

**DR. REDDY'S LABORATORIES (PTY) LTD.
APPROVED PATIENT INFORMATION LEAFLET:
ZYTORVI
(Toripalimab)
(concentrate for solution for infusion)**

SCHEDULING STATUS

S4

ZYTORVI (concentrate for solution for infusion)

Toripalimab

Contains sugar (mannitol)

Each vial contains 150 mg mannitol

Read all of this leaflet carefully before you start receiving ZYTORVI

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

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1. What ZYTORVI is and what it is used for

ZYTORVI contains the active substance toripalimab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Toripalimab, works by attaching to a target protein called programmed death-1 receptor (PD-1). PD-1 can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences), which prevents your immune system from fighting the cancer. By attaching to PD-1, toripalimab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the cancer.

ZYTORVI is a medicine used to treat adults with a type of head and neck cancer called nasopharyngeal carcinoma (NPC).

- ZYTORVI may be used in combination with the chemotherapy medicines cisplatin and gemcitabine, as your first treatment when your NPC has spread to other parts of your body (metastatic) or has returned (recurrent) in nearby tissues (locally advanced).
- ZYTORVI may be used alone to treat your NPC when it:
 - has returned and cannot be removed with surgery or has spread (metastatic), and
 - you received chemotherapy that contains platinum, and it did not work or is no longer working.

ZYTORVI is given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these medicines. If you have any questions about ZYTORVI or these other medicines, please ask your doctor.

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2. What you need to know before you are given ZYTORVI

You should not be administered with ZYTORVI if you

- are hypersensitive (allergic) to toripalimab or any of the ingredients of ZYTORVI (see section 6).

Warnings and precautions

Special care should be taken with ZYTORVI if you have:

- autoimmune diseases (illnesses where the body attacks its own cells) such as Crohn's disease, ulcerative colitis, or lupus;
- lung problems or breathing problems (called pneumonitis);
- stomach and intestinal problems;
- liver problems including an active viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
- hormone gland problems;
- liver problems;
- kidney problems;
- skin problems;
- heart problems;
- vasculitis which is a group of diseases where inflammation causes the walls of blood vessels to thicken, which can narrow the vessels and restrict blood flow, potentially damaging organs;
- eye problems;
- muscle and joint problems;

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- systemic autoimmune diseases or severe inflammatory responses;
- infusion reactions;
- received an organ transplant;
- received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic);
- received radiation treatment to your chest area;
- had a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome;
- active tuberculosis (TB);
- human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS).

Children and adolescents

Talk to your doctor, pharmacist or nurse before you are given this medicine if you, or your child, is under 18 years of age.

It is not known if ZYTORVI is safe and effective in children and adolescents.

Using other medicines with ZYTORVI

Always tell your healthcare professional if you are taking any other medicine.

(This includes complementary or traditional medicines).

If you are taking medicines that suppress your immune system, such as corticosteroids (like prednisone).

These medicines may interfere with the effect of ZYTORVI.

However, once you are treated with ZYTORVI, your doctor may give you corticosteroids to reduce the side-effects that you may have with ZYTORVI. Corticosteroids may also be given to you before receiving ZYTORVI in combination with chemotherapy to prevent and/or treat nausea, vomiting, and other side effects caused by

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chemotherapy.

Receiving ZYTORVI with food and drink

There is no information to suggest that the consumption of food and drink affects the way ZYTORVI works.

Pregnancy, breastfeeding and fertility

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

ZYTORVI can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare professional should do a pregnancy test before you start treatment with ZYTORVI.
- You should use an effective method of birth control during your treatment and for 4 months after your last dose of ZYTORVI.
- Talk to your healthcare professional about birth control methods that you can use during this time.

It is not known if ZYTORVI passes into your breast milk.

Do not breastfeed during treatment and for 4 months after the last dose of ZYTORVI.

Driving and using machines

ZYTORVI may have a minor effect on your ability to drive or use machines, as feeling dizzy or tired are possible side effects. Do not drive or use machines unless you are sure you are feeling well.

ZYTORVI contains mannitol

ZYTORVI contains mannitol which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using ZYTORVI.

