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

This medicine is dispensed with a doctor's prescription only

VENCLEXTA® 10 mg TABLETS
VENCLEXTA® 50 mg TABLETS
VENCLEXTA® 100 mg TABLETS
Film-coated Tablets

The active ingredient and its quantity:

Each Venclexta 10 mg tablet contains 10 mg venetoclax
Each Venclexta 50 mg tablet contains 50 mg venetoclax
Each Venclexta 100 mg tablet contains 100 mg venetoclax

For the list of inactive ingredients, please see section 6 "Further Information" in this leaflet.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for your ailment/ for you. Do not pass it on to others. It may harm them even if it seems to you that their ailment/medical condition is similar.

In addition to the leaflet, the medicine Venclexta has a 'Quick Start Guide' for CLL/SLL patients. This guide includes important guidelines regarding the start of the treatment, which you should know. Read the 'Quick Start Guide' that comes with the 'CLL/SLL Starting Pack', before starting treatment with the medicine. Keep the guide for later reference if needed.

1. WHAT IS THE MEDICINE INTENDED FOR?

Venclexta, as monotherapy or in combination with rituximab, is intended for the treatment of patients with chronic lymphocytic leukemia (CLL) or patients with small lymphocytic lymphoma (SLL), who have received at least one prior treatment.
Venclexta, in combination with obinutuzumab, is intended for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) or patients with small lymphocytic lymphoma (SLL).
Venclexta, in combination with hypomethylating agents or in combination with low-dose cytarabine, is intended for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are not eligible for intense chemotherapy.

Therapeutic group: Antineoplastic, BCL-2 inhibitor.

Venclexta works by inhibiting a protein in the body called "BCL-2". This is a protein that helps cancer cells survive. Blocking this protein helps to kill and lower the number of cancer cells. It also slows down the worsening of the disease.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:
- You are sensitive (allergic) to the active substance or any of the other ingredients of this medicine (for the list of inactive ingredients, see section 6).
- You are taking a herbal medicine called *Hypericum* (St. John's wort), used for depression.
- You have CLL or SLL and are taking a medicine that is a strong CYP3A enzyme inhibitor. **When starting treatment and during the ramp-up stage** (generally over 5 weeks) because the risk of suffering from a dangerous syndrome called tumour lysis syndrome (TLS) will increase when taking Venclexta with these medicines.

It is important that you tell your doctor, pharmacist, or nurse about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Do not start new medicines during treatment with Venclexta without first consulting with your doctor.

Special warnings regarding use of the medicine:

Before beginning treatment with Venclexta, tell the doctor if:
- you have any kidney problems, as your risk for a side effect called tumour lysis syndrome (TLS) may increase
- you have liver problems
- you have problems with your body salts or electrolytes, such as potassium, phosphorus, or calcium
- you have a history of high uric acid levels in your blood or gout
- you think you may have an infection or have had a long-lasting or repeated infection
- you are scheduled to receive a vaccine. You should not receive a "live vaccine" before, during, or after treatment with Venclexta without first consulting the attending doctor
- you are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist, or nurse before taking this medicine.

Tumour Lysis Syndrome (TLS)
Some people may develop unusual levels of some body salts (such as potassium and uric acid) in the blood caused by the fast breakdown of cancer cells during treatment. This is called TLS (tumour lysis syndrome).
TLS can cause kidney failure, the need for dialysis treatment, abnormal heartbeat, seizures and may lead to death. The risk for TLS is in the first few weeks of treatment with Venclexta.
Your doctor will do blood tests to evaluate the risk of getting TLS before you start taking Venclexta.
Your doctor may also give you other medicines before starting and during treatment with Venclexta to help reduce your risk of TLS.
Drinking plenty of water, at least 1.5 to 2 liters (approx. 6 to 8 glasses) each day, starting two days before taking the first dose, on the day you start the treatment and each time the dose is increased, helps to remove cancer cell breakdown products from your body through urine, and may reduce your risk of TLS (see section 3).
Tell your doctor, pharmacist or nurse immediately if you get any of the symptoms of TLS listed in section 4.
If you are at risk of TLS, you may be treated in the hospital so that you can be given fluids into the vein if needed, have blood tests done more often and be checked for side effects. This is to see if you can continue to take Venclexta safely.
Your doctor may adjust the dose or stop your treatment due to side effects.
When restarting treatment with Venclexta after stopping for one week or longer, your doctor may again check for your risk of TLS and change your dose.

