PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed according to a physician's prescription only

Volibris 5 mg film-coated tablets

Each tablet contains:

Ambrisentan 5 mg

Volibris 10 mg film-coated tablets

Each tablet contains:

Ambrisentan 10 mg

For a list of inactive and allergenic ingredients in the medicine, see section 2 – "Important information about some of the ingredients of the medicine" and section 6 – "Additional information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the physician or the pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

Volibris patient safety information card

In addition to the leaflet, Volibris has a patient safety information card regarding potential harm to the fetus and potential liver injury. This card contains important safety information that you must know and act upon before starting and during treatment with Volibris. Read the patient safety information card and the patient leaflet before starting to use the preparation. Keep the card and the leaflet for further reading if necessary.

Do not take Volibris if you are pregnant since the use of this medicine may harm the fetus (see section 2 "Do not use the medicine", section 2 "Pregnancy" and "Breast-feeding").
If you are a woman of child-bearing age who may become pregnant, a pregnancy test should be performed before starting treatment with Volibris and routinely each month while you are taking this medicine, and a month after stopping the treatment. Ensure a negative result at each pregnancy test.
You must use a reliable form of birth control (contraception) during the treatment with Volibris, and for an additional one month after stopping the treatment (see section 2 "Pregnancy").

1. WHAT IS THE MEDICINE INTENDED FOR?

Volibris is used to treat pulmonary arterial hypertension (PAH) in adults, including in combination treatment with tadalafil.

Therapeutic group:
Endothelin receptor antagonist.

Volibris contains the active substance ambrisentan. It belongs to a group of medicines called other antihypertensives (used to treat high blood pressure).

Pulmonary arterial hypertension (PAH) is high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. In people with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy and short of breath.

Volibris widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure and relieves the symptoms.

2. BEFORE USING THE MEDICINE

Do not use the medicine:
- if you are **sensitive (allergic)** to ambrisentan, soya, or any of the additional ingredients contained in the medicine (listed in section 6)
- if you are **pregnant**, if you are **planning to become pregnant**, or if you **could become pregnant** because you are not using a reliable birth control (contraception). Please read the information under section 2 – "Pregnancy"
- if you are **breast-feeding**. Read the information under section 2 –"Breast-feeding"
- if you have **liver disease**. Talk to the physician, who will decide whether this medicine is suitable for you
- if you have **scarring of the lungs**, of unknown cause (idiopathic pulmonary fibrosis).

Special warnings regarding the use of the medicine
Before treatment with Volibris, talk to your physician if you have:
- liver problems
- anaemia (a reduced number of red blood cells)
- swelling in the hands, ankles or feet caused by fluid (*peripheral oedema*)
- a lung disease where the veins in the lungs are blocked (*pulmonary veno-occlusive disease*).

→ **The physician will decide** whether Volibris is suitable for you.

You will need regular blood tests
Before you start taking Volibris, and at regular intervals while you are taking the medicine, the physician will take blood tests to check:
- whether you have anaemia
- whether your liver is functioning properly.

→ It is important that you undergo these regular blood tests for as long as you are taking Volibris.

Signs that your liver may not be functioning properly include:
- loss of appetite
- nausea
- vomiting
- high temperature (fever)
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin.

If you notice any of these signs:

→ **Tell the physician immediately.**

Children and adolescents
Volibris is not intended for use in children and adolescents aged under 18 years.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the physician or the pharmacist.

If you start taking cyclosporine A (a medicine used after transplant or to treat psoriasis), the physician may need to adjust your dose of Volibris.

If you are taking rifampicin (an antibiotic used to treat serious infections), the physician will monitor you when you first start taking Volibris.

If you are taking other medicines to treat pulmonary arterial hypertension (PAH) (e.g., iloprost, epoprostenol, sildenafil), the physician may need to monitor you.

→ **Tell the physician or pharmacist** if you are taking any of these medicines.

Pregnancy

Volibris may cause harm to the fetus of a pregnancy that began before, during or soon after treatment with the medicine.

