PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

IMBRUVICA® 140 mg film-coated tablets

IMBRUVICA® 280 mg film-coated tablets

IMBRUVICA® 420 mg film-coated tablets

IMBRUVICA® 560 mg film-coated tablets

ibrutinib

Contains sugar

Each 140 mg film-coated tablet contains 28 mg of lactose monohydrate

Each 280 mg film-coated tablet contains 56 mg of lactose monohydrate

Each 420 mg film-coated tablet contains 84 mg of lactose monohydrate

Each 560 mg film-coated tablet contains 112 mg of lactose monohydrate

Read all of this leaflet carefully before you start using IMBRUVICA

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- IMBRUVICA has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What IMBRUVICA is and what it is used for

IMBRUVICA is an anticancer medicine. It is used to treat the following blood cancers in adults:

- **Mantle Cell Lymphoma (MCL)**, a type of cancer affecting the lymph nodes; when the disease has come back or has not responded to treatment.
- **Chronic Lymphocytic Leukaemia (CLL)**, a type of cancer affecting white blood cells called lymphocytes that also involves the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for CLL or when the disease has come back or has not responded to treatment.
- **Waldenström's Macroglobulinaemia (WM)**, a type of cancer affecting white blood cells called lymphocytes. It is used in patients who have not previously been treated for WM or when the disease has come back or has not responded to treatment or in patients for whom chemotherapy given together with an antibody is not a suitable therapy.

2. What you need to know before you take IMBRUVICA

Do not take IMBRUVICA

- you are allergic (hypersensitive) to ibrutinib or any of the other ingredients of IMBRUVICA (listed in section 6).

If you are not sure about this, talk to your doctor before taking IMBRUVICA. If you have any of signs of an allergic reaction (hives, difficulty breathing, or swelling of your face, lips, tongue, or throat) while taking IMBRUVICA, get emergency medical help right away.

- If you are pregnant or might be pregnant (see "**Pregnancy, breastfeeding and fertility").**
- If you are breastfeeding your baby (see "**Pregnancy, breastfeeding and fertility").**
- If you are taking any of the medicines as listed under the section "**Other medicines and IMBRUVICA"***.* If you are not sure about this, talk to your doctor before taking IMBRUVICA.
- If you are taking any herbal medicines that contain St.John's Wort (see "**Other medicines and IMBRUVICA"**).

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

Warnings and precautions

Take special care with IMBRUVICA:

Before taking IMBRUVICA, tell your doctor or healthcare professional:

- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see "**Other medicines and IMBRUVICA"**),
- if you have or have ever had heart rhythm problems or severe heart failure, or if you feel any of the following: your heartbeat is fast and irregular, lightheadedness, dizziness, weakness, shortness of breath, chest discomfort, swollen feet, fainting or near fainting,

- if you notice breathlessness, difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness (these may be signs of heart failure) during treatment with IMBRUVICA,
- if you have liver problems, including if you ever had or now have a hepatitis B infection (a liver infection),
- if you have high blood pressure,
- if you have recently had any surgery, especially if this might affect how you absorb food or medicines from your stomach or gut,
- if you are planning to have any surgery or spinal / epidural anaesthetic procedures – your doctor may ask you to stop taking IMBRUVICA for a short time before and after your surgery,
- if you have kidney problems,
- if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML),
- if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke,
- if you develop left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of rupture of the spleen) after you stop taking IMBRUVICA,
- Haemophagocytic lymphohistiocytosis

  There have been reports of excessive activation of white blood cells associated with inflammation (haemophagocytic lymphohistiocytosis), which can be fatal if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, bruising, or skin rash, contact your doctor immediately.

If any of the above apply to you or you are not sure, talk to your doctor or healthcare professional before taking IMBRUVICA.

Effects on the heart

Treatment with IMBRUVICA may affect the heart, especially if you already have heart diseases such as rhythm problems, heart failure, high blood pressure or have diabetes. The effects may be severe and could cause death, including sometimes sudden death. Your heart function will be checked before and during treatment with IMBRUVICA. Tell your doctor immediately if you feel breathless, have difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness during treatment with IMBRUVICA – these may be signs of heart failure.