Children and adolescents
There is no information on the safety and efficacy of use of this preparation in children and adolescents.

Drug interactions
If you are taking, have recently taken or might take any other medicines, including nonprescription medicines, herbal medicines and nutritional supplements, tell your doctor or pharmacist.
This is because Venclexta may affect the way some medicines work. Also, some medicines can affect the way Venclexta works and cause serious side effects. Tell your doctor or pharmacist if you take any of the following medicines as they can increase or decrease the amount of Venclexta in your blood:
- medicines for fungal infections – ketoconazole, itraconazole, fluconazole, voriconazole, or posaconazole
- antibiotics to treat bacterial infections – clarithromycin, ciprofloxacin, erythromycin, nafcillin or rifampicin
- medicines to prevent seizures or to treat epilepsy – carbamazepine, phenytoin
- medicines for HIV infection – efavirenz, etravirine, ritonavir
- medicines to treat raised blood pressure or angina – verapamil, diltiazem, captopril, carvedilol, felodipine, ranolazine
- a medicine used to treat a lung condition called pulmonary arterial hypertension – bosentan
- a medicine to treat sleep disorder (narcolepsy) known as modafinil
- a herbal medicine known as *Hypericum* (St. John's wort)
- a medicine to treat heart rhythm disturbances - dronedarone, amiodarone, quinidine
- a medicine to prevent blood clots – ticagrelor
- a medicine used to prevent organ rejection - cyclosporine
- antioxidant supplement - quercetin

Your doctor may change your dose of Venclexta.
Tell your doctor if you take any of the following medicines as Venclexta may affect how they work:
- a medicine that prevents blood clots - warfarin
- a medicine used to treat heart problems known as digoxin
- a medicine for cancer known as everolimus
- a medicine used to prevent organ rejection known as sirolimus

Use of the medicine and food
Do not eat grapefruit products, Seville oranges (bitter oranges often used in marmalades), or starfruit (carambola) while you are taking Venclexta – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because they can increase the amount of Venclexta in your blood.

Pregnancy
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor, pharmacist, or nurse before taking this medicine.
- Venclexta may harm your unborn baby.

Contraception
- Before you start treatment with Venclexta, your doctor will ask you to do a pregnancy test to rule out pregnancy. Women who are able to become pregnant should use highly effective birth control during treatment and for a period of 30 days after the last dose of Venclexta, to avoid becoming pregnant.
- Tell your doctor immediately if you become pregnant while you are taking this medicine.

Breastfeeding
If you are breastfeeding or plan to breastfeed, inform your doctor, pharmacist or nurse before taking this medicine. It is not known whether the active ingredient in Venclexta passes into breast milk. Do not breastfeed during the treatment and for one week after the last dose of Venclexta.

Fertility
Venclexta may cause male infertility (low or no sperm count). This may affect your ability to father a child. Ask your doctor for advice before starting treatment with Venclexta.

Driving and using machines
You may feel tired after taking Venclexta, which may affect your ability to drive or use tools or machines.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use this preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation. The dosage and treatment regimen will be determined by the doctor only.
Your dose may need to be adjusted for side effects or for other considerations.
You may need to take Venclexta at a hospital to be monitored for TLS.

For CLL or SLL patients

The usual dose is:
You will begin treatment with Venclexta at a low dose for 1 week. Your doctor will gradually increase the dose over the next 5 weeks to the full standard dose. Read the Quick Start Guide that comes with Venclexta before your first dose.
- the starting dose is 20 mg (two 10 mg tablets), once a day, for 7 days.
- the dose will be increased to 50 mg (one 50 mg tablet), once a day, for 7 days.
- the dose will be increased to 100 mg (one 100 mg tablet), once a day, for 7 days.
- the dose will be increased to 200 mg (two 100 mg tablets), once a day, for 7 days.
- the dose will be increased to 400 mg (four 100 mg tablets), once a day, for 7 days.
  - When you are taking Venclexta only, you will continue taking a dosage of 400 mg per day, which is the recommended dosage, for as long as necessary.
  - When you are taking Venclexta in combination with rituximab, you will receive a dosage of 400 mg per day, for 24 months.
  - When you are taking Venclexta in combination with obinutuzumab, you will receive a dosage of 400 mg per day, for 12 months.