If you are a woman of child-bearing age, **the physician will ask you to take a pregnancy test** before you start taking Volibris and regularly each month while you are taking this medicine, and a month after ending the treatment. Please ensure a negative result at each pregnancy test.

→ **Do not take Volibris if you are pregnant or planning to become pregnant.**
You must use a reliable form of birth control (contraception) during the treatment with Volibris, and for an additional one month after ending the treatment.

The physician or gynecologist will guide you about reliable contraceptive methods while you are taking Volibris.

The physician will advise you on one highly effective contraceptive method, for example: an intrauterine device (IUD) or tubal sterilization or the use of a combination of methods (such as a hormonal contraceptive method and a barrier contraceptive method [for example: a diaphragm, a contraceptive sponge or that your partner should also use a condom] or two barrier contraceptive methods).

If vasectomy is the chosen contraceptive method for your partner, it is mandatory to use a hormonal or barrier contraceptive method in parallel.

Consult with the physician regarding the use of two contraception methods.

→ **Tell the physician immediately** if you got pregnant while you are taking Volibris or if you are planning to become pregnant in the near future or think you may be pregnant.

Breast-feeding
It is not known if the active substance of Volibris can pass into breast milk.

→ **Do not breast-feed while you are taking Volibris.** Talk to the physician about this.

Fertility
If you are a man taking Volibris, it is possible that this medicine may lower your sperm count. Talk to the physician if you have any questions or concerns about this.

Driving and using machines
Volibris may cause side effects, such as low blood pressure, dizziness, tiredness (see section 4), that may affect your ability to drive or use machines. The symptoms of your condition can also make you less fit to drive or use machines.

→ **Do not drive or use machines if you are feeling unwell.**

Important information about some of the ingredients of the medicine
Volibris contains lactose
Volibris tablets contain small amounts of a sugar called lactose. If you have been told by the physician that you have an intolerance to some sugars:

→ **Contact the physician** before taking the medicine.

Volibris contains lecithin derived from soya
If you are allergic to soya, do not use this medicine (see section 2 "Do not use the medicine").

Volibris tablets contain a colouring called Allura red AC aluminium lake (E129)
which can cause allergic reactions (see section 4).

Volibris contains sodium
This medicine contains less than 1 mmol sodium (23 mg) in each tablet and is therefore considered "sodium-free".

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the physician's instructions. You should check with the physician or the pharmacist if you are unsure regarding the dosage and treatment regimen of the preparation.

How much Volibris to take
The dosage and treatment regimen will be determined by the physician only.
The usual dosage of Volibris is generally one 5 mg tablet, once a day. The physician may decide to increase your dose to 10 mg, once a day.

If you take cyclosporine A, do not take more than one 5 mg tablet of Volibris, once a day.

Do not exceed the recommended dose.

How to take Volibris
It is best to take your tablet at the same time each day. Swallow the tablet whole, with a glass of water. Do not split, crush or chew the tablet. You can take Volibris with or without food.

If you accidentally have taken a higher dosage
If you have taken too many tablets, you may be more likely to have side effects, such as headache, flushing, dizziness, nausea, or low blood pressure that could cause light-headedness.

→ **Ask the physician or pharmacist for advice** if you take more tablets than prescribed.

If you took an overdose or if a child has accidentally swallowed the medicine, refer immediately to a physician or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine
If you forgot a dose of Volibris, take the tablet as soon as you remember, then carry on as before.

→ **Do not take a double dose at the same time to make up for a forgotten dose.**

If you stop taking the medicine
Volibris is a treatment that you will need to keep on taking to control your pulmonary arterial hypertension (PAH).

→ **Do not stop taking Volibris unless you have agreed to this with the physician.**

Adhere to the treatment regimen as recommended by the physician.

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 other questions regarding the use of the medicine, consult the physician or the pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Volibris may cause side effects in some of the users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

Serious side effects
Tell the physician if you get any of these:

Allergic reactions
This is a common side effect that may affect **up to 1 in 10** people. You may notice:
- a rash or itching and swelling (usually of the face, lips, tongue or throat), which may cause difficulty in breathing or swallowing.

Swelling (oedema), especially of the ankles and feet
This is a very common side effect that may affect **more than 1 in 10** people.

Heart failure
This is due to the heart not pumping out enough blood. This is a common side effect that may affect **up to 1 in 10** people. Symptoms include:
- shortness of breath
- extreme tiredness
- swelling in the ankles and legs.

Reduced number of red blood cells (anaemia)
This is a very common side effect that may affect **more than 1 in 10** people.
Sometimes this requires a blood transfusion. Symptoms include:
- tiredness and weakness
- shortness of breath
- generally feeling unwell.

Low blood pressure (hypotension)
This is a common side effect that may affect **up to 1 in 10** people. Symptoms include:
- light-headedness.

→ **Tell the physician straight away** if you get these effects or if they happen suddenly after taking Volibris.

It is important to have regular blood tests, to check for anaemia and that your liver is functioning properly. **Make sure that you have also read the information in section 2** under "You will need regular blood tests" and "Signs that your liver may not be functioning properly".

Other side effects
Very common side effects (may affect **more than 1 in 10** people):
- headache
- dizziness
- palpitations (fast or irregular heart beats)
- shortness of breath getting worse shortly after starting treatment with Volibris
- a runny or blocked nose, congestion or pain in the sinuses
- nausea
- diarrhoea
- feeling tired.

In combination with tadalafil (another PAH medicine)
In addition to the above:
- flushing (redness of the skin)
- vomiting
- chest pain/discomfort.

Common side effects (may affect **up to 1 in 10** people):
- blurry or other changes to vision
- fainting
- abnormal blood test results for liver function
- a runny nose
- constipation
- pain in your stomach (abdomen)
- chest pain or discomfort
- flushing (redness of the skin)
- vomiting
- feeling weak
- nose bleed
- rash.

In combination with tadalafil
In addition to the above (except abnormal blood test results for liver function):
- ringing in the ears (tinnitus).

Uncommon side effects (may affect **up to 1 in 100** people):
- liver injury
- inflammation of the liver caused by the body's own defences (*autoimmune hepatitis*).

In combination with tadalafil
- sudden loss of hearing.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the physician.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il), that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il/

5. HOW TO STORE THE MEDICINE?

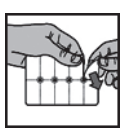
- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from the physician.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- There are no special storage instructions. It is recommended to store at room temperature.
- Do not throw away any medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. ADDITIONAL INFORMATION

- **In addition to the active ingredient the medicine also contains:**
  Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate, Polyvinyl alcohol, Talc (E553b), Titanium dioxide (E171), Macrogol/Polyethylene glycol 3350, Lecithin (soya) (E322) and Allura red AC aluminium lake (E129).
- **What Volibris looks like and the contents of the package**
  Volibris 5 mg is a pale pink, square, 6.6 mm, convex, film-coated tablet engraved with 'GS' on one face and 'K2C' on the other.
  Volibris 10 mg is a deep pink, oval, 9.8x4.9 mm, convex, film-coated tablet engraved with 'GS' on one face and 'KE3' on the other.
  Volibris is supplied as 5 mg and 10 mg film-coated tablets in unit dose blister packs of 30 tablets.
- **License Holder:** GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.
- **Manufacturer:** Patheon Inc., Mississauga, Canada.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Volibris 5 mg: 140-08-31883
  Volibris 10 mg: 140-09-31884

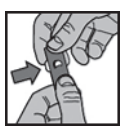
Taking out a tablet from a blister pack
These tablets come in special packaging to prevent children removing them.

1. **Separate one tablet:** tear along the cutting lines to separate one 'pocket' from the strip.



2. **Peel back the outer layer:** starting at the coloured corner, lift and peel over the pocket.

3. **Push out the tablet:** gently push one end of the tablet through the foil layer.



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