PATIENT INFORMATION LEAFLET

WARNING: (A) PREMATURE DISCONTINUATION OF IXAROLA INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HAEMATOMA

A. Premature discontinuation of IXAROLA increase the risk of thrombotic events:
Premature discontinuation of any oral anticoagulant, including IXAROLA, increases the risk of thrombotic events. If anticoagulation with IXAROLA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

B. Spinal/epidural haematoma:

Epidural or spinal hematomas have occurred in patients treated with IXAROLA who are receiving neuraxial anaesthesia or undergoing spinal puncture. These haematomas may result in long-term or permanent paralysis.

Consider these risks when scheduling patients for spinal procedures.

Factors that can increase the risk of developing epidural or spinal haematomas in these patients include:

• Use of indwelling epidural catheters

• Concomitant use of other drugs that affect haemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants

• History of traumatic or repeated epidural or spinal punctures

• History of spinal deformity or spinal surgery

• Optimal timing between the administration of IXAROLA and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

SCHEDULING STATUS: S4

IXAROLA® 15 Film-coated tablets
IXAROLA® 20 Film-coated tablets
rivaroxaban

Read all of this leaflet carefully before you start taking IXAROLA 15 or IXAROLA 20.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- IXAROLA 15 or IXAROLA 20 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 IXAROLA 15 AND IXAROLA 20 IS AND WHAT IT IS USED FOR:

IXAROLA 15 and IXAROLA 20 tablets are used to:

- **prevent blood clots in the brain (stroke) and other blood vessels in your body** if you have a form of irregular heart rhythm called non-valvular atrial fibrillation
- **treat blood clots** in the veins of your legs (deep vein thrombosis) and to **prevent blood clots** from re-occurring in the veins of your legs and/or lungs (pulmonary embolism)
- **treat blood clots** in the blood vessels of your lungs (pulmonary embolism) and to **prevent blood clots** from re-occurring in the blood vessels of your lungs and/or legs (deep vein thrombosis).

IXAROLA 15 and IXAROLA 20 belong to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (Factor-Xa) and thus reduces the tendency of the blood to clot.

2. What you need to know before you use IXAROLA 15 or IXAROLA 20

Do not take IXAROLA 15 or IXAROLA 20 and tell your doctor if any of the following apply to you:

Do not take IXAROLA

- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g. stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open.
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast-feeding

Do not take IXAROLA and tell your doctor if any of these apply to you.

Warnings and precautions

Talk to your doctor or pharmacist before taking IXAROLA.

Take special care with IXAROLA 15 or IXAROLA 20:

- if you have an increased risk of bleeding, as could be the case in situations such as: severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
- if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section “Other medicines and IXAROLA”)
- bleeding disorders
- very high blood pressure, not controlled by medical treatment
- diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet), e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus)
- a problem with the blood vessels in the back of your eyes (retinopathy)

- a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung

- if you have a prosthetic heart valve
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.

Also take care if you have an active cancer – this may also mean you have an increased risk of bleeding. An active cancer means that in the last 6 months you:
• have been diagnosed with cancer
• had a relapse of cancer
• were being treated for cancer

If any of the above apply to you, tell your doctor before you take IXAROLA. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If you need to have an operation
- it is very important to take IXAROLA before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take IXAROLA before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

~~In~~ Children and adolescents
IXAROLA 15 and IXAROLA 20 are **not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents.

Other medicines and IXAROLA

Always tell your doctor or pharmacist if you are taking any other medicine. (This includes all complementary or traditional medicines).

Taking IXAROLA 15 or IXAROLA 20 with food and drink:
IXAROLA 15 and IXAROLA 20 have to be taken with food.

- **If you are taking**
  - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin

- ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
- some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
- some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
- other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
- anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
- dronedarone, a medicine to treat abnormal heart beat
- some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs))

If any of the above apply to you, tell your doctor before taking IXAROLA, because the effect of IXAROLA may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- **If you are taking**
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort (*Hypericum perforatum*), a herbal product used for depression
  - rifampicin, an antibiotic

If any of the above apply to you, tell your doctor before taking IXAROLA, because the effect of IXAROLA may be reduced. Your doctor will decide, if you should be treated with IXAROLA and if you should be kept under closer observation.