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ZYTORVI contains sodium

ZYTORVI contains 0,4 mmol (or 7,57 mg) sodium per vial. This needs to be taken into consideration if you are on a low- sodium diet.

3. How to use ZYTORVI

Your doctor will decide on the most suitable treatment for you including:

- the correct dose
- how often and for how long you should be treated and whether you should also receive other medicines with ZYTORVI or not.

Your doctor will give you all the necessary information on your treatment plan.

ZYTORVI will always be prepared and given to you by a healthcare professional, as an intravenous infusion (drip) over 30 or 60 min.

ZYTORVI is usually given every two or three weeks as an intravenous (IV) infusion.

Your healthcare professional will test your blood to check you for certain side effects.

If you miss any appointments, call your healthcare professional as soon as possible to reschedule.

Do not stop treatment early without discussing this with your doctor.

If you have the impression that the effect of ZYTORVI is too strong or too weak, tell your doctor or another healthcare professional.

If you forget to receive ZYTORVI

If you forget to receive ZYTORVI for any reason, discuss this with your doctor or another healthcare professional immediately.

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If you stop receiving ZYTORVI

Discuss the effects of stopping treatment with ZYTORVI if you choose to do so with your doctor.

If you are receiving more ZYTORVI than you should

The treatment schedule and dose will be decided by your doctor, who will monitor your response. If you are concerned that you have been given too much ZYTORVI, contact your doctor or another healthcare professional immediately.

4. Possible side effects

ZYTORVI can have side effects. Side effects are mild to moderate but some may be serious and fatal.

Not all side effects reported for ZYTORVI are included in this leaflet.

Should your general health worsen or if you experience any untoward effects while taking ZYTORVI, please consult your doctor, pharmacist or other health care professional for advice.

If any of the following happens, stop using ZYTORVI and tell your doctor immediately or go to the casualty department at your nearest hospital:

Allergic reactions

If you have an allergic reaction, tell your doctor or a member of the medical staff straight away.

Allergic reactions include:

- 'swelling of the hands, feet, ankles, face, mouth, lips, gums, tongue, throat and neck which may cause difficulty in swallowing or breathing', throat tightness.
- shortness of breath and wheezing;
- rash, hives (raised bumps), blisters or itching.

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Allergic reactions, including death, can happen in patients taking ZYTORVI even after only one dose.

These are all very serious side effects. If you have them, you may have had a serious reaction to ZYTORVI.

You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Uncommon (may affect up to 1 in 100 people):

- decreased in number of platelet (immune mediated thrombocytopenia)
- inflammation of thyroid (hyperthyroidism/thyroiditis)
- inflammation of thyroid gland (hypothyroidism)
- inflammation of pituitary gland (hypophysitis)
- inflammation of insulin-producing cells (diabetes mellitus/ hyperglycaemia)
- inflammation of the heart muscle (myocarditis)
- inflammation of lungs (pneumonitis)
- inflammation of the large bowel (colitis)
- inflammation of the liver (hepatitis)
- inflammation of the skin (immune-related skin reactions)
- inflammation in the muscles (myositis)
- inflammation of adrenal glands (adrenal insufficiency)
- inflammation of the kidneys (nephritis)
- infusion reactions.

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Rare (may affect up to 1 in 1 000 people):

- confusion, delirium, drowsiness, and a reduced level of consciousness, bleeding in the brain, paralysis of the lower extremities
- inflammation of the pancreas (pancreatitis)
- inflammation of the joints (arthritis/arthralgia)
- inflammation of bladder (cystitis).

Frequency cannot be estimated from the available toripalimab data but have been reported with this class of medicines

- inflammation of the brain (encephalitis) which may include symptoms of confusion, fever, memory problems or seizure.
- Myasthenic syndrome, a condition in which the muscles become weak and there is a rapid fatigue of the muscles
- inflammation of the nerves, including Guillain Barré syndrome: symptoms may include weakness in the arm and leg muscles, or face muscles, double vision, and tingling in hands and feet
- rhabdomyolysis, symptoms may include stiffness in muscles and joints, muscle spasm.
- organ transplant rejection
- inflammation of the uvea (uveitis).

