PATIENT PACKAGE INSERT IN ACCORDANCE WITH
THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

IMBRUVICA® Capsules 140 mg

IBRUTINIB 140 mg

IMBRUVICA® 140 mg Tablets

IBRUTINIB 140 mg

IMBRUVICA® 280 mg Tablets

IBRUTINIB 280 mg

IMBRUVICA® 420 mg Tablets

IBRUTINIB 420 mg

IMBRUVICA® 560 mg Tablets

IBRUTINIB 560 mg

Inactive and allergenic ingredients in the preparation – see section 6 "Further Information".

Read the 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 the treatment of your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

- The medicine is intended for the treatment of MCL (Mantle Cell Lymphoma) in adults who have received at least one prior therapy.
- The medicine is intended for the treatment of SLL (Small Lymphocytic Lymphoma)/ CLL (Chronic Lymphocytic Leukemia) in adults who have received at least one prior therapy.
- The medicine is intended as a first-line treatment of SLL (Small Lymphocytic Lymphoma)/CLL (Chronic Lymphocytic Leukemia) in adults over the age of 65.
- The medicine is intended for the treatment of CLL (Chronic Lymphocytic Leukemia)/ SLL (Small Lymphocytic Lymphoma) in adults with a deletion of a segment on chromosome 17 (17p deletion).
- The medicine is intended for the treatment of Waldenström's Macroglobulinemia (WM).
- The medicine is intended for the treatment of MZL (Marginal Zone Lymphoma) in patients who require systemic therapy and who received at least one previous treatment with anti-CD20.
- The medicine is intended for the treatment of cGVHD (Chronic Graft-Versus-Host Disease) in adults after failure of one or more lines of systemic therapy.

Therapeutic group: BTK (Bruton's Tyrosine Kinase) inhibitors

2. BEFORE USING THE MEDICINE

Do not use the preparation if:

- You are sensitive (allergic) to the active ingredient ibrutinib or to any of the additional ingredients contained in the medicine Imbruvica. For a list of the additional ingredients, see section 6 "Further Information".
- You are taking strong CYP3A4 inhibitors (liver enzymes that may affect the level of the medicine in the blood). For details, see "Drug interactions" section. If you are uncertain – consult the doctor, pharmacist or a nurse before taking the medicine.
- You are taking strong CYP3A4 inducers. See "Drug interactions" section. If you are uncertain – consult the doctor, pharmacist or a nurse before taking the medicine.
- You are pregnant or are planning to become pregnant. Imbruvica may harm the fetus. If you are of child-bearing age, the attending doctor will refer you for a pregnancy test before starting treatment with Imbruvica.
  - **Women:** Avoid becoming pregnant during treatment and for **3 months** after taking the last dose of Imbruvica.
  - **Men:** Avoid getting your partner pregnant during treatment and for **one month** after taking the last dose of Imbruvica (see "Pregnancy and breastfeeding" section).
- You are breastfeeding or are planning to breastfeed. Do not breastfeed during the course of treatment with Imbruvica and for one week after taking the last dose of Imbruvica (see "Pregnancy and breastfeeding" section.

Special warnings regarding use of the medicine

Before beginning treatment with Imbruvica, tell the doctor if:

- You have recently undergone surgery, or are planning to undergo surgery. The doctor may discontinue treatment with Imbruvica before a planned medical procedure, surgery or dental treatment.
- You have bleeding problems.
- You have a deficiency of one or more types of blood cells – white blood cell deficiency, red blood cell deficiency (anemia), platelet deficiency.
- You suffer, or have suffered in the past, from heart rate problems, if you smoke or if you have any medical condition that may increase your risk for heart disease, such as: high blood pressure, high cholesterol or diabetes.
- If you plan to undergo any surgery – your doctor may tell you to stop taking Imbruvica for a short while (3-7 days) before and after the surgery.
- You suffer from a viral, bacterial or fungal infection.
- You suffer, or have suffered in the past, from a hepatitis B infection. This is because Imbruvica can cause hepatitis B to recur. Before starting treatment, your doctor will check for signs of this infection.
- You suffer from liver or kidney problems.
- During treatment with Imbruvica, tell the doctor immediately if you or someone else notices that you have: memory loss, thinking problems, walking problems or loss of vision – these effects may be due to a very severe and rare, possibly life-threatening infection in the brain called Progressive Multifocal Leukoencephalopathy (PML).

Children and adolescents

This medicine is not intended for children and adolescents under 18 years of age. The efficacy and safety of the medicine have not been tested in this population.