Pregnancy and breastfeeding:

- **If you are pregnant or breastfeeding** do not take IXAROLA 15 or IXAROLA 20. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking IXAROLA 15 or IXAROLA 20. If you become pregnant while you are taking IXAROLA 15 or IXAROLA 20, immediately tell your doctor, who will decide how you should be treated.

Driving and using machines:

- IXAROLA 15 and IXAROLA 20 may cause side effects such as dizziness or fainting (see "Possible side effects"). You should not drive or use machines if you are affected by these symptoms.

Important information about some ingredients
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. Patients with rare hereditary conditions of lactose/fructose or galactose intolerance should not take IXAROLA. IXAROLA contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take IXAROLA 15 or IXAROLA 20:

Do not share medicines prescribed for you with others.
Always take IXAROLA 15 or IXAROLA 20 exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You must take IXAROLA together with a meal.
Swallow the tablet(s) preferably with water.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take IXAROLA. The tablet may be crushed and mixed with water or a soft food such as apple puree immediately before you take it. If necessary, your doctor may give you the crushed IXAROLA tablet through a stomach tube.

How much to take:

- To prevent blood clots in brain (stroke) and other blood vessels in your body
  The recommended dose is one tablet IXAROLA 20 mg once a day.
  If you have kidney problems, the dose may be reduced to one tablet IXAROLA 15 mg once a day.

  If you need a procedure to treat blocked blood vessels in your heart (called a percutaneous coronary intervention - PCI with an insertion of a stent), there is limited evidence to reduce the dose to one tablet IXAROLA 15 mg once a day (or to one tablet IXAROLA 10 mg once a day in case your kidneys are not working properly) in addition to an antiplatelet medicinal product such as clopidogrel.

- To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs, and for preventing blood clots from re-occurring
  The recommended dose is one tablet IXAROLA 15 mg twice a day for the first 3 weeks. For treatment after 3 weeks, the recommended dose is one tablet IXAROLA 20 mg once a day.
  After at least 6 months blood clot treatment your doctor may decide to continue treatment with either one 10 mg tablet once a day or one 20 mg tablet once a day.
  If you have kidney problems and take one tablet IXAROLA 20 mg once a day, your doctor may decide to reduce the dose for the treatment after 3 weeks to one tablet IXAROLA 15 mg once a day if the risk for bleeding is greater than the risk for having another blood clot.

When to take IXAROLA 15 or IXAROLA 20:

Take the tablet(s) every day until your doctor tells you to stop.
Try to take the tablet(s) at the same time every day to help you to remember it.
Your doctor will decide how long you must continue treatment for.

To prevent blood clots in the brain (stroke) and other blood vessels in your body:
If your heart beat needs to be restored to normal by a procedure called cardioversion, take IXAROLA at the times your doctor tells you.

If you take more IXAROLA 15 or IXAROLA 20 than you should:

Contact your doctor immediately if you have taken too many IXAROLA 15 or IXAROLA 20 tablets. Taking too much IXAROLA 15 or IXAROLA 20 increases the risk of bleeding.

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

If you forget to take IXAROLA 15 or IXAROLA 20:

- **If you are taking one IXAROLA 20 tablet or one IXAROLA 15 tablet once a day** and have missed a dose, take it as soon as you remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.
- **If you are taking one IXAROLA 15 tablet twice a day** and have missed a dose, take it as soon as you remember. Do not take more than two IXAROLA 15 tablets in a single day. If you forget to take a dose you can take two IXAROLA 15 tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one IXAROLA 15 tablet twice a day.

If you stop taking IXAROLA 15 or IXAROLA 20:

Don't stop taking IXAROLA 15 or IXAROLA 20 without talking to your doctor first, because IXAROLA 15 and IXAROLA 20 treats and prevents serious conditions.

If you have any further questions on the use of IXAROLA 15 or IXAROLA 20, ask your doctor or pharmacist.

4. Possible side effects:

IXAROLA 15 and IXAROLA 20 can have side effects.

Not all side effects reported for IXAROLA 15 and IXAROLA 20 are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking IXAROLA 15 or IXAROLA 20, please consult your doctor, pharmacist or other healthcare professional for advice.

IXAROLA 15 and IXAROLA 20 may cause bleedings which may potentially be life threatening. Excessive bleeding may lead to sudden drop in blood pressure (shock). In some cases these bleedings may not be obvious.