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

Tell your doctor if you notice any of the following:

Very common side effects (may affect more than 1 in 10 people):

- upper respiratory tract infection (nose and throat infection)

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- anaemia (low levels of red blood cells), leukopenia (low levels of white blood cells), neutropenia (low levels of neutrophils, a type of white blood cell), thrombocytopenia (low levels of blood platelets, components which help the blood to clot)
- hypothyroidism (an underactive thyroid gland with tiredness, weight gain, and skin and hair changes)
- decreased appetite and weight, hyponatraemia (low blood sodium levels), hypoproteinaemia (low blood protein levels), hypokalaemia (low blood potassium levels which can cause weakness, muscle cramps, tingling)
- hyperglycaemia (high blood glucose levels), hyperuricaemia (increase in uric acid in the blood causing the big toe to be swollen and painful)
- nerve damage (neuropathy)
- arrhythmia (abnormal or irregular heartbeat)
- cough
- nausea (feeling sick), indigestion/belching, vomiting (throwing up), constipation/ difficulty passing stools, diarrhoea (runny tummy), colitis (inflammation in the large bowel), stomach pain
- hyperbilirubinaemia (high blood levels of bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes)
- rash, itching
- muscle and bone pain
- proteinuria (excess protein in the urine), haematuria (blood in the urine)
- tiredness, fever, pain
- abnormal results for tests of liver function, abnormal results for tests of blood levels of lipids, abnormal

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results for tests of urine analysis.

Common (may affect up to 1 in 10 people):

- different types of infection (e.g., lung, urinary tract, ear, mouth)
- tumour pain
- overactive thyroid gland activity
- trouble sleeping
- inflammation of the nerves causing numbness, weakness, tingling or burning pain; headache; dizziness, problems with taste
- blurred vision
- ear disorder, ear pain, ringing; hearing loss
- high or low blood pressure; dizziness on standing up, clots
- shortness of breath; inflammation of the lungs, fluid around the lungs; nose bleeding, coughing up blood, upper respiratory tract congestion or irritation, hiccups, change in voice, hayfever
- sore, inflamed mouth, bloating, gas, acid reflux, dry mouth, pain on swallowing, toothache, blood in the stool
- skin colour change in patches (including loss of pigmentation, vitiligo), hair loss
- muscle weakness and inflammation of the joints, decrease of joint movement, “frozen shoulder”
- kidney damage
- swelling, flu-like sickness, swelling including of the face, chills, eye disorder (dry or itchy eye, cataract).

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Uncommon side effects (may affect up to 1 in 100 people):

- inflammation of the conjunctiva (conjunctivitis), inflammation of the gums (gingivitis), infections of skin and subcutaneous tissue, skin, toe and nail infections
- tumour bleeding, tumour rupture
- decreased secretion of hormones produced by the adrenal glands; inflammation of the pituitary gland situated at the base of the brain; inflammation of the thyroid
- Type 1 diabetes, including diabetic ketoacidosis
- feeling sad, uneasy and anxious
- sleepiness, epilepsy, tremor, speech disorder, slurred speech
- inflammation of the eye (which causes eye pain and redness), problems with coordinated eye movement; swelling of the optic nerve
- the sensation that you or your surroundings are spinning or swaying, often accompanied by dizziness, loss of balance, deafness
- accumulation of fluid around the heart; inflammation of the heart muscle; heart muscle damage, heart discomfort
- inflammation of the veins
- sinus congestion, breathing difficulties, wheezing, hoarseness
- inflammation of the stomach, a decreased sense of touch or feeling in the mouth, pain in the rectum
- liver pain, inflammation of the gall bladder
- night sweats, peeling of the skin, increased sweating, dry skin, skin ulcers, hair colour changes, skin sensitivity to light, darkening of the skin

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- muscle spasms, bulging disc
- swelling of the kidneys and the ureter, urinating frequently
- breast pain, swelling in the genital area and of the scrotum
- facial pain, swelling, temperature intolerance, thirst
- reactions related to the infusion of the medicine, muscle injury, rib fracture.

