leaflet carefully before using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, refer to your doctor or pharmacist.

This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them, even if you think that their illness is similar.

This medicine is intended for patients over 18 years of age.

1. What is the Medicine Intended for?

Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO (World Health Organization) 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 of Uptravi has been shown in a PAH population including idiopathic (unknown cause) and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

Therapeutic group: Platelet aggregation inhibitors excluding Heparin.

2. Before Using this Medicine

Do not take this medicine if:

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

Special warnings regarding the use of this medicine

Before treatment with Uptravi tell your PAH doctor (a doctor for pulmonary arterial hypertension) if:

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

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

Tell your doctor or pharmacist if you are taking, or have recently taken, or if you may be taking any other medicines including non-prescription drugs and nutritional supplements.

Taking other medicines with Uptravi may affect how Uptravi works.

Tell your PAH doctor if you are taking any of the following medicines:

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

Children and adolescents
This medicine is not intended for children under 18 years of age, because it has not been tested in children and adolescents.

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

Use of this Medicine and Food
The medicine can be taken with or without food. Taking the medicine with food may improve tolerance to the medicine.

Pregnancy and Breastfeeding
Uptravi is not recommended for use during pregnancy and breastfeeding.

If you are a woman of child-bearing age, you should use an effective contraceptive method while taking Uptravi.
If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

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

3. How to Use this Medicine?
- Uptravi should only be prescribed by a doctor experienced in the treatment of PAH.
- Always take Uptravi exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure or have any questions.
- If you have poor vision or experience any type of blindness, get help from another person when taking Uptravi during the titration period.

The dosage and administration will be determined by your doctor only.
Finding the right dose for you
At the start of treatment, you will take the lowest dose: one 200 mcg tablet **in the morning and another 200 mcg tablet in the evening**. Treatment should be initiated in the evening.
Your doctor will instruct you to gradually increase your dose. This is called titration and it lets your body adjust to the medicine.
The goal of titration is to reach the most appropriate dose. This will be the highest dose you can tolerate, which may reach the maximum dose of 1,600 mcg in the morning and 1,600 mcg in the evening.

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

With each step, you will add one 200 mcg tablet to your morning dose and another 200 mcg tablet to your evening dose. The first intake of the increased dose should be in the evening.

Read the detailed instructions, regarding starting treatment and titration process, in the Titration Guide, which is included in the Titration Pack (Uptravi 200 mcg, 140 tablets).
In the titration guide you may record the number of tablets you take every day.

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

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

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

If, at any time, after taking the same maintenance dose for a long time, you experience side effects that you cannot tolerate or side effects that have an impact on your normal daily activities, contact your doctor as your dose may need to be reduced. The doctor may then prescribe you a lower single-tablet strength.

Do not exceed the recommended dose.

- **Take Uptravi once in the morning and once in the evening, about 12 hours apart.**
- Take the tablets with meals as you might tolerate your medicine better.
- Swallow the tablets whole with a glass of water.
- Do not split, crush or chew the tablets.

If you have accidentally taken a higher dosage or if a child has accidentally swallowed the medicine, refer immediately to your doctor or to a hospital emergency room and bring the package of the medicine with you.

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

Continue with the treatment as recommended by your doctor.
Even if there has been an improvement in your health, do not stop the treatment with this medicine without consulting your doctor.

If you stop taking this medicine
Suddenly stopping your treatment with Uptravi might lead to your symptoms getting worse.
Do not stop taking Uptravi unless your doctor tells you to.
Your doctor may tell you to reduce the dose gradually until stopping completely.
If, for any reason, you stop taking Uptravi for more than 3 consecutive days (if you missed 3 morning and 3 evening doses, or 6 doses in a row or more), **contact your doctor immediately as your dose may need to be adjusted to avoid side effects.**
Your doctor may decide to restart your treatment on a lower dose, gradually increasing to your previous maintenance dose.

- Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

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

4. Side Effects

Like any medicine, the use of Uptravi may cause side effects in some users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.
You may experience side effects not only during the titration period, when your dose is being increased, but also later after taking the same dose for a long time.

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

Very common side effects (may affect more than 1 in 10 people)
- Headache
- Flushing (reddening of the face)
- Nausea and vomiting
- Diarrhoea
- Jaw pain, muscle pain, joint pain, leg pain
- Nasopharyngitis (stuffy nose)

Common side effects (may affect 1-10 in 100 people)
- Anaemia (low red blood cell levels)
- Hyperthyroidism (overactive thyroid gland)
- Decreased appetite
- Weight loss
- Hypotension (low blood pressure)
- Stomach pain
- Pain
- Changes in some blood test results including those measuring blood cell counts or your thyroid function
- Rashes, including hives, which may cause a burning or stinging sensation and skin redness

Uncommon side effects (may affect 1-10 in 1,000 people)
- Increased heart rate

If a side effect appears, if any of the side effects worsen or if you suffer from a side effect not mentioned in the leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health via the link "Report Side Effects of Drug Treatment" found on the home page of the Ministry of Health's website (www.health.gov.il), which refers to the online form for reporting side effects, or via the following link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. How to Store the Medicine?

- Avoid poisoning! This medicine, and any other medicine, must be kept in a safe place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your doctor.
- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.
- Store at a temperature below 30°C.

6. Additional Information

In addition to the active ingredient, the medicine also contains:
Mannitol, maize starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate.

The film-coating contains:
Hypromellose, propylene glycol, titanium dioxide, carnauba wax with iron oxide red and/or iron oxide yellow and/or iron oxide black.

What the medicine looks like and the contents of the package
Uptravi 200 mcg:
Each package contains 60 or 140 tablets. The tablets are packed in blisters.

Uptravi 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg:
Each package contains 60 tablets. The tablets are packed in blisters.

Uptravi 200 mcg: round, light yellow tablets imprinted with "2" on one side.
Uptravi 400 mcg: round, red tablets imprinted with "4" on one side.
Uptravi 600 mcg: round, light violet tablets imprinted with "6" on one side.
Uptravi 800 mcg: round, green tablets imprinted with "8" on one side.
Uptravi 1,000 mcg: round, orange tablets imprinted with "10" on one side.
Uptravi 1,200 mcg: round, dark violet tablets imprinted with "12" on one side.
Uptravi 1,400 mcg: round, dark yellow tablets imprinted with "14" on one side.
Uptravi 1,600 mcg: round, brown tablets imprinted with "16" on one side.

Registration holder and address: J-C Health Care Ltd.,
Kibbutz Shefayim 6099000, Israel.

Manufacturer and address: Actelion Pharmaceuticals Ltd., Allschwil, Switzerland.

Drug registration number at the national registry of the Ministry of Health: Uptravi 200 mcg: 158 07 34938 00 ; Uptravi 400 mcg: 158 08 34939 00
Uptravi 600 mcg: 158 09 34940 00 ; Uptravi 800 mcg: 158 10 34941 00
Uptravi 1,000 mcg: 158 11 34942 00 ; Uptravi 1,200 mcg: 158 12 34943 00
Uptravi 1,400 mcg: 158 13 34944 00 ; Uptravi 1,600 mcg: 158 14 34945 00

The format of this leaflet has been determined by the Israeli Ministry Of Health and its content was checked and approved by the Ministry of Health in March 2017, and was updated in accordance with the Ministry of Health instructions in November 2017.