PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

RIQVIVA 100 (concentrate for solution for intravenous infusion)

RIQVIVA 400 (concentrate for solution for intravenous infusion)

Bevacizumab

Contains sugar (α,α trehalose dihydrate)

Read all of this leaflet carefully before you start receiving RIQVIVA

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist, nurse or a healthcare practitioner.
- RIQVIVA 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 RIQVIVA is and what it is used for
2. What you need to know before you use RIQVIVA
3. How to use RIQVIVA
4. Possible side effects
5. How to store RIQVIVA
6. Contents of the pack and other information

1. What RIQVIVA is and what it is used for

RIQVIVA contains the active substance bevacizumab, which is a humanised monoclonal antibody (a type of protein that is normally made by the immune system to help defend the body from infection

and cancer). Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour.

RIQVIVA may be used in adults for the treatment of:

- advanced cancer in the large bowel, i.e., in the colon or rectum;
- metastatic breast cancer;
- advanced non-small cell lung cancer when cancer cells have specific mutations of a protein called epidermal growth factor receptor (EGFR);
- with advanced kidney cancer;
- persistent, recurrent or metastatic cervical cancer;
- glioblastoma, a form of brain cancer.

RIQVIVA will be administered in combination with other cancer therapy medicine, as your doctor prescribes.

2. What you need to know before you take RIQVIVA

Should not be administered with RIQVIVA if you:

- are hypersensitive (allergic) to bevacizumab or any of the ingredients of RIQVIVA;
- are hypersensitive (allergic) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies;
- are pregnant and breastfeeding;
- are taking a medicine called sunitinib which is used in the treatment of some types of cancers;
- are being injected with it into your eye.

Warnings and precautions with RIQVIVA

Talk to your doctor health care provider before receiving RIQVIVA:

- If you have abdominal inflammation (e.g., diverticulitis, stomach ulcers, colitis associated with chemotherapy), as it is possible that RIQVIVA and chemotherapy may increase the risk of perforation of (or holes in) the gut.
- RIQVIVA may increase the risk of developing an unusual opening that develops between the vagina and another organ, such as the bladder, colon or rectum or in other organs.
  Your health care provider might describe it as a hole in the vagina that allows urine, gas or stool to pass through the vagina or an abnormal connection between your food pipe (oesophagus) and windpipe (trachea).
- RIQVIVA can increase the risk of bleeding or increase the risk of problems with wound healing after surgery. If you are going to have an operation, if you have had major surgery within the last 28 days or if you still have an unhealed wound following surgery, you should not receive RIQVIVA.
- RIQVIVA may increase the risk of developing serious infections of the skin or deeper layers under the skin, especially if you have open wounds that are not yet healed or after an operation.
- RIQVIVA can increase the incidence of high blood pressure. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting RIQVIVA treatment.
- RIQVIVA increases the risk of having protein in your urine especially if you already have high blood pressure.
- A rare neurological side effect named posterior reversible encephalopathy syndrome (PRES) has been associated with RIQVIVA treatment. If you have headaches, vision changes, confusion or seizures with or without high blood pressure, please contact your doctor.

- The risk of developing blood clots in your arteries (a type of blood vessel) can increase if you are over 65 years old, if you have diabetes, or if you have had previous blood clots in your arteries.

  Please talk to your doctor since blood clots can lead to heart attack

  and stroke.
- RIQVIVA can also increase the risk of developing blood clots in your veins (a type of blood vessel).
- This medicine may cause bleeding, especially tumour-related bleeding. Please consult your doctor if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for any reason.
- It is possible that RIQVIVA may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.
- It is possible that RIQVIVA can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- RIQVIVA can increase the risk of developing a weak heart. It is important that your doctor knows if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, or if you have heart disease.
- RIQVIVA may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).
- It is possible that RIQVIVA can cause hypersensitivity and/or infusion reactions (reactions related to your injection of the medicine). Please let your doctor, pharmacist or nurse know if you have previously experienced problems after injections, such as dizziness/feeling of fainting, breathlessness, swelling or skin rash.

Before you are given RIQVIVA or while you are being treated with RIQVIVA:

- if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
- if you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with RIQVIVA, in particular when you are also receiving or have received an injection of bisphosphonate into your blood.

You may be advised to have a dental check-up before you start treatment with RIQVIVA.

- If you have eye problems.

Children and adolescents

RIQVIVA use is not recommended in children and adolescents under the age of 18 years because the safety and benefit have not been established in these patient populations.

Death of bone tissue (osteonecrosis) in bones other than the jaw have been reported in patients under 18 years old when treated with RIQVIVA.

Taking other medicines with RIQVIVA

Always tell your health care provider if you are taking any other medicine.

(This includes complementary or traditional medicines).