Tests and check-ups before and during treatment

Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Lymphocytosis: Laboratory tests may show that your blood count contains more white blood cells (called “lymphocytes”), in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before or during the treatment and in rare cases they may need to give you another medicine. Talk to your doctor about what your test results mean.

Events related to the liver: Your doctor will do some blood tests to check whether your liver is working properly or that you do not have a liver infection, known as viral hepatitis, or whether hepatitis B has become active again, which could be fatal.

Children and adolescents

IMBRUVICA should not be used by anyone under 18 years of age because it has not been studied in this age group.

Other medicines and IMBRUVICA

Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines.) This is because IMBRUVICA may affect how some other medicines work. Also, some other medicines can affect how IMBRUVICA works.

IMBRUVICA may make you bleed more easily. Tell your healthcare professional if you take other medicines that increase your risk of bleeding, including:

- aspirin and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen,
- blood thinners such as warfarin, heparin or other medicines for blood clots,
- supplements that may increase your risk of bleeding such as fish oil and vitamin E.

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

The effects of IMBRUVICA or other medicines may be influenced if you take IMBRUVICA together with any of the following medicines. ***Tell your healthcare professional if you take***:

- medicines called antibiotics to treat bacterial infections - clarithromycin, telithromycin, ciprofloxacin, erythromycin or rifampicin.

- medicines for fungal infections - posaconazole, ketoconazole, itraconazole, fluconazole or voriconazole.
- medicines for HIV infection - ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, darunavir/ritonavir or fosamprenavir.
- medicine to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicine for depression – nefazodone.
- medicines called kinase inhibitors for treatment of other cancers - crizotinib, imatinib.
- medicines called calcium channel blockers for high blood pressure or chest pain - diltiazem, verapamil.
- medicines called statins to treat high cholesterol – rosuvastatin.
- heart medicines/anti-dysrhythmics - amiodarone, dronedarone.
- medicines to prevent seizures or to treat epilepsy or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine, phenytoin.
- a herbal medicine used for example for depression - St. John's Wort.

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

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after IMBRUVICA.

Ask your doctor if you are not sure if your medicine is one listed above. Know the medicines you take. Keep a list of them to show your doctor or healthcare professional when you get a new medicine.

IMBRUVICA with food and drink

Do not take IMBRUVICA with grapefruit or Seville oranges (bitter oranges) - this includes eating them, drinking the juice, or taking supplements that might contain them. This is because they can increase the amount of IMBRUVICA in your blood.

Pregnancy, breastfeeding and fertility

IMBRUVICA should not be used during pregnancy.

Do not get pregnant while you are taking IMBRUVICA.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.

Women of childbearing age must use an effective method of birth control during and up to three months after receiving IMBRUVICA to avoid becoming pregnant while being treated with IMBRUVICA. The time period following treatment with IMBRUVICA where it is safe to become pregnant is not known.

- Tell your doctor immediately if you become pregnant.
- Do not breastfeed while you are taking IMBRUVICA.

Do not father a child while taking IMBRUVICA and for 3 months after stopping treatment. Use condoms and do not donate sperm during treatment and for 3 months after your treatment has finished. If you plan to father a child, talk to your doctor or healthcare professional before taking IMBRUVICA.

Driving and using machines:

You may feel tired or dizzy after taking IMBRUVICA, which may affect your ability to drive or use any tools or machinery.

IMBRUVICA contains lactose

IMBRUVICA contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

IMBRUVICA contains sodium

IMBRUVICA contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take IMBRUVICA

Do not share medicines prescribed for you with any other person.

Always take IMBRUVICA exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Swallow IMBRUVICA film-coated tablets whole with a glass of water.

Do not break or chew them.

Take IMBRUVICA at approximately the same time each day.

Drink plenty of fluids to stay hydrated while taking IMBRUVICA. This will help your kidneys continue to function properly.

The usual dose for:

Mantle Cell Lymphoma (MCL) is 560 mg once a day.

Chronic Lymphocytic Leukemia (CLL): 420 mg once a day either as a single agent or when used in combination with other medicines as prescribed by your doctor.

Waldenström's Macroglobulinaemia (WM): 420 mg once a day either as a single agent or when used in combination with other medicines as prescribed by your doctor.