Tests and follow up

Tumor Lysis Syndrome (TLS) – a syndrome caused by breakdown of cancerous tumor cells. During the course of treatment and during the course of the disease without treatment, there may be abnormal levels of chemicals in the blood due to the broken-down components of the tumor cells, which may lead to changes in kidney function, abnormal heart rate or seizures. The attending doctor may refer you for TLS blood tests.

Lymphocytosis – lab tests may show a rise in white blood cells (lymphocytes) in your blood in the first few weeks of treatment. This effect is expected and may continue for a few months. An increase in the levels of these white blood cells does not necessarily indicate worsening of the cancer. The doctor will refer you for a blood count before and during treatment, and in rare cases, an additional medicine will be necessary.

Drug interactions

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

Taking Imbruvica concomitantly with other medicines may affect the activity of Imbruvica and may affect the activity of other medicines, especially if you are taking:

Cytochrome P450 (CYP3A) is an important enzyme in the body, primarily found in the liver and intestine. This enzyme reacts with small foreign organic molecules to remove them from the body:

- Moderate to strong CYP3A inhibitors –
  posaconazole, voriconazole, ketoconazole, itraconazole, fluconazole (to treat fungal infections),
  clarithromycin, telithromycin, ciprofloxacin, erythromycin (antibiotics to treat bacterial infections),
  ritonavir, indinavir, nelfinavir, saquinavir, atazanavir, darunavir, telaprevir, boceprevir, fosamprenavir, amprenavir (medicines for HIV infections),
  aprepitant (medicine to prevent nausea and vomiting resulting from chemotherapy),
  nefazodone (medicine to treat depression),
  crizotinib, imatinib (medicines from the kinase inhibitor group for treatment of cancer),
  diltiazem, verapamil (medicines from the calcium channel blocker group to treat high blood pressure and chest pains).

The above-mentioned CYP3A inhibitors may increase Imbruvica levels in your blood and thereby increase the chance of toxicity due to the medicine.

- Strong CYP3A inducers –
  rifampicin (an antibiotic for the treatment of bacterial infections),
  efavirenz (medicine to treat HIV).

The above-mentioned CYP3A inducers may decrease the concentration of Imbruvica in your blood.

Imbruvica may cause you to bleed more easily. Before taking Imbruvica, tell the doctor if you are taking other medicines that increase the risk of bleeding, such as warfarin or other anticoagulants. Taking digoxin, a medicine given for heart problems, or methotrexate, a medicine given for other types of cancer and to reduce immune system activity (e.g., rheumatoid arthritis or psoriasis), together with Imbruvica, may increase their levels in the blood.

Use of the medicine and food

During the course of treatment with Imbruvica, do not eat grapefruit or Seville oranges, often used to make jams. Likewise, do not drink grapefruit juice or Seville orange juice or take any food or supplement that may contain them. These products may increase the level of the medicine in the blood.

Pregnancy and breastfeeding

Pregnancy:

- Inform the doctor if you are pregnant or are planning to become pregnant. Imbruvica may harm the fetus. If you are of child-bearing age, the attending doctor will refer you for a pregnancy test before starting treatment with Imbruvica.
- **Women:** Avoid becoming pregnant during treatment and for **3 months** after taking the last dose of Imbruvica. Women of child-bearing age must use a highly effective method of birth control during the course of treatment with Imbruvica and for a period of 3 months after discontinuing its use. If you are using hormonal contraceptives, such as birth control pills or intrauterine devices, you must also use a mechanical method of contraception (e.g., condoms).
- **Men:** Avoid getting your partner pregnant during the course of treatment and for **one month** after taking the last dose of Imbruvica.

Breastfeeding:

Inform the doctor if you are breastfeeding or are planning to breastfeed. Because of the risk for serious reactions in the infant, avoid breastfeeding during the course of treatment with Imbruvica and for one week after taking the last dose of Imbruvica.

Driving and operating machinery

Do not drive or operate dangerous machinery while using the medicine since you may feel tired or dizzy.

3. HOW SHOULD THE MEDICINE BE USED?

Always use the preparation according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain about the preparation dosage or instructions for use.

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

The usual dosage is:

Mantle Cell Lymphoma (MCL) and Marginal Zone Lymphoma (MZL) – 560 mg, once a day.

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) and Waldenström's Macroglobulinemia (WM) – 420 mg, once a day.

For CLL/SLL, Imbruvica can be given as a monotherapy or in combination with obinutuzumab.