For AML patients in combination with azacitidine or decitabine

The usual dose is:
You will begin treatment with Venclexta at a low dose. Your doctor will gradually increase the dosage over the subsequent 3 days until the full dosage is reached. Follow your doctor's instructions carefully while increasing to the full dose.
- The starting dosage is 100 mg (one 100 mg tablet), once a day, for 1 day.
- The dosage will be increased to 200 mg (two 100 mg tablets), once a day, for 1 day.
- The dosage will be increased to 400 mg (four 100 mg tablets), once a day. You will continue taking a dosage of 400 mg per day, which is the recommended dosage, for as long as necessary.

For AML patients with low-dose cytarabine

The usual dose is:
You will begin treatment with Venclexta at a low dose. Your doctor will gradually increase the dosage over the subsequent 4 days until the full dosage is reached. Follow your doctor's instructions carefully while increasing to the full dose.
- The starting dosage is 100 mg (one 100 mg tablet), once a day, for 1 day.
- The dosage will be increased to 200 mg (two 100 mg tablets), once a day, for 1 day.
- The dosage will be increased to 400 mg (four 100 mg tablets), once a day, for 1 day.
- The dosage will be increased to 600 mg (six 100 mg tablets), once a day. You will continue taking a dosage of 600 mg per day, which is the recommended dosage, for as long as necessary.

Do not exceed the recommended dose.

How to take Venclexta
- Take the tablets with a meal at around the same time each day
- Swallow the tablets whole with a glass of water
- Do not chew, crush, or break the tablets

Instructions for getting the tablets out of the blister:
1. Open the tablet wallet.
2. Pull the daily tablet cover (marked with an arrow Δ and with the number of the day).
3. Push down on the tablet.

The tablet will come out from the opposite side of the wallet.

Drink plenty of water
It is very important that you drink plenty of water during the course of treatment with Venclexta, to reduce the risk of tumour lysis syndrome (TLS).
You should start drinking at least 1.5 to 2 liters (approx. 6 to 8 glasses) of water daily, two days before starting treatment with Venclexta. You may include non-alcoholic and non-caffeinated drinks in this amount, but exclude grapefruit, Seville orange, or starfruit (carambola) juices. You should continue to drink at least 1.5 to 2 liters of water (approx. 6-8 glasses) on the day you start Venclexta. Drink the same amount of water (at least 1.5 to 2 liters daily) two days before and on the day that your dose is increased.
If your doctor thinks that you are at risk of TLS, you may be treated in the hospital so that you can be given extra fluids into the vein if needed, have your blood tests more often and be checked for side effects. This is to see if you can continue to take Venclexta safely.

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

If you forget to take Venclexta
- If it is less than 8 hours since the time you usually take your dose, take it as soon as possible.
- If it is more than 8 hours since the time you usually take your dose, do not take the dose that day. Return to your normal dosing schedule the next day.
- If you vomited after taking Venclexta, do not take another dose. Continue with your usual dosing schedule the next day.
- If you are not sure, talk to your doctor, pharmacist or nurse.

Persist with the treatment as recommended by the doctor.

Do not stop taking Venclexta
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.
- **Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.**

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

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

Tumour lysis syndrome (TLS)
(common – may affect up to 1 in 10 people):
Stop taking Venclexta and seek medical attention immediately if you notice any of the symptoms of TLS:
- fever or chills
- feeling or being sick (nausea or vomiting)
- feeling confused
- feeling short of breath
- irregular heartbeat
- dark or cloudy urine
- feeling unusually tired
- muscle pain or uncomfortable joints
- fits or seizures

Low white blood cell count (neutropenia)
(very common – may affect more than 1 in 10 people):
Low white blood cell counts are common during treatment with Venclexta but can be severe. Your doctor will check your blood count during treatment with Venclexta and may pause (temporarily stop) the treatment.

Infection: Death and serious infections such as pneumonia and blood infection (sepsis) have happened during treatment with Venclexta. Your doctor will closely monitor and treat you right away if you have fever or any signs of infection during treatment with Venclexta.

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

In CLL or SLL patients

Very common (may affect more than 1 in 10 people)
- upper respiratory tract infection – signs include runny nose, sore throat or cough
- diarrhoea
- feeling or being sick (nausea or vomiting)
- constipation
- feeling tired
- cough
- muscle or joint pains
- swelling of the arms, legs, hands and feet
- headache
- rash
- fever
- lower respiratory tract inflammation
- abdominal pain
- inflammation of and pain in the mouth, esophageal and intestinal tissues (mucositis)
- dizziness
- shortness of breath
- pneumonia