Your doctor will tell you how long your treatment with IMBRUVICA will last. Do not change your dose or stop taking IMBRUVICA until your doctor tells you to. If you have the impression that the effect of IMBRUVICA is too strong or too weak, tell your doctor or pharmacist.

If you take more IMBRUVICA than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control center.

If you forget to take IMBRUVICA

If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Do not take a double dose to make up the missed dose. Call your doctor or healthcare professional if you are not sure of what to do.

If you stop taking IMBRUVICA

Do not stop taking IMBRUVICA unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

IMBRUVICA can cause side effects. Not all side effects reported for IMBRUVICA are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking IMBRUVICA, please consult your doctor, pharmacist or other health care provider for advice.

Stop taking IMBRUVICA and tell a doctor straight away if you notice any of the following side effects:

- Allergic reaction: symptoms may include: a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives), redness of the skin.

These are very serious side effects. If you have them, you may have had a serious allergic reaction to IMBRUVICA. Stop using IMBRUVICA and get medical help.

The following are serious side effects which may need urgent medical attention.
If you notice or have been tested for any of the following side effects tell your doctor immediately.

- Bleeding problems: you may experience bruising or nosebleeds during treatment with IMBRUVICA. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur, sometimes resulting in death. If you take other medicines or supplements that increase your risk of bleeding, see **Other medicines and IMBRUVICA**. Call your doctor or healthcare professional if you have signs or symptoms of serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.
- Leukostasis: you may experience an increase in the number of white blood cells, specifically lymphocytes in your blood. In rare cases, this increase may be severe, causing cells to clump together (see **Warnings and precautions**). Your doctor will monitor your blood counts.

- Infections: including viral, bacterial, fungal or severe infections throughout the body (sepsis) have been reported. Contact your doctor if you have fever, chills, weakness, confusion, body aches, feeling tired, cold or flu symptoms, being short of breath. These could be signs of an infection.
- Decrease in blood cell counts: use of IMBRUVICA may cause you to have a low number of red blood cells (anaemia), a type of white blood cells (neutrophils) or platelets (cells that help blood to clot). Your doctor or healthcare professional should check your blood counts regularly.
- Interstitial lung disease (ILD): Inflammation within the lungs that may lead to permanent damage has happened with IMBRUVICA treatment. Contact your doctor if you have difficulty breathing or have a persistent cough.
- Heart rhythm problems: Heart rhythm problems have happened with IMBRUVICA treatment. Tell your doctor or healthcare professional if you have any symptoms of heart rhythm problems such as feeling as if your heartbeat is fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort or you faint.
- Tumour lysis syndrome (TLS): characterised by unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome). This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.
- Non-melanoma skin cancers: Types of skin cancers that are not melanoma, most frequently squamous cell or basal cell skin cancers, have happened in people taking IMBRUVICA.
- High blood pressure: New or worsening high blood pressure has been reported in people treated with IMBRUVICA. Your healthcare provider may start you on blood pressure medicine or change current medicines to treat your blood pressure.

Frequently reported side effects include:

- Infections of the lung, nose, sinuses or throat (upper respiratory tract infections), or urinary tract or sinus, or skin.
- severe infections throughout the body (sepsis)
- non-melanoma skin cancer
- low number of 'platelets' (cells that help blood to clot)
- low white blood cell counts with fever (febrile neutropenia)
- an increase in the number or proportion of white blood cells shown in blood tests
- high level of 'uric acid' in the blood (shown in blood tests), which may cause gout
- headache or feeling dizzy
- blurred vision
- fast heart rate, missed heartbeats, weak or uneven pulse (symptoms of heart rhythm problems)
- bleeding
- bruising or an increased tendency of bruising
- nose bleeds, small red or purple spots caused by bleeding under the skin
- high blood pressure
- diarrhoea (if you have diarrhoea that lasts for more than a week, your doctor may need to give you a fluid and salt replacement or another medicine).
- mouth sores
- nausea and/or vomiting
- constipation
- skin rash, redness and itchiness of the skin
- joint pain, muscle cramps, aches or spasms
- fever, swollen hands, ankles or feet
- an increased level of creatinine in the blood

Less frequently reported side effects include:

- severely increased white blood cell count that may cause cells to clump together (leukostasis syndrome)
- allergic reaction (may include swelling and itchy rash)
- Hepatitis B reactivation
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells (tumour lysis syndrome).