For patients with CLL/SLL without the chromosome 17 fragment deficiency, which is resistant or has worsened, who received at least one previous treatment, the recommended dosage of Imbruvica in combination with bendamustine and rituximab (given every 28 days for up to 6 cycles) is 420 mg, once a day.

For WM, Imbruvica can be given as a monotherapy or in combination with rituximab.

The doctor may adjust a different dosage for you.

Do not exceed the recommended dosage.

Take Imbruvica once a day, every day, at a fixed time, as much as possible. Swallow the capsule or tablet whole with a glass of water.

Do not open, break or chew the capsule.

Do not break, crush or chew the tablet.

During the course of treatment with Imbruvica, do not drink grapefruit juice, eat grapefruit or Seville oranges, often used to make jams.

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 forgot to take the medicine, take it on the same day, when you remember. Take the next dose at the usual time on the following day. Do not take a double dose in one day to compensate for a forgotten dose. If you are unsure as to what to do, consult the doctor or pharmacist about when to take the next dose.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment without consulting the doctor.

Do not take medicines in the dark! Check the label and the 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 Imbruvica 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.

Discontinue use and refer to a doctor immediately if you experience any of the following side effects: itchy, bumpy rash, difficulty breathing, swelling of the face, lips, tongue or throat – these effects may be indicative of an allergic reaction to the medicine.

Imbruvica may cause serious side effects, including:

- **Bleeding problems** – common. Bleeding may occur during the course of treatment with Imbruvica and may be serious and even lead to death. The risk of bleeding may increase if you are concomitantly taking blood thinners. Refer to the doctor immediately if you experience signs of bleeding, including:
  blood in the stools or black stools (look like tar), increased bruising, pink or brown urine, unexpected bleeding, severe or uncontrollable bleeding, bloody vomit or vomit that looks like coffee grounds, bloody cough or cough with blood clots, increased tendency to bruise, feeling of dizziness or weakness, confusion, change in speech, headache that lasts a long time or severe headache.
- **Infections** – may occur during the course of treatment with Imbruvica. The infections may be severe and lead to death. Inform the doctor immediately if you are suffering from fever, chills, weakness, confusion or any other sign or symptom of an infection during the course of treatment with Imbruvica.
- **Decrease in blood count** – decreased blood count (white blood cells, platelets and red blood cells) is a common effect upon treatment with Imbruvica but may also be severe. The attending doctor should refer you to have a blood count every month.
- **Heart problems** – severe heart rate problems (ventricular fibrillation, atrial fibrillation and atrial flutter), heart failure and even death have occurred in people being treated with Imbruvica, especially in people with an increased risk of heart disease, people with infections or people who have suffered from heart rate problems in the past. Inform the doctor if you suffer from symptoms of heart problems, such as a feeling that the heart is beating at a fast and irregular rate, dizziness, shortness of breath, swelling of the feet, ankles or legs, chest discomfort or fainting. If you develop one of these symptoms, the doctor may refer you for an electrocardiogram (ECG) and change the dosage of the medicine.
- **High blood pressure** – onset or worsening of high blood pressure has occurred in people being treated with Imbruvica. The attending doctor may decide to give you a new medicinal treatment to lower blood pressure, or will change the existing treatment.
- **Development of an additional primary cancerous tumor** – new cancerous tumors have been detected in patients treated with Imbruvica, including cancer of the skin or of other organs.
- **Tumor Lysis Syndrome (TLS)** – a syndrome caused by rapid breakdown of the cancer cells. The syndrome may cause kidney failure and the need for dialysis treatment, abnormal heart rate, seizures and even death. The attending doctor may instruct you to perform blood tests for **TLS**.
- **Cerebrovascular events** – there have been reports of uncommon cerebrovascular events, transient ischemic attacks and ischemic stroke, that included death, during the course of treatment with Imbruvica. Your doctor will monitor your condition regularly.

Additional side effects:

Liver problems: liver failure, including severe and even fatal events, liver problems (cirrhosis)

Respiratory problems: lung inflammation

Immune system problems: anaphylactic shock, angioedema, urticaria

Skin and subcutaneous tissue problems: Steven's-Johnson syndrome (**SJS**), nail-breaking problems, infection in the subcutaneous fat layers, neutrophilic dermatoses (skin disease)

Infections: recurrence of hepatitis B

Nervous system problems: peripheral neuropathy

Diarrhea is a common side effect in patients taking Imbruvica. Drink a lot of fluid during the course of treatment with Imbruvica to reduce the risk of significant loss of fluids (dehydration) due to diarrhea. Inform the doctor if you suffer from persistent diarrhea.

