PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Uptravi® 200 microgram,

Uptravi® 400 microgram,

Uptravi® 600 microgram,

Uptravi® 800 microgram,

Uptravi® 1,000 microgram,

Uptravi® 1,200 microgram,

Uptravi® 1,400 microgram,

Uptravi® 1,600 microgram

Film-coated tablets

The active ingredient and its quantity:
Uptravi 200 micrograms: each film-coated tablet contains 200 micrograms of selexipag
Uptravi 400 micrograms: each film-coated tablet contains 400 micrograms of selexipag
Uptravi 600 micrograms: each film-coated tablet contains 600 micrograms of selexipag
Uptravi 800 micrograms: each film-coated tablet contains 800 micrograms of selexipag
Uptravi 1,000 micrograms: each film-coated tablet contains 1,000 micrograms of selexipag
Uptravi 1,200 micrograms: each film-coated tablet contains 1,200 micrograms of selexipag
Uptravi 1,400 micrograms: each film-coated tablet contains 1,400 micrograms of selexipag
Uptravi 1,600 micrograms: each film-coated tablet contains 1,600 micrograms of selexipag

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

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.

Patient Titration Guide

In addition to the Patient Leaflet, a Titration Guide for the patient is provided with the Uptravi 200 microgram pack.

This guide contains important safety information that you must be aware of and adhere to before starting and during the course of treatment with Uptravi. Read the Titration Guide for the patient and patient leaflet before using the preparation. Keep the guide for further reading, if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

Uptravi is used 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 THE MEDICINE

Do not take this medicine if:

- you are sensitive (allergic) to the active ingredient (selexipag) or any of the other ingredients of this medicine (see section 6 “Additional information”).
- you have heart problems, such as:
  - poor blood flow to the heart muscles (severe coronary heart disease or unstable angina); symptoms can include chest pain.
  - heart attack within the last 6 months.
  - cardiac failure (weak heart) that is not under close medical observation.
  - severe irregular heartbeat.
  - 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 (e.g., transient brain ischaemia).
- you are taking gemfibrozil (medicine used to lower the level of fats [lipids] in the blood).

Special warnings regarding the use of this medicine

Before treatment with Uptravi, tell your doctor, who treats pulmonary arterial hypertension (PAH doctor), 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

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

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

Drug Interactions
Tell your doctor or pharmacist if you are taking, or have recently taken, or might take any other medicines, including non-prescription medications and nutritional supplements.
Taking other medicines together 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 bloodstream)
- 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)

Use of this medicine and food
Take the tablets with food as you might tolerate your medicine better.

Pregnancy and breastfeeding
Uptravi is not recommended for use during pregnancy and breastfeeding.
If you are a woman of childbearing 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 commencing treatment with the medicine.

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

3. HOW SHOULD THE MEDICINE BE USED?

Uptravi should only be prescribed by a doctor experienced in the treatment of PAH.

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain or have questions about the dosage and treatment regimen of the preparation. Tell your doctor if you experience side effects, as your doctor may recommend that you change your Uptravi dose.

Tell your doctor if you are taking other medications, as your doctor may recommend that you take Uptravi only once daily.

If you have poor vision or any visual impairment, get help from another person when taking Uptravi during the titration period (process of gradually increasing your dose).

The dosage and treatment regimen will be determined by the doctor only.

Finding the right dose for you

At the start of treatment, you will take the lowest dose: one 200 microgram tablet **in the morning and another 200 microgram tablet in the evening, about 12 hours apart.** It is recommended to initiate treatment in the evening.

Your doctor will instruct you to gradually increase your dose, this process is called titration and it lets your body adjust to the new 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 microgram in the morning and 1,600 microgram in the evening.

The first pack of tablets you receive will contain the light-yellow 200 microgram tablets.

Your doctor will tell you to increase your dose in steps, usually every week, but the interval between dose increases could be longer.

With each step, you will add one 200 microgram tablet to your morning dose and another 200 microgram tablet to your evening dose. **The first intake of the increased dose is recommended to 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 of the medicine (Uptravi 200 microgram, 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 tablet in the evening, instead of multiple tablets each time.**

For a full description of the Uptravi tablets, including color and marking, please

see section 6 “Additional information” in this leaflet.
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 food as you might tolerate your medicine better.
- Swallow the tablets whole with a glass of water.

Splitting/crushing/chewing
The tablet coating provides protection. 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 the 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 the medicine 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 the medicine 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 further questions regarding use of the medicine, consult 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 gradually increased, but also later, after taking the same dose (your maintenance dose) for a long time.

If you experience any of the side effects below, that you cannot tolerate or cannot be treated, contact your doctor as the dose you are taking may be too high and may need to be reduced:
Headache, diarrhea, nausea, vomiting, jaw pain, muscle pain, leg pain, joint pain or reddening of the face.

Very common side effects (may occur in more than 1 user in 10)
- 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 occur in up to 1 user in 10)
- Anaemia (low red blood cell levels)
- Hyperthyroidism (overactive thyroid gland)
- Reduced appetite
- Weight loss
- Hypotension (low blood pressure)
- Stomach pain, including indigestion
- 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 occur in up to 1 in 100 users)
- 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 by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health home page (www.health.gov.il), that directs you to the online form for reporting side effects, or via the following link:
https://sideeffects.health.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 the 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, propyleneglycol, titanium dioxide, iron oxide red and/or iron oxide yellow and/or iron oxide black and carnauba wax.

What the medicine looks like and the contents of the package

Uptravi 200 microgram:

Each package contains 60 or 140 tablets. The tablets are packed in blisters.

Uptravi 400 microgram, 600 microgram, 800 microgram, 1,000 microgram, 1,200 microgram, 1,400 microgram, 1,600 microgram:

Each package contains 60 tablets. The tablets are packed in blisters.

Uptravi 200 microgram: round, light yellow, film-coated tablets imprinted with “2” on one side.

Uptravi 400 microgram: round, red, film-coated tablets imprinted with “4” on one side.

Uptravi 600 microgram: round, light violet, film-coated tablets imprinted with “6” on one side.

Uptravi 800 microgram: round, green, film-coated tablets imprinted with “8” on one side.

Uptravi 1,000 microgram: round, orange, film-coated tablets imprinted with “10” on one side.

Uptravi 1,200 microgram: round, dark violet, film-coated tablets imprinted with “12” on one side.

Uptravi 1,400 microgram: round, dark yellow, film-coated tablets imprinted with “14” on one side.

Uptravi 1,600 microgram: round, brown, film-coated tablets imprinted with “16” on one side.

Manufacturer: Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, 4123 Allschwil, Switzerland

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

Drug registration number of the medicine in the National Drug Registry of the Ministry of Health:

Uptravi 200 microgram: 158 07 34938 00

Uptravi 400 microgram: 158 08 34939 00
Uptravi 600 microgram: 158 09 34940 00
Uptravi 800 microgram: 158 10 34941 00
Uptravi 1,000 microgram: 158 11 34942 00
Uptravi 1,200 microgram: 158 12 34943 00
Uptravi 1,400 microgram: 158 13 34944 00
Uptravi 1,600 microgram: 158 14 34945 00

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