If you are taking medicines on a regular basis, using RIQVIVA at the same time with another medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice.

Combinations of RIQVIVA with another medicine called sunitinib malate (prescribed for kidney and gastrointestinal cancer) may cause severe side effects. Discuss with your health care provider to make sure that you do not combine these medicines.

Tell your health care provider if you are using platinum- or taxane-based therapies for lung or metastatic breast cancer. These therapies in combination with RIQVIVA may increase the risk of severe side effects.

Please tell your health care provider if you have recently received, or are receiving, radiotherapy.

Pregnancy, breast feeding and fertility

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 RIQVIVA.

You must not use RIQVIVA if you are pregnant. RIQVIVA may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using highly effective contraception during treatment with RIQVIVA and for at least 6 months after the last dose of RIQVIVA.

You must not breastfeed your baby during treatment with RIQVIVA and for at least 6 months after the last dose of RIQVIVA, as RIQVIVA may interfere with the growth and development of your baby.

RIQVIVA may impair female fertility. Please consult your doctor for more information.

If you are a male patient you should not father a child while receiving treatment with RIQVIVA. You must use an effective method of contraception while using RIQVIVA for at least 3 months after stopping treatment with RIQVIVA.

Driving and using machines

RIQVIVA may impair your ability to drive or to operate machinery.

Important information about some of the ingredients of RIQVIVA

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

3. How you are given RIQVIVA

Do not share medicines prescribed for you with any other person. RIQVIVA must always be administered by a doctor.

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

Receiving RIQVIVA

Dosage and frequency of administration

The dose of RIQVIVA needed depends on your body weight and the kind of cancer to be treated. Your doctor will prescribe a dose of RIQVIVA that is right for you. You will be treated with RIQVIVA once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until RIQVIVA fails to stop your tumour growing. Your doctor will discuss this with you.

Method and route of administration

RIQVIVA is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the RIQVIVA vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted RIQVIVA solution by intravenous infusion (a drip into your vein). The first infusion will be given to you over 90 minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes.

The administration of RIQVIVA should be temporarily discontinued

- if you develop severe high blood pressure requiring treatment with blood pressure medicines;
- if you have problems with wound healing following surgery;
- if you undergo surgery.

The administration of RIQVIVA should be permanently discontinued if you develop:

- severe high blood pressure which cannot be controlled by blood pressure medicines, or a sudden severe rise in blood pressure;
- presence of protein in your urine accompanied by swelling of your body;

- a hole in your gut wall;
- an abnormal tube-like connection or passage between the windpipe and the gullet, between internal organs and skin, between the vagina and any parts of the gut or between other tissues that are not normally connected (fistula), and are judged by your doctor to be severe;
- serious infections of the skin or deeper layers under the skin;
- a blood clot in your arteries;
- a blood clot in the blood vessels of your lungs;
- any severe bleeding.

Your doctor will tell you how long your treatment with RIQVIVA will last.

You should not receive RIQVIVA for longer than absolutely necessary.

If you take more RIQVIVA than you should

You may develop a severe migraine. If this happens you should talk to your doctor, pharmacist or nurse immediately.

Since a healthcare professional will administer this medicine, he/she will control the dosage.

However, in the event of overdosage your doctor will manage the overdosage.

If you missed a dose of RIQVIVA

Your doctor will decide when you should be given your next dose of RIQVIVA. You should discuss this with your doctor.

If you stop treatment with RIQVIVA

Stopping your treatment with RIQVIVA may stop the effect on tumour growth. Do not stop treatment with RIQVIVA unless you have discussed this with your doctor.

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

4. Possible side effects

RIQVIVA can have side effects.

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

Allergic reactions

If you have an allergic reaction, tell your doctor or a member of the medical staff straight away. The signs may include: difficulty in breathing or chest pain. You could also experience redness or flushing of the skin or a rash, chills and shivering, feeling sick (nausea) or being sick (vomiting).

Tell your doctor or nurse straight away, if you notice any of the following side effects:

Frequent:

- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever) and cells that help the blood to clot,
- decrease number of red blood cells,
- loss of appetite and weight,
- low levels of magnesium which may cause spasms of hands and feet, muscular twitching, cramps,
- low levels of salt which maybe characterised by weakness, drowsiness and muscle cramps,
- feeling thirsty,
- feeling of numbness or tingling in hands or feet,
- difficulty speaking,
- headache,
- problems with taste,
- reduced blood supply to the brain or stroke,
- fainting,