Side effects by indication:

The most common side effects of Imbruvica in adults suffering from B cell malignancies (**MCL, CLL/SLL, WM and MZL**) include:

diarrhea
muscle and bone pains
rash or urticaria
bruising
tiredness

Additional side effects associated with **Mantle Cell Lymphoma – MCL**:

Body system	Side effect
Gastrointestinal disturbances	Nausea Constipation Abdominal pain Vomiting Stomatitis Digestion difficulties
General disturbances and administration site conditions	Peripheral edema High fever Weakness
Skeletal and connective tissue disturbances	Muscle contractions Joint pains
Infections and lesions	Upper respiratory tract infection Urinary tract infection Lung inflammation Skin infections Sinusitis
Skin and subcutaneous tissue disorders	Bleeding Small hematomas under the skin
Respiratory and chest cavity disturbances	Shortness of breath Cough Nosebleed
Metabolic and nutritional disturbances	Poor appetite Dehydration
Nervous system disturbances	Dizziness Headache
Hematology test result abnormalities	Low platelet level Low neutrophil level Low hemoglobin level

Additional side effects associated with **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL):**

Body system	Side effect
Gastrointestinal disturbances	Nausea Constipation Stomatitis Vomiting Abdominal pain Digestion difficulties
Infections and lesions	Upper respiratory tract infection Sinusitis Skin infections Lung inflammation Urinary tract infection Bronchitis Nasopharyngitis Conjunctivitis
General disturbances and administration site conditions	High fever Peripheral edema Weakness Chills Pain
Skin and subcutaneous tissue disorders	Bleeding Small hematomas under the skin
Respiratory and chest cavity disturbances	Cough Pharyngeal pain Shortness of breath
Skeletal and connective tissue disturbances	Joint pains Muscle contractions
Nervous system disturbances	Dizziness Headache Peripheral neuropathy
Metabolic and nutritional disturbances	Poor appetite High blood levels of uric acid, which can cause gout
Benign, malignant or undefined tumors	Secondary malignant tumors*
Blood vessel disturbances	High blood pressure Bleeding
Hematology test result abnormalities	Low platelet level Low neutrophil level Low hemoglobin level
Injuries, poisoning and procedural complications	Infusion site-related reaction
Optical disturbances	Blurred vision Dry eyes Increased tearing Reduced visual acuity
Heart disturbances	Atrial fibrillation
Psychiatric disturbances	Insomnia
Blood and lymph system disturbances	Low white blood cell count Low platelet count Reduced hemoglobin level Anemia
Investigations	Weight loss
Laboratory result abnormalities	Creatinine increase Bilirubin increase Liver enzyme increase

* One report of death due to **Histiocytic Sarcoma** has been reported

Additional side effects associated with **Waldenström's Macroglobulinemia – WM:**

Body system	Side effect
Gastrointestinal disturbances	Nausea Stomatitis Constipation Reflux Digestion difficulties
Skin and subcutaneous tissue disorders	Bleeding
Blood vessel disturbances	Bleeding High blood pressure Peripheral edema
General disturbances and administration site conditions	High fever Peripheral edema Weakness
Skeletal and connective tissue disturbances	Skeletal muscle pains Muscle contractions Joint pains
Infections and lesions	Upper respiratory tract infection Skin infections Sinusitis Lung inflammation Urinary tract infection Bronchitis Flu Viral inflammation of the upper respiratory tract
Nervous system disturbances	Headache Dizziness
Respiratory and chest cavity disturbances	Cough
Hematology test result abnormalities	Low platelet level Low neutrophil level Low hemoglobin level
Heart disturbances	Abnormal heartbeats (atrial fibrillation)
Psychiatric disturbances	Insomnia
Metabolic and nutritional disturbances	Low blood potassium level
Blood system disturbances	Low white blood cell count

Additional side effects associated with **Marginal Zone Lymphoma – MZL:**

Body system	Side effect
Gastrointestinal disturbances	Nausea Digestion difficulties Stomatitis Abdominal pain Constipation Upper abdominal pain Vomiting
General disturbances and administration site conditions	High fever Weakness Peripheral edema
Skin and subcutaneous tissue disturbances	Bleeding Tingling
Skeletal and connective tissue disturbances	Joint pains Muscle contractions
Infections and lesions	Upper respiratory tract infection Sinusitis Bronchitis Lung inflammation
Metabolic and nutritional disturbances	Poor appetite High blood uric acid level, which may cause gout Low blood albumin level Low blood potassium level
Blood vessel disturbances	Bleeding High blood pressure
Respiratory and chest cavity disturbances	Cough Shortness of breath
Nervous system disturbances	Dizziness Headache
Psychiatric disturbances	Anxiety
Hematology test result abnormalities	Low platelet level Low hemoglobin level Low neutrophil level

