

Package leaflet: Information for the patient

RAVICTI 1.1 g/ml oral liquid glycerol phenylbutyrate

Read all of this leaflet carefully before you start taking this medicine, because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What RAVICTI is and what it is used for
2. What you need to know before you take RAVICTI
3. How to take RAVICTI
4. Possible side effects
5. How to store RAVICTI
6. Contents of the pack and other information

1. What RAVICTI is and what it is used for

RAVICTI contains the active substance ‘glycerol phenylbutyrate’ which is used to treat six known ‘urea cycle disorders’ (UCDs) in adults and children. The UCDs include deficiencies of certain liver enzymes such as carbamoyl phosphate synthetase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH).

RAVICTI must be combined with a diet reduced in protein intake, and in some cases a diet with supplements such as essential amino acids (arginine, citrulline, protein-free calorie supplements).

About urea cycle disorders

- In urea cycle disorders, the body cannot remove the nitrogen from the protein that we eat.
- Normally, the body turns the extra nitrogen in the protein into a waste compound called ‘ammonia’. The liver then removes ammonia from the body through a cycle called the ‘urea cycle’.
- In urea cycle disorders, the body is not able to produce enough liver enzymes to remove the extra nitrogen.
- This means that ammonia builds up in the body. If ammonia is not removed from the body, it can harm the brain and lead to low levels of consciousness or coma.
- Urea cycle disorders are rare.

How RAVICTI works

RAVICTI helps the body to eliminate waste nitrogen. This reduces the amount of ammonia in your body.

2. What you need to know before you take RAVICTI

Do not take RAVICTI

- if you are allergic to glycerol phenylbutyrate

- if you have acute hyperammonaemia (high levels of ammonia in your blood), which requires more rapid intervention (see section “Warnings and precautions”)

If you are not sure if the above apply to you, talk to your doctor or pharmacist before taking RAVICTI.

Warnings and precautions

Talk to your doctor or pharmacist before taking RAVICTI:

- if you have problems with your kidneys or liver - this is because RAVICTI is removed from your body through the kidneys and liver
- if you have problems with your pancreas, stomach or gut (‘intestines’) - these organs are responsible for absorption of RAVICTI into the body

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

In some cases such as infection or post-surgery, the amount of ammonia may go up despite treatment with this medicine and may damage the brain (hyperammonaemic encephalopathy).

In other cases the amount of ammonia in the blood goes up quickly. In this case, RAVICTI will not stop the level of ammonia in your blood from becoming seriously high.

High levels of ammonia leads to feeling sick (nausea), being sick (vomiting) or feeling confused.

Tell your doctor or go to the hospital straight away if you notice any of these signs.

Laboratory tests will be needed so your doctor can determine and maintain the correct dose for you.

Other medicines and RAVICTI

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines, which may be less effective when used with RAVICTI. If you take these medicines, you may need regular blood tests:

- midazolam and barbiturates - used for sedation, trouble sleeping or epilepsy
- contraceptives

Also, tell your doctor if you are taking the following medicines as they may increase the amount of ammonia in your body or change how RAVICTI works:

- corticosteroids - used to treat inflamed areas of the body
- valproate - a medicine for epilepsy
- haloperidol - used to treat some mental health problems
- probenecid - to treat high levels of uric acid in the blood which can cause gout (‘hyper-uricaemia’)
- lipase inhibitors (such as orlistat) – used to treat obesity
- lipase in pancreatic replacement therapies

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

Pregnancy, contraception and breast-feeding

- If you are pregnant, tell your doctor before you start taking RAVICTI. If you become pregnant while taking RAVICTI, talk to your doctor. RAVICTI should not be used during pregnancy, as a risk for your unborn baby cannot be excluded.
- If you are a woman who could become pregnant, you must use an effective method of contraception, during treatment with RAVICTI. Talk to your doctor about the best method of contraception for you.

- You should discuss with your physician before you plan to breast-feed while taking RAVICTI. A decision should be made whether to breast-feed or stop taking RAVICTI taking into account the benefit of the treatment for you and the benefit of breast-feeding for your baby. This is because RAVICTI may pass into breast milk and a risk to the newborn/infant cannot be excluded.

Driving and using machines

RAVICTI may have major influence on the ability to drive and use machines. When taking RAVICTI you may feel dizzy or have a headache. Do not drive or use machines whilst experiencing these side effects.

3. How to take RAVICTI

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

You must follow a special low protein diet during treatment with RAVICTI.

- This diet will be designed for you by your doctor and dietician.
- You must follow this diet carefully.
- You may need to take supplemental amino acid formulations.
- You will need to have treatment and to follow a diet throughout your life, unless you have a successful liver transplantation.

How much to take

Your doctor will tell you how much RAVICTI you should take each day.

- Your daily dose will depend on your size and weight, the amount of protein in your diet, and your overall urea cycle disorder condition.
- Your doctor may give you a lower dose if you have kidney or liver problems.
- You will need regular blood tests so your doctor can determine the correct dose for you.
- Your doctor might tell you to take RAVICTI more than 3 times each day. In small children, this may be 4 to 6 times a day. There must be at least 3 hours between each dose.

Taking this medicine

Your doctor will tell you how to take RAVICTI oral liquid. It can be taken in the following ways:

- by mouth
- through a tube that goes through your tummy ('abdomen') to the stomach - called