- sleepiness,
- eye problems,
- increased production of tears,
- heart failure,
- increase in heart rate (pulse),
- high blood pressure,
- blocking of the arteries by a blood clot,
- bleeding,
- blocking of the veins of the legs by a blood clot,
- shortness of breath,
- runny nose,
- nose bleeds,
- cough,
- low levels of oxygen in the blood,
- blood clot that blocks and stops blood flow to an artery in the lung,
- diarrhoea,
- nausea,
- vomiting,
- abdominal pain,
- constipation,
- inflammation of the mouth,
- bleeding in the rectum,
- perforation of the gut (stomach pain or cramping, bloating, fever or chills),
- blockage in the gut or bowel,
- fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut,

- pain due to a spasm of the pelvic floor muscles, the muscles of the anal sphincter, or the muscles of the rectum,
- a condition in which the ovaries stop working and it has a negative effect on a woman's ability to have children,
- inflammation of the skin,
- dry skin,
- change in skin colour,
- redness, peeling, tenderness, pain, or blistering on the fingers or feet,
- muscle and joint pain,
- muscular weakness,
- back pain,
- abnormal urine test (protein in the urine),
- urinary tract infections,
- feeling weak and having no energy,
- tiredness,
- fever,
- pain,
- inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts,
- pelvic pain,
- loss of body weight.

Less frequent:

- a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES),
- symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure.

Side effects of unknown frequency include:

- serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing,
- allergic reactions (the signs may include difficulty breathing, facial redness, rash, low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting),
- blood clot formation in the very small blood vessel(s) in the kidney, causing high levels of protein in the urine picked up by a urine test,
- abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal,
- a hole in the cartilage wall separating the nostrils of the nose,
- abnormal voice changes,
- stomach and intestinal ulcers,
- hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and nausea/vomiting),
- lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue,
- pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs and symptoms of bone damage in the jaw (osteonecrosis),
- foetal abnormalities.

These are all serious side effects. You may need urgent medical attention.

Patients older than 65 years have an increased risk of experiencing the following side effects:

- blood clot in the arteries which can lead to a stroke or a heart attack,
- reduction in the number of white cells in the blood, and cells that help the blood clot,
- diarrhoea,
- sickness,
- headache,

- fatigue,
- high blood pressure.

RIQVIVA may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); increased serum creatinine (a protein measured by a blood test to see how well your kidneys are working); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

Pre-menopausal women (women who have a menstrual cycle) may notice that their periods become irregular or are missed and may experience impaired fertility. If you are considering having children you should discuss this with your doctor before your treatment starts.

RIQVIVA has been developed and made to treat cancer by injecting it into the bloodstream. It has not been developed or made for injection into the eye. It is therefore not authorised to be used in this way.

When RIQVIVA is injected directly into the eye (unapproved use), the following side effects may occur:

- Infection or inflammation of the eye globe,
- Redness of the eye, small particles or spots in your vision (floaters), eye pain,
- Seeing flashes of light with floaters, progressing to a loss of some of your vision,
- Increased eye pressure,
- Bleeding in the eye.

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 or pharmacist or nurse.

You can also report side effects to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of RIQVIVA.

5. How to store RIQVIVA

Storage of unopened vials

Store in a refrigerator between 2 °C to 8 °C.

Do not freeze. Do not shake.

Keep the vial in the carton in order to protect from light.

Storage of diluted product

RIQVIVA does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated at 5 ± 3 °C or 30 ± 2 °C up to 48 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C.

Do not use this medicine if you notice any particulate matter or discoloration prior to administration.

Discard any unused solution.

Do not use this medicine after the expiry date which refers to the last day of that month.

Do not dispose medicines in drains or sewerage systems (e.g., toilets).

Return all unused and expired medicines to your pharmacist.

Keep this medicine out of the sight and reach of children.

6. Contents of the pack and other information

What RIQVIVA contains

The active substance is bevacizumab.

The other ingredients are:

α, α-trehalose dihydrate,

polysorbate 20,

sodium phosphate (dibasic, anhydrous),

sodium phosphate (monobasic, monohydrate),

water for injection.

What RIQVIVA looks like and contents of the pack

RIQVIVA is a clear or opalescent, colourless to slightly brownish liquid.

RIQVIVA 100: 5 mL clear tubular USP Type I glass vial with a 20 mm butyl rubber stopper with fluorotic coating and a blue 20 mm flip-off aluminium seal containing 100 mg of bevacizumab.

RIQVIVA 400: 20 mL clear tubular USP Type I glass vial with a 20 mm butyl rubber stopper with fluorotic coating and a blue 20 mm flip-off aluminium seal containing 400 mg of bevacizumab**.**

Holder of the certificate of registration

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Registration numbers

RIQVIVA 100: 56/26/0604

RIQVIVA 400: 56/26/0605

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration: Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

Access to the corresponding Professional Information

Detailed information on this medicine is available on the Dr. Reddy's Laboratories (Pty) Ltd. website:

http://www.drreddys.co.za