Side effects associated with **Chronic Graft-Versus-Host Disease (cGVHD)**

The most common side effects of Imbruvica in adults suffering from **cGVHD** include:

tiredness
bruising
diarrhea
inflammation in the mouth (stomatitis)
muscle contractions
nausea
lung inflammation

Additional side effects associated with **Chronic Graft-Versus-Host Disease (cGVHD):**

Body system	Side effect
General disturbances and administration site conditions	High fever Peripheral edema
Skin and subcutaneous tissue disturbances	Bleeding Rash
Gastrointestinal disturbances	Constipation
Skeletal muscle and connective tissue disturbances	Skeletal muscle pain
Blood vessel disturbances	Bleeding
Infections and lesions	Upper respiratory tract infection Severe infection widespread throughout the body (sepsis)
Nervous system disturbances	Headache
Injuries, toxicity, and procedural complications	Falls
Hematology test result abnormalities	Low platelet level Low hemoglobin level Low neutrophil level
Respiratory and chest cavity disturbances	Cough Shortness of breath
Metabolic and nutritional disturbances	Low blood potassium level

If a side effects occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult with the 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 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 SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine, and any other medicine, should be kept in a safe 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 package. The expiry date refers to the last day of that month.

Storage conditions:

Store Imbruvica Capsules and Imbruvica Tablets at a temperature of 20 to 25 degrees Celsius.

Imbruvica Capsules:

Store the preparation in its original package, with the cap tightly closed.

After first opening the package, use within 120 days.

Imbruvica Tablets:

Store the preparation in its original package.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:

Imbruvica Capsules:

Microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate

The capsule shell contains:

Gelatin and titanium dioxide and black printing ink (pharmaceutical glaze, iron oxide black, n-butyl alcohol, 2-propanol, propylene glycol and ammonium hydroxide)

Imbruvica Tablets:

Lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, povidone, sodium lauryl sulfate, colloidal anhydrous silica, magnesium stearate

Imbruvica 140 mg Tablets: Opadry II film coating powder 85F210036 green (polyvinyl alcohol, titanium dioxide, macrogol, talc, yellow iron oxide, black iron oxide)

Imbruvica 280 mg Tablets: Opadry II film coating powder 85F200011 purple (polyvinyl alcohol, titanium dioxide, macrogol, talc, black iron oxide, red iron oxide)

Imbruvica 420 mg Tablets: Opadry II film coating powder 85F210036 green (polyvinyl alcohol, titanium dioxide, macrogol, talc, yellow iron oxide, black iron oxide)

Imbruvica 560 mg Tablets: Opadry II film coating powder 85F32547 yellow (polyvinyl alcohol, titanium dioxide, macrogol, talc, yellow iron oxide, red iron oxide)

What the medicine looks like and the contents of the package:

Capsules

Imbruvica Capsules 140 mg is an opaque, white capsule, made of gelatin, with "ibr 140 mg" imprinted on it in black. The capsule contains a white/whitish powder.

Package size: a bottle containing 120 capsules and a bottle containing 90 capsules.

Tablets

- Imbruvica 140 mg Tablets is a round, yellow-green tablet, with "ibr" imprinted on one side and "140" on the other side. The box has two pouches, with 15 tablets in each, totaling 30 film-coated tablets.
- Imbruvica 280 mg Tablets is an oblong, purple tablet, with "ibr" imprinted on one side and "280" on the other side. The box has two pouches, with 15 tablets in each, totaling 30 film-coated tablets.
- Imbruvica 420 mg Tablets is an oblong, yellow-green tablet, with "ibr" imprinted on one side and "420" on the other side. The box has two pouches, with 15 tablets in each, totaling 30 film-coated tablets.
- Imbruvica 560 mg Tablets is an oblong, yellow-orange tablet, with "ibr" imprinted on one side and "560" on the other side. The box has two pouches, with 15 tablets in each, totaling 30 film-coated tablets.

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

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

Capsules:
151-98-34062

Tablets:
Imbruvica 140 mg: 167-61-36458-99
Imbruvica 280 mg: 167-62-36459-99
Imbruvica 420 mg: 167-63-36460-99
Imbruvica 560 mg: 167-64-36461-99

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