

1.3.2 PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS:

S4

Fotivda 890 microgram, hard capsule

Fotivda 1340 microgram, hard capsule

Tivozanib, 890 microgram and 1340 microgram

Contains sugar: Fotivda 890 microgram and Fotivda 1340 microgram hard capsules contain sugar (mannitol 78,2 mg and 77,7 mg respectively).

Read all of this leaflet carefully before you start taking Fotivda

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- Fotivda 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 Fotivda is and what it is used for.
2. What you need to know before you take/ use Fotivda.

3. How to take /use Fotivda.
4. Possible side effects.
5. How to store Fotivda.
6. Contents of the pack and other information.

1. What Fotivda is and what it is used for

The active substance in Fotivda is tivozanib, which is a protein kinase inhibitor. Tivozanib reduces the supply of blood to the cancer, which slows down the growth and spread of cancer cells. It works by blocking the action of a protein called vascular endothelial growth factor (VEGF). Blocking the action of VEGF prevents the formation of new blood vessels. Fotivda is used to treat adults with advanced kidney cancer. It is used where other treatments such as interferon-alpha or interleukin-2 have either not yet been used or have not helped to stop your disease.

- **What you need to know before you take Fotivda**

Do not take Fotivda :

- If you are allergic (hypersensitive) to tivozanib or any of the other ingredients of Fotivda.
- If you are taking St. John's Wort (also known as *Hypericum perforatum*, a herbal remedy used for treatment of depression and anxiety).
- If you are pregnant and breastfeeding your baby.
- If you have severe liver disease.
- If you have uncontrolled / not well controlled severe high blood pressure.

- If you have an “under active” thyroid gland (hypothyroidism) not well controlled with treatment.
- If you have uncontrolled / not well controlled heart failure.
- If you have recently suffered from the effects of venous or arterial blood clots.
- If you have or have had a condition of the brain called “posterior reversible encephalopathy syndrome” (PRES).
- If you have an unresolved or not well controlled bleeding tendency.

Warnings and precautions

Take special care with Fotivda:

- If you have high blood pressure.

Fotivda can increase your blood pressure. Your doctor will monitor your blood pressure regularly and, if it is too high, may either give you a medicine to lower it, or reduce your dose of Fotivda. However, if your blood pressure remains too high, your doctor may decide to interrupt or to stop treatment with Fotivda. If you are already taking a medicine to treat high blood pressure, and your doctor reduces the dose of Fotivda or interrupts or stops treatment, you will be regularly checked for low blood pressure.

- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- If you have had problems with blood clots.

Treatment with Fotivda may raise the risk of developing a blood clot (thrombus) in your blood vessels that could break loose and be carried by the blood stream to block another blood vessel.

- Tell your doctor if you have ever had one of the following:
 - a blood clot in your lungs (with cough, chest pain, sudden shortness of breath or coughing up blood),
 - blood clot in your legs or arms, eye, or brain (with pain or swelling in your hands or feet, reduced vision, or changes in your mental state),
 - a stroke, or signs and symptoms of a 'mini-stroke' (transient ischaemic attack),
 - a heart attack,
 - high blood pressure,
 - diabetes,
 - major surgery,
 - multiple injuries such as broken bones and damage to internal organs,
 - inability to move for a long period,
 - heart failure which can cause shortness of breath or ankle swelling
- inability to breathe, bluish colour on your skin, fingertips or lips, restlessness, anxiety, confusion, altered consciousness or sense of awareness, rapid, shallow breathing, a racing heart or excessive sweating.
- If you suffer or have suffered from any of these symptoms or are treated for heart failure:
 - Shortness of breath, (dyspnoea) when you exert yourself or when you lie down,
 - Feeling weak and tired,
 - Swelling (oedema) in your legs, ankles and feet,
 - Reduced ability to exercise,

- Persistent cough and wheezing with white or pink blood-tinged phlegm.

Signs and symptoms of heart failure will be monitored whilst you are taking your medicine.

If necessary, your doctor may reduce your dose of Fotivda, or interrupt or stop this treatment.

- If you have or are treated for an abnormal rate and rhythm of the heartbeat (dysrhythmia). Your doctor will monitor the effect of Fotivda on your heart by recording the electrical activity of your heart (an electrocardiogram) or by measuring your blood calcium, magnesium and potassium levels during your treatment.

- If you have problems with your liver.

Your doctor will regularly monitor how well your liver is working before and during treatment with Fotivda (e.g. with blood tests), and if necessary may need to reduce how often you take Fotivda.

- If you have problems with your thyroid gland or use medicines to treat thyroid disease.