The following post-marketing side effects have been reported:

- bleeding in the eye
- inflammation within the lungs that may lead to permanent damage
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells (tumour lysis syndrome)
- liver failure, including events with fatal outcome
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- breaking of the nails
- heart rhythm problems
- Inflammation of the fatty tissue underneath the skin
- Weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy)
- temporary or permanent decrease of brain or nerve function due to reduced blood flow to the brain (mini-stroke or stroke)
- tender or painful bumps or ulcers on the skin, sometimes with a fever (neutrophilic dermatoses).

If you have diarrhoea that lasts for more than a week, your doctor may need to give you a fluid and salt replacement or another medicine.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8
By reporting side effects, you can help provide more information on the safety of IMBRUVICA.

Alternatively, you may report side effects experienced with IMBRUVICA directly to Janssen Pharmaceutica (see section 'Holder of the Certificate of Registration' for contact details or visit www.janssen.com).

5 How to store IMBRUVICA

- Store all medicines out of reach of children.
- Store at or below 30 °C.
- Do not use this medicine after the expiry date stated on the label / carton. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Return all unused medicines to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets). These measures will help protect the environment.

6 Contents of the pack and other information

What IMBRUVICA contains

The active substance is ibrutinib.

- IMBRUVICA 140 mg film-coated tablets: Each tablet contains 140 mg of ibrutinib.
- IMBRUVICA 280 mg film-coated tablets: Each tablet contains 280 mg of ibrutinib.
- IMBRUVICA 420 mg film-coated tablets: Each tablet contains 420 mg of ibrutinib.
- IMBRUVICA 560 mg film-coated tablets: Each tablet contains 560 mg of ibrutinib.

The other ingredients are:

- *Tablet core*: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate (see section 2 “IMBRUVICA contains lactose”), magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate (E487) (see section 2 “IMBRUVICA contains sodium”).
- *Tablet film-coat*: polyvinyl alcohol, macrogol, talc, titanium dioxide (E171);
  IMBRUVICA 140 mg and IMBRUVICA 420 mg film-coated tablets also contain black iron oxide (E172) and yellow iron oxide (E172);
  IMBRUVICA 280 mg film-coated tablets also contain black iron oxide (E172) and red iron oxide (E172);
  IMBRUVICA 560 mg film-coated tablets also contain red iron oxide (E172) and yellow iron oxide (E172).

What IMBRUVICA looks like and contents of the pack

Film-coated tablet (tablet).

<u>IMBRUVICA 140 mg film-coated tablets</u>

Yellow-green to green round tablets (9 mm), debossed with “ibr” on one side and “140” on the other side.

IMBRUVICA 280 mg film-coated tablets

Purple oblong tablets (15 mm in length and 7 mm in width), debossed with “ibr” on one side and “280” on the other side.

IMBRUVICA 420 mg film-coated tablets

Yellow-green to green oblong tablets (17,5 mm in length and 7,4 mm in width), debossed with “ibr” on one side and “420” on the other side.

IMBRUVICA 560 mg film-coated tablets

Yellow to orange oblong tablets (19 mm in length and 8,1 mm in width), debossed with “ibr” on one side and “560” on the other side.

IMBRUVICA film-coated tablets are packaged in clear colourless polyvinyl chloride (PVC) laminated with silver coloured polychlorotrifluoroethylene (PCTFE)/aluminum push-through blisters.

The blister package is available in 14 film-coated tablets in a cardboard wallet. Each cardboard carton contains (28 film-coated tablets) 2 wallets.
The blister package is available in 10 film-coated tablets in a cardboard wallet. Each cardboard carton contains (30 film-coated tablets) 3 wallets.

Not all pack sizes may be marketed.

Holder of certificate of registration

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Registration numbers

IMBRUVICA® 140 mg film-coated tablets: 55/26/0297

IMBRUVICA® 280 mg film-coated tablets: 55/26/0298

IMBRUVICA® 420 mg film-coated tablets: 55/26/0299

IMBRUVICA® 560 mg film-coated tablets: 55/26/0300

Access to the corresponding Professional Information

Included in the carton, accompanying this patient information leaflet.