Rare (may affect up to 1 in 1 000 people):

- the inflammation or infection of small pouches (diverticula) in the wall of the large intestine, causing symptoms like sudden lower abdominal pain, fever, and changes in bowel habits (diverticulitis), hepatitis B reactivation, muscle abscess, urinary tract infection spreads to the blood stream
- mental disorder, a sudden, rapid, and repetitive motor or vocal action (tic)
- swelling, itching eyelid; farsightedness
- bulge in the aorta, flushing
- inflammation of the layers that cover the lungs; increased amount of sputum
- vocal cord thickening
- gas in the intestinal wall, loss of sensation in the mouth, sore throat, swollen or discoloured tongue
- inflammation of the skin (thickened, sometimes scaly skin growth; chronic itching or scaling, pain of skin
- shedding of the nails
- inflammation of subcutaneous fat, skin bruises and rashes
- spider veins that can appear as fine red, blue, or purple lines

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- a lump or swelling in an arm or leg
- widening of one or both ureters (the tubes connecting the kidneys to the bladder) due to a buildup of urine. It results from a partial or complete blockage of urine flow (hydronephrosis)
- abnormal menstruation including light, heavy or prolonged bleeding
- vaginal discharge or itching or pain of the skin outside vagina
- stones in the prostate causing frequent urination, pain, or difficulty urinating
- administration site reactions, an increase in the number of cells in a tissue or organ, which can cause enlargement (hyperplasia), medical device pain, secretion discharge.

Changes in test results

ZYTORVI alone or in combination may cause changes in the results of tests carried out by your doctor.

These include:

- abnormal liver function tests (including increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, or alkaline phosphatase in your blood)
- abnormal thyroid function tests; anti-thyroid antibody positive
- increased or decreased lipids in blood
- abnormal urine analysis
- abnormal kidney function tests (increased amounts of creatinine or other waste products, uric acid, urea in your blood; increase in the number of cells or amount of protein in urine, abnormal amount of waste products in urine)
- an increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch

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- blood in your stools
- weight increased
- decreased amount of potassium, calcium, sodium, magnesium, chloride, phosphate, and protein in the blood
- increased amount of calcium, potassium, magnesium, sodium, or phosphate in the blood
- increased blood level of muscle enzymes
- and protein in the blood
- changes to the acid base balance in blood
- decreased in more than one type of blood cells (white blood cells, red blood cells, platelets)
- increased white blood cells, neutrophils; eosinophil count abnormal, platelet count increased
- increase or decrease blood levels of endocrine gland hormones
- heart test abnormal.

If you are taking ZYTORVI with other medicines, some of the side effects, you may experience may be due to the other medicines.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist or health care professional. You can also report side effects to SAHPRA via the 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 ZYTORVI.

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5. How to store ZYTORVI

Storage of unopened vials

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

Do not freeze. Store in the outer carton until required for use.

Storage of diluted solution for infusion

ZYTORVI does not contain a preservative.

If the diluted solution is not administered immediately, store either:

- at room temperature, 20 °C to 25 °C, for no more than 8 hours from the time of preparation of the diluted solution to the completion of the infusion OR
- under refrigeration at 2 °C to 8 °C for no more than 24 hours from the time of preparation of the diluted solution to the completion of the infusion.

Discard the diluted solution after 8 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

6. Contents of the pack and other information

What ZYTORVI contains

The active substance is toripalimab.

Each vial contains 240 mg of toripalimab concentrate for solution for infusion.

The other ingredients are citric acid monohydrate, mannitol, polysorbate 80, sodium citrate dihydrate, sodium

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chloride, water for injection.

What ZYTORVI looks like and contents of the pack

Single-use, colorless and transparent, Type I 6 ml neutral borosilicate glass vial with a grey Flurotec-coated chlorobutyl rubber stopper and a 20 mm aluminium blue plastic flip-off seal.

Holder of Certificate of Registration

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

This leaflet was last revised in

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Registration number

59/30.1/0810

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

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Other sources of information

Detailed information on this medicine is available on the Dr. Reddy's Laboratories web site:

www.drreddys.co.za