Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Tibsovo

Film-coated tablets

Active ingredient and quantity
Each film-coated tablet contains ivosidenib 250 mg.

Inactive ingredients and allergens – see section 6 **'Additional information'**. See also '**Important information about some of this medicine's ingredients'** in section 2.

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

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

In addition to the patient information leaflet, Tibsovo also has a patient safety information card. This card contains important safety information that you need to know and that you should follow before starting and during treatment with Tibsovo. Carefully read the patient safety information card and patient information leaflet before using this medicine. Keep the card in case you need to read it again.

1. What is this medicine intended for?

Tibsovo in combination with azacitidine is intended for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH-1) R132 mutation, who are not eligible to receive standard induction chemotherapy.

Tibsovo monotherapy is intended for the treatment of adult patients with locally advanced or metastatic bile duct cancer (cholangiocarcinoma) with an IDH-1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

Therapeutic group: Antineoplastics, miscellaneous antineoplastics.

Tibsovo contains the active ingredient ivosidenib. It is a medicine used to treat specific cancers that contain a mutated (changed) gene that makes a protein called isocitrate dehydrogenase-1 (IDH-1). This protein plays an important role in energy production in the body's cells. When the IDH1 gene is mutated, the IDH1 protein is changed and does not function properly, and this leads to changes in the cell which can lead to the development of cancer.
Tibsovo blocks the IDH1 proteins that have mutated and helps to slow or stop the cancer from growing.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient (ivosidenib) or to any of the other ingredients in this medicine (see section 6 - **'Additional information'**).
- If you are taking medicines that are known to reduce the levels of Tibsovo such as dabigatran (a medicine used for preventing the formation of blood clots), St. John's wort (Hypericum, a herbal remedy used to treat depression and anxiety), rifampicin (a medicine used for bacterial infections) or certain medicines used to treat epilepsy (e.g. carbamazepine, phenobarbital, phenytoin). (See '**Interactions with other medicines**' in section 2.)
- If you have a heart problem that you were born with called 'long QTc syndrome'.
- If you have a family history of sudden death or an irregular or abnormal heartbeat in the lower chambers of the heart.
- If you have a severe abnormality of electrical activity of the heart that affects its rhythm called 'QTc prolongation'.

Special warnings about using this medicine

Differentiation syndrome in patients with acute myeloid leukaemia (AML):
Tibsovo can cause a serious condition known as differentiation syndrome in patients with AML. This is a condition that affects your blood cells and may be life-threatening if not treated.

Seek urgent medical attention if you have any of the following symptoms after taking Tibsovo:

- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or light-headedness
- rapid weight gain
- swelling of your arms or legs

These may be signs of differentiation syndrome.
The pack contains a patient safety information card to carry with you at all times. The card contains important information for you and your healthcare professionals about what to do if you have any of the symptoms of differentiation syndrome (see section 4, 'Side effects').

QTc interval prolongation
Tibsovo can cause a serious condition known as QTc interval prolongation which can cause irregular heartbeats and life-threatening arrhythmias (abnormal electrical activity of the heart that affects its rhythm). Your doctor will check the electrical activity of your heart before and during treatment with Tibsovo (see '**Tests and follow-up**' in section 2). Seek urgent medical attention if you feel dizzy, light-headed, palpitations or faint after taking Tibsovo (see section 4, **'Side effects'**).

During treatment, tell your doctors you are taking Tibsovo before starting treatment with any new medicine as these may increase the risk of an abnormal heart rhythm.

If you have any of the serious side effects described above, your doctor may give you other medicines to treat them or may instruct you to stop treatment with Tibsovo temporarily or stop taking it altogether.

Tell your doctor before starting treatment if:
- you have heart problems or abnormal electrolyte levels (such as sodium, potassium, calcium or magnesium).
- you are taking certain medicines that can affect the heart (e.g. medicines used to prevent arrhythmias (anti-arrhythmics), certain antibiotics, certain antifungals and medicines used to prevent nausea and vomiting - see '**Interactions with other medicines**' in section 2).
- you have kidney problems.
- you have liver problems.

Tests and follow-up
Your doctor will closely monitor your condition before and during treatment with Tibsovo. You will need to have regular electrocardiograms (ECGs - a recording of the electrical activity of your heart) to monitor your heartbeat. You will be referred for an ECG before starting treatment with Tibsovo, once a week for the first three weeks of treatment, and then monthly thereafter. Additional ECGs may be performed as instructed by your doctor. If you start taking certain medicines that can affect your heart, your doctor will refer you for an ECG before starting and during treatment with the new medicine as needed.
You will also have a blood test before starting treatment with Tibsovo and then at least once weekly during the first month, once every two weeks during the second month, and at every medical checkup throughout the treatment period, according to clinical need.
If necessary, your doctor may reduce the dose of the medicine, stop your treatment temporarily or stop it altogether.