Tell your doctor immediately, if you experience any of the following side effects:

- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain (angina pectoris). These may be signs of bleeding.

Your doctor may decide to keep you under closer observation or change how you should be treated.

It has been reported for IXAROLA 15 and IXAROLA 20 that the following side effects can occur:

Possible side effects which may be a sign of severe allergic reactions

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

- swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure. The frequencies of these side effects are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

Frequent side effects

- bleeding in the stomach or bowel, blood in the urine (urogenital bleeding), heavy periods (menstrual bleeding), nose bleeds, bleeding of the gum
- bleeding in the eye (including bleeding from the whites of the eyes)
- bleeding in tissue (bruising) or deep in (a cavity of) the body (hematoma)
- bleeding following an operation
- swelling in the limbs
- pain in the limbs
- increase in body temperature (fever)
- pale skin, weakness and breathlessness due to a reduction in red blood cells (anemia)
- stomach, indigestion, feeling or being sick, constipation, diarrhoea
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up (hypotension))
- weakness, tiredness, headache, dizziness
- rash, itchy skin
- blood tests may show an increase in some liver enzymes
- coughing up blood

Less frequent side effects

- - bleeding in the brain or inside the skull
- bleeding in a joint causing pain and swelling
- oozing of blood or fluid from surgical wound
- feeling unwell
- dry mouth
- allergic reactions, including allergic skin reactions
- itchy, raised rash (hives)
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- raised heartbeat
- fainting
- bleeding in the muscle
- collection of blood (hematoma) following complication in a cardiac procedure where a catheter is inserted to treat narrowed coronary arteries (pseudoaneurysm)
- swelling in a particular area
- yellowing of the skin and eyes (jaundice)

Side effects where frequency is not known:
(frequency cannot be estimated from the available data)

- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome)
- decrease in urine, swelling in limbs, shortness of breath and fatigue after a severe bleeding (kidney failure)

The following side effects have been reported since authorisation:

- allergic reaction causing swelling of the face, lips, mouth, tongue or throat(angioedema and allergic edema)
- diarrhoea, trapped gas, stomach cramp, weight loss caused by blocked bile flow (choloestasis), swollen or tender in right side of abdomen, inflamed liver including liver injury (hepatitis)
- low number of platelets, which are cells that help blood to clot (thrombocytopenia)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the "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 NIMOTOP 30mg.

5. How to Store IXAROLA 15 AND IXAROLA 20:

Store at or below 30 °C. Keep blister strips in the original carton until use.
Do not use IXAROLA 15 or IXAROLA 20 after the expiry date which is stated on the carton and on each blister.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).
Store all medicines out of the reach of children.

6. Contents of the pack and other information

WHAT IXAROLA 15 AND IXAROLA 20 CONTAIN:

The active substance is rivaroxaban. Each tablet contains 15 mg (IXAROLA 15) or 20 mg (IXAROLA 20) of rivaroxaban.

The other ingredients are:
Tablet core: cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium lauryl sulphate.
Film-coat: ferric oxide red E172, hypromellose 15 cP, macrogol 3350, titanium dioxide E171.

What IXAROLA 15 AND IXAROLA 20 looks like and contents of the packs

IXAROLA 15: Round, biconvex, red film-coated tablets, 6 mm in diameter, 9 mm radius of curvature, debossed with a triangle over "15" on the top side and the BAYER cross on the bottom side of the tablet.

IXAROLA 20: Round, biconvex, brown red film-coated tablets, 6 mm in diameter, 9 mm radius of curvature, debossed with a triangle over "20" on the top side and the BAYER cross on the bottom side of the tablet.

IXAROLA 15 film-coated tablets are packed in colourless, transparent PP (polypropylene)/aluminium blister strips or colourless, transparent PVC/PVDC/aluminium blister strips. Pack sizes: 14 tablets, 28 tablets, 42 tablets, 98 tablets or 100 tablets.

IXAROLA 20 film-coated tablets are packed in colourless, transparent PP (polypropylene)/aluminium blister strips or colourless, transparent PVC/PVDC/aluminium blister strips. Pack sizes: 14 tablets, 28 tablets, 42 tablets, 98 tablets or 100 tablets.

Not all pack sizes may be marketed.

Holder of Certificate of Registration

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