Treatment with Fotivda may cause your thyroid gland to work less well than usual.

Your doctor will regularly monitor how well your thyroid gland is working before and during treatment with Fotivda (e.g. with blood tests).

Talk to your doctor, pharmacist or nurse while taking Fotivda:

- If you get shortness of breath or ankle swelling.

Tell your doctor right away as these may be symptoms of heart failure. Your doctor will monitor this, and depending on the severity may reduce your dose of Fotivda, or interrupt or stop treatment with Fotivda.

- If you have had problems with bleeding.

Treatment with Fotivda may increase the risk of bleeding. If you get bleeding problems (with painful swollen stomach (abdomen), vomiting blood, coughing up blood, black stools, blood in your urine, headache or changes in your mental state), tell your doctor right away. Treatment with Fotivda may need to be temporarily stopped.

- If laboratory tests show that there is protein in your urine.

Your doctor will monitor this at the beginning and during your treatment.

Depending on the results, your doctor may reduce your dose of Fotivda, or interrupt or stop this treatment.

- If you suffer from a disease of the brain, called posterior reversible encephalopathy syndrome (PRES).

Tell your doctor right away if you have symptoms such as headache, seizure (fit), lack of energy, confusion, blindness or other visual and neurologic disturbances such as weakness in an arm or a leg. If PRES is diagnosed, your doctor will stop treatment with Fotivda.

- If the skin on the palms of your hands and the soles of your feet become dry, cracked, scaling, or peeling, or is stinging or tingling.

These may be symptoms of a condition called hand foot skin reaction. Your doctor will treat the condition and, depending on the severity, the doctor may reduce your dose of Fotivda, or interrupt or stop this treatment.

- If you have symptoms of gastrointestinal perforation or fistula formation (developing a hole in the stomach or intestine or abnormal passages forming between parts of

the intestine) such as severe stomach pain, chills, fever, nausea, vomiting or painful bowel obstruction, diarrhoea or rectal bleeding.

Your doctor will regularly monitor you for these symptoms during your treatment with Fotivda.

- If you need to have an operation or another form of surgery.

Your doctor may recommend that you temporarily stop taking Fotivda if you have an operation or surgery, as it could affect wound healing.

Children/ and adolescents

Do not give Fotivda to children and adolescents under 18 years of age because this medicine has not been studied in children and adolescents

Other medicines and Fotivda:

Always tell your healthcare provider if you are taking any other medicine (this includes complementary or traditional medicines).

Fotivda may work less well when taken with some medicines. Tell your doctor if you are taking any of the following medicines; they may decide to change your medicines.

Tell your doctor if you are taking any of the following medicines:

- dexamethasone (a corticosteroid to reduce inflammation and treat disorders of the immune system);
- rosuvastatin (a medicine used to help lower cholesterol levels in your blood);
- phenobarbitone, phenytoin, carbamazepine (used to treat epilepsy);
- nafcillin, rifampicin, rifabutin, rifapentin (antibiotics);

- St. John's Wort (also known as *Hypericum perforatum*, a herbal remedy used for treatment of depression and anxiety) as this herbal remedy should not be used at the same time as Fotivda.

Fotivda with food and drink and alcohol

Fotivda must be taken with a glass of water and can be taken either with or without food.

Swallow the capsule whole. Do not chew, dissolve or open the capsule before swallowing.

Pregnancy and breastfeeding and fertility:

You should not take Fotivda while you are pregnant or trying to become pregnant as

Fotivda may cause harm to your unborn baby (see "Do not take Fotivda").

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice **before** you start taking Fotivda.

Both you and your partner must use effective contraception. If you or your partner are taking hormonal contraceptives (the pill, an implant or patch) you must use an additional barrier method throughout treatment and for another month after completing treatment.

You should not breastfeed your baby while taking Fotivda.

Talk to your doctor when planning a baby, as Fotivda may affect the fertility of men and women.

You and your partner should consider conservation of sperm or ova before treatment with Fotivda.

Driving and using machinery:

Fotivda may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision e.g. driving, riding, flying, sailing, operating machines/equipment. (see '**Undesirable effects**')

Avoid driving or using machines if you feel weak, tired, or dizzy.

Fotivda contains tartrazine.

The printing ink used on the Fotivda 890 microgram capsule contains tartrazine (E102), which may cause allergic reactions.

Fotivda 890 microgram and Fotivda 1340 microgram hard capsules contain sugar (mannitol 78,2 mg and 77,7 mg respectively), which may have an effect on the control of your blood sugar if you have diabetes mellitus.

If you have been told that you have an intolerance to some sugars, you should not take Fotivda.

2. How to take Fotivda:

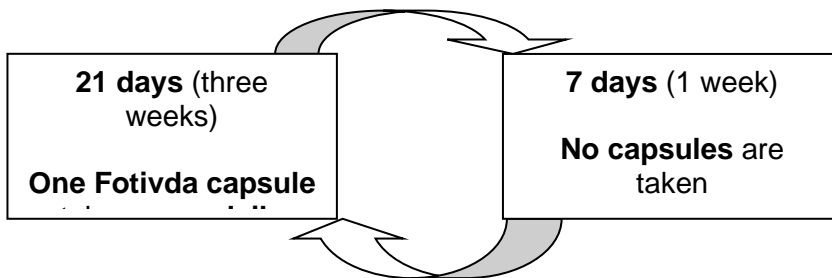
Do not share medicines prescribed for you with any other person.

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

Your doctor will prescribe the correct dose for you.

The usual dose is one Fotivda 1340 microgram capsule, taken once daily for 21 days (3 weeks), followed by a 7-day (1-week) period when no capsules are taken.

This schedule is repeated in cycles of 4 weeks.



Your doctor will check you regularly, and you will normally continue to take Fotivda as long as it is working, and you do not suffer unacceptable side effects.

Reduced dose

In case you experience severe side effects, your doctor may decide to interrupt Fotivda therapy and/or lower the dose to:

One Fotivda 890 microgram capsule, taken once daily for 21 days (3 weeks), followed by a 7-day (1-week) period when no capsules are taken.

This schedule is repeated in cycles of 4 weeks.

Liver problems

If you have liver problems, your doctor may reduce how often you take your dose to every other day (i.e. one 1340 microgram capsule every other day).

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

If you have the impression that the effect of Fotivda is too strong or too weak, tell your doctor or pharmacist.

If you take more Fotivda than you should:

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

Tell your doctor straightaway if you have taken more than your prescribed dose of 1 capsule per day.

Taking too much Fotivda makes side effects more likely or to become more severe, especially high blood pressure. Get medical help straightaway if you experience confusion, changes in your mental state or headaches. These are all symptoms of high blood pressure

If you forget to take / missed a dose of Fotivda:

If you have missed taking a capsule do not take a replacement capsule. Continue to take your next dose at the usual time.

Do not take a double dose to make up for forgotten individual doses.

If you vomit after taking Fotivda, do **not** take a replacement capsule. Continue to take your next dose at the usual time.

If you stop taking/using Fotivda

Do not stop taking Fotivda unless your doctor tells you to. If you stop taking the capsules your condition may get worse.

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

3. Possible side effects

Fotivda can have side effects.

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

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

- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing;
- rash or itching;
- fainting;
- yellowing of the skin and eyes, also called jaundice.

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

High blood pressure is the most serious and a very common side effect (see also "Take special care with Fotivda").

Tell your doctor immediately if you think you have high blood pressure. Symptoms include severe headaches, blurred vision, shortness of breath, changes in your mental state, such as feeling anxious, confused or disorientated.

Your doctor will check your blood pressure regularly during treatment with Fotivda. If you develop high blood pressure, your doctor may prescribe a medicine to treat your high blood pressure, lower your dose of Fotivda, or stop your treatment with Fotivda.

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

The following side effects have been reported more frequently:

- Difficulty speaking
- Diarrhoea
- Loss of appetite; weight loss
- Headache
- Difficult breathing; shortness of breath during exercise; coughing.
- Tiredness; unusual weakness; pain (including in the mouth, bone, extremities, side of the body, groin, tumour).
- Inflammation of the mouth; slight mouth pain or discomfort; feeling sick; pain, discomfort and tightness in the stomach.
- Hand-foot-syndrome with skin reddening, swelling, numbness and skin peeling on palms and soles.
- Back pain
- Tiredness and lack of energy.
- Underactive thyroid gland which may cause symptoms such as tiredness, lethargy, muscle weakness, slow heart rate, weight gain.
- Unable to sleep
- Nerve damage including numbness, pins and needles, sensitive skin or numbness and weakness in the arms and legs.

- Sight problems including blurred vision.
- Rapid heart rate; tightness of the chest; heart attack/reduced blood flow to heart; blood clot in an artery (blood vessel).
- Blood clot in the lung. Symptoms include cough, chest pain, sudden shortness of breath or coughing up blood.
- Blood clot in a deep vein such as in the leg.
- Very high blood pressure leading to a stroke; flushed skin.
- Nose bleed; runny nose; blocked nose.
- Flatulence; heartburn; difficult and painful swallowing; sore throat; bloated stomach; swollen and painful tongue; inflamed painful and/or bleeding gums.
- Taste changes or loss of taste.
- Dizziness; ringing in the ears; dizziness and a spinning sensation (vertigo).
- Bleeding, e.g. in the brain, from the mouth, gums, lungs, stomach, gut ulcers, female genitals, anus, adrenal gland.
- Coughing up blood; vomiting up blood.
- Paleness and tiredness from excess bleeding.
- Being sick; indigestion; constipation; dry mouth.
- Itchy skin; rash; itching of the body; skin peeling; dry skin; hair loss; redness of the skin including the hands and body; acne.
- Fever; chest pain; swelling of feet and legs; chills and low body temperature.
- Joint pain; muscle pain.
- Increased amount of protein in the urine.
- Abnormal blood test results for liver, pancreas, kidney, and thyroid.

Inflammation of the pancreas causing severe stomach pain which may spread to your back.

The following side effects have been reported less frequently:

- Rashes with pus; fungal infections.
- Bruising easily, bleeding into the skin.
- Overactive thyroid gland (which may cause symptoms like increased appetite, loss of weight, intolerance to heat, increased sweating, tremors, rapid heart rate); enlarged thyroid gland.
- Increase in number of red blood cells.
- Memory loss.
- Temporary reduced blood flow to the brain.
- Watery eyes.
- Blocked ears.
- Lack of blood flow through the heart blood vessels.
- Peptic ulcer in the small intestines.
- Red, swollen and sore skin; blistering skin; excessive sweating; hives.
- Muscle weakness.
- Swelling or irritation of the mucous membranes.
- Abnormal electrocardiogram (ECG), rapid and/or irregular heartbeat.
- Heart failure. Symptoms include shortness of breath or ankle swelling. Swelling in the lungs caused by fluid build-up.

- Posterior reversible encephalopathy syndrome (PRES). Symptoms include headache, seizure, lack of energy, confusion, blindness or other visual and neurologic disturbances.

The following side effects have been reported, but the frequency is not known:

- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

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 or pharmacist or nurse. 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 Fotivda.

4. How to store Fotivda

- Store all medicines out of reach of children.
- Store at or below 25 °C.
- Store in the original container.
- Keep the container tightly closed to protect from moisture.
- Do not store in a bathroom.

- Do not use after the expiry date stated on the label or carton.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

5. Contents of the pack and other information

What Fotivda contains

Fotivda 890 microgram

The active substance is 890 microgram tivozanib.

The other ingredients are:

Capsule content:

Mannitol, magnesium stearate.

Capsule shell:

Gelatine, titanium dioxide (E171), indigo carmine (E132), yellow iron oxide. (E172).

Printing ink (yellow):

Shellac, propylene glycol, strong ammonia solution, titanium dioxide (E171), tartrazine aluminium lake (E102).

Printing ink (blue):

Shellac, propylene glycol, strong ammonia solution, indigo carmine aluminium lake (E132).

Excipients with known effect:

Each hard capsule contains trace amounts of tartrazine (E102) (8 – 12 % of the yellow printing ink composition).

Fotivda 1340 microgram

The active substance is 1340 microgram tivozanib.

The other ingredients are:

Capsule content:

Mannitol, magnesium stearate.

Capsule shell:

Gelatine, titanium dioxide (E171), yellow iron oxide (E172)

Printing ink (blue)

shellac, propylene glycol, strong ammonia solution, indigo carmine aluminium lake (E132)

Fotivda 890 microgram and Fotivda 1340 microgram hard capsules contain sugar (mannitol 78,2 mg and 77,7 mg respectively).

What Fotivda looks like and contents of the pack

Fotivda 890 microgram: Size 4 intact capsule containing white to off-white powder and consisting of: Cap: Dark blue, opaque imprinted in yellow with "TIVZ"

Body: Bright yellow, opaque imprinted in dark blue with "LD"

Fotivda 890 microgram: Size 4 intact capsule containing white to off-white powder and consisting of: Cap: Dark blue, opaque imprinted in yellow with "TIVZ"

Body: Bright yellow, opaque imprinted in dark blue with "LD"

The capsules are packed in white HDPE bottle with a white child resistant polypropylene closure containing 21 hard capsules. Each bottle is packed into an outer cardboard carton.

Holder of Certificate of Registration

Key Oncologics (Pty) Ltd

39 Eleventh Avenue

Houghton Estate, 2198

South Africa

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Registration numbers

FOTIVDA 890 µg: 53/26/0503

FOTIVDA 1340 µg: 53/26/0504

Access to the corresponding Professional Information

Can be obtained on the SAHPRA website