Blood tests may also show:
- low red blood cell count (anemia)
- low white blood cell count (neutropenia, lymphopenia or leukopenia, in particular)
- increased body salt (electrolytes) levels, including phosphate or potassium
- decreased body salt (electrolytes) levels, including phosphate, calcium or sodium
- low platelet count
- high levels of liver enzymes called aspartate aminotransferase (AST/GOT)
- high blood sugar levels
- low levels of a protein called albumin
- high uric acid levels
- high blood creatinine levels

Common (may affect up to 1 in 10 people)
- fever with a low white blood cell count (neutropenic fever)
- severe infection in the blood (sepsis)
- urinary tract infection

Blood tests may also show:
- increase in body salt (electrolyte) levels, including calcium and magnesium
- decreased body salt (electrolyte) level, called potassium
- low blood sugar levels

In AML patients

Very common (may affect more than 1 in 10 people)
- feeling or being sick (nausea or vomiting)
- diarrhoea
- constipation
- swelling of the arms, legs, hands and feet
- feeling tired
- pneumonia
- fever with a low white blood cell count (neutropenic fever)
- severe infection in the blood (sepsis)
- rash
- bleeding
- shortness of breath
- abdominal pain
- dizziness
- cough
- pain in muscles or back
- low blood pressure
- sore throat and mouth
- fever
- urinary tract infection
- cellulitis
- deficiency in the oxygen that is passed to the body tissues (hypoxia)
- high blood pressure
- device related infection
- reduced appetite

Blood tests may also show:
- low platelet count
- low white blood cell count (in general and neutropenia or lymphopenia in particular)
- low red blood cell count (anemia)
- high blood sugar levels
- reduced body salt (electrolytes) levels, which include calcium, sodium, potassium, inorganic phosphorous, magnesium or bicarbonate
- low levels of a protein called albumin
- high levels of general bilirubin
- high blood creatinine levels

Common (may affect up to 1 in 10 people)
- decreased muscle mass (cachexia)
- body organ dysfunction
- localized infection

If a side effect has occurred, if any of the side effects worsen or if you experience a side effect not mentioned in the leaflet, consult the doctor.

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

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine must 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 unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the carton package. The expiry date refers to the last day of that month.

Storage conditions:
- In the bottle pack, Venclexta tablets can be used for up to 6 weeks after first opening. **Do not** transfer the tablets to a pillbox or other container.
- Store at a temperature below 30°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

What Venclexta contains
In addition to the active ingredient, the medicine also contains:
- The other ingredients in the tablet core are: Copovidone (K value 28), polysorbate 80, colloidal anhydrous silica, anhydrous dibasic calcium phosphate, sodium stearyl fumarate.
- The 10 mg tablet pale yellow film coating contains: Iron oxide yellow (E172), polyvinyl alcohol, titanium dioxide, macrogol 3350, talc.
- The 50 mg tablet beige film coating contains: Iron oxide yellow (E172), iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc.
- The 100 mg tablet pale yellow film coating contains: Iron oxide yellow (E172), polyvinyl alcohol, titanium dioxide, macrogol 3350, talc.

What Venclexta looks like and the contents of the package:
- Venclexta 10 mg film-coated tablet is pale yellow, round, biconvex-shaped, with V on one side and 10 on the other side.
- Venclexta 50 mg film-coated tablet is beige, oblong, biconvex-shaped, with V on one side and 50 on the other side.
- Venclexta 100 mg film-coated tablet is pale yellow, oblong, biconvex-shaped, with V on one side and 100 on the other side.

Venclexta is marketed in the following packs:

Packaging Presentation	Number of Tablets
CLL/SLL Starting Pack	Each pack contains four weekly wallet blister packs: • Week 1 (14 tablets of 10 mg) • Week 2 (7 tablets of 50 mg) • Week 3 (7 tablets of 100 mg) • Week 4 (14 tablets of 100 mg)
10 mg Wallet	14 tablets of 10 mg
50 mg Wallet	7 tablets of 50 mg
10 mg Unit Dose	2 tablets of 10 mg
50 mg Unit Dose	1 tablet of 50 mg
100 mg Unit Dose	1 tablet of 100 mg
100 mg Bottle	120 tablets of 100 mg
100 mg Bottle	180 tablets of 100 mg

Not all pack sizes may be marketed.
- License holder and its address: AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel.
- Manufacturer name and its address: AbbVie Inc., North Chicago, IL 60064 USA.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  VENCLEXTA 10 mg TABLETS 158-19-34868
  VENCLEXTA 50 mg TABLETS 158-20-34869
  VENCLEXTA 100 mg TABLETS 158-21-34870

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