Children and adolescents
Tibsovo is intended for administration in adults aged 18 and up. Do not give this medicine to children and adolescents under 18 years old because there is no information about its safety and effectiveness in this age group.

Interactions with other medicines
If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. This is because they may reduce the effectiveness of Tibsovo or increase the risk of side effects, or Tibsovo may affect the way they work.

- If you are taking medicines that accelerate the clearance of Tibsovo such as dabigatran (a medicine used for preventing the formation of blood clots), St. John's wort (a herbal remedy used to treat depression and anxiety), rifampicin, carbamazepine, phenobarbital, phenytoin. See section 2, '**Do not use this medicine if**'.
- antibiotics – used to treat bacterial infections (e.g. erythromycin, clarithromycin, benzylpenicillin, ciprofloxacin, levofloxacin).

- warfarin (used to prevent blood clots).
- medicines used to treat fungal infections (e.g. itraconazole, ketoconazole, fluconazole, isavuconazole, posaconazole, voriconazole).
- medicines that affect your heartbeat (anti-arrhythmics) (e.g. diltiazem, verapamil, quinidine).
- medicines used to treat nausea and vomiting (anti-emetics) (e.g. aprepitant, ondansetron, tropisetron, granisetron).
- medicines used after organ transplants (immunosuppressants) (e.g. ciclosporin, everolimus, sirolimus, tacrolimus).
- medicines for the treatment of HIV (e.g. raltegravir, ritonavir).
- alfentanil (used for anaesthesia in surgery).
- fentanyl (used to treat severe pain).
- pimozide (used to treat schizophrenia).
- medicines used to treat cancer (e.g. cyclophosphamide, ifosfamide, paclitaxel).
- methadone (used to treat morphine or heroin addiction, or severe pain).
- medicines for treatment of type 2 diabetes (e.g. pioglitazone, repaglinide).
- omeprazole (used to treat stomach ulcers and acid reflux).
- furosemide (used to treat fluid build-up in the body - oedema).
- medicines used to treat high cholesterol, called statins (e.g. atorvastatin, pravastatin, rosuvastatin).
- lamotrigine (to treat epilepsy).
- Hormonal contraception - Tibsovo may reduce the effectiveness of hormonal contraceptives. (See section 2, **'Pregnancy, breast-feeding and fertility'**).

Using this medicine and food
Do not have grapefruit or grapefruit juice during treatment with Tibsovo as it can affect how this medicine works.
Take the tablets without food. Do not eat for 2 hours before taking the tablets through 1 hour after taking them.

Pregnancy, breast-feeding and fertility
Pregnancy
Tibsovo is not recommended for use during pregnancy as it may harm the unborn baby. Women of child-bearing age should have a pregnancy test prior to starting treatment with Tibsovo and should avoid becoming pregnant during the treatment period.

If you are pregnant, think you may be pregnant or are planning to become pregnant, consult your doctor before taking this medicine. Contact your doctor immediately if you become pregnant during treatment with Tibsovo.

Contraception
Women who might become pregnant or men with partners who might become pregnant must use effective contraception to avoid pregnancy during treatment with Tibsovo and for at least one month after taking the last dose.

Tibsovo may reduce the effectiveness of hormonal contraceptives. Couples who use a hormonal contraceptive (e.g. birth control pills, contraceptive patches or implants), must also use a barrier method (e.g. condoms or a diaphragm) to prevent pregnancy. Talk to your doctor about the right contraceptive for you.

Breast-feeding
It is not known whether Tibsovo passes into breast milk. Do not breast-feed your baby during treatment with Tibsovo and for at least one month after taking the last dose. A risk to the breast-feeding infant cannot be ruled out.

Fertility
It is not known whether Tibsovo affects fertility. If you are concerned about your fertility during treatment with Tibsovo, discuss this with your doctor.

Driving and using machines
Tibsovo has minor influence on your ability to drive and operate machines. Tiredness and dizziness were reported in some of the patients who took this medicine. Consult your doctor regarding your ability to drive and operate machines.

Important information about some of this medicine's ingredients
Tibsovo contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially sodium-free.

3. How to use this medicine?
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually 2 tablets (500 mg ivosidenib) to be taken once daily at a set time.

Your doctor may instruct you to take 1 tablet (250 mg ivosidenib) if you are taking some other medicines or to help you better cope with some possible side effects.

Do not exceed the recommended dose.

- Take the tablets without food. Do not eat for 2 hours before taking the tablets through 1 hour after taking them.
- Swallow the tablets whole with water.
- **Do not** swallow the desiccant found in the bottle. The desiccant helps protect the tablets from moisture. (see section 5, **'How to store this medicine?'** and section 6, **'Additional information'**).
- If you vomit after taking your usual dose, do not take additional tablets. Take your next dose as usual the following day.

If you have accidentally taken a higher dose
If you have taken an overdose or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine
If you missed a dose or did not take it at the usual time, take the tablets as soon as possible unless there are less than 12 hours until the next dose. Do not take two doses within a time frame of less than 12 hours. Take the next dose as usual the following day.

Duration of the treatment with Tibsovo
Adhere to the treatment as recommended by your doctor. Even if your health improves, do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>
As with any medicine, using Tibsovo may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

Serious side effects
Seek urgent medical attention if you experience any of the following side effects: The symptoms listed below could be due to a serious medical condition known as **differentiation syndrome** or **QTc interval prolongation**, which can both be life-threatening.

Differentiation syndrome
Contact your doctor straight away if you have any of the following symptoms:
- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or light-headedness
- rapid weight gain
- swelling of your arms or legs

Some or all of these symptoms may be signs of a medical condition called differentiation syndrome (may affect more than 1 in 10 patients).
Differentiation syndrome in patients with AML appeared up to 46 days after starting treatment with Tibsovo.

Heart rhythm disorders (QTc interval prolongation)
Contact your doctor straight away if you experience a change in your heartbeat, or if you feel dizzy, light-headed or faint after taking Tibsovo. These may be signs of a heart problem called QT prolongation (may appear in more than 1 in 10 patients).

Other side effects
Tell your doctor if you notice any of the following side effects:

For patients with acute myeloid leukaemia (AML)
Very common side effects (appear in more than one in ten users)
- vomiting.
- neutropenia (low levels of neutrophils, a type of white blood cell that fights infections).
- thrombocytopenia (low levels of blood platelets which can lead to bleeding and bruising).
- leukocytosis (high levels of white blood cells).
- insomnia (difficulty sleeping).
- pain in extremity, joint pain.
- headache.
- dizziness.
- back pain.

Common side effects (effects that appear in 1-10 in 100 users)
- pain in your mouth or throat.
- peripheral neuropathy (nerve damage in arms and legs causing pain or numbness, sense of burning and tingling).
- leukopenia (low levels of white blood cells).

For patients with bile duct cancer
Very common side effects (appear in more than one in ten users)
- fatigue.
- nausea.
- abdominal pain.
- diarrhoea.
- decreased appetite.
- ascites (a build-up of fluid in the abdomen).
- vomiting.
- anaemia (low levels of red blood cells).
- headache.
- changes in results of liver function tests (aspartate aminotransferase increased).
- peripheral neuropathy (nerve damage in arms and legs causing pain or numbness, sense of burning and tingling).
- rash.
- blood bilirubin (a breakdown product of red blood cells) levels increased, which can cause yellowing of the skin and eyes.

Common side effects (effects that appear in 1-10 in 100 users)
- white blood cell count decreased.
- platelet count decreased.
- changes in results of liver function tests (alanine aminotransferase increased).
- falls.
- hyperbilirubinemia (high levels of blood bilirubin).
- jaundice cholestatic (build-up of bile causing yellowing of the skin or eyes).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.
You can report side effects to the Ministry of Health by following the 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il) which opens an online form for reporting side effects, or you can also use this link: https://sideeffects.health.gov.il.

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by your doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

- No special storage conditions. Storage at room temperature is recommended.
- Keep the bottle tightly closed in order to protect from moisture.
- Keep the desiccant inside the bottle (see section 6, **'Additional information'**).
- After opening for the first time, it can be used for 30 days and no later than the expiry date that appears on the package and when stored below 30°C.

Do not throw away medicine via wastewater or household waste. Ask the pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredients, this medicine also contains:
Tablet core:
hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, colloidal silica anhydrous, magnesium stearate, sodium lauryl sulfate.
Tablet coating:
hypromellose, titanium dioxide, lactose monohydrate, triacetin, indigo carmine aluminium lake (FD&C Blue #2).

What the medicine looks like and contents of the pack:
The film-coated tablets are blue, oval shaped, with "IVO" embossed on one side and "250" on the other side.

Tibsovo tablets are packaged in a plastic bottle with child-resistant cap. The bottle contains 60 film-coated tablets and a desiccant. **Do not** remove the desiccant from the bottle. **Do not** swallow the desiccant.

Registration holder's name and address
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Registration number of the medicine in the Ministry of Health's National Drug Registry 179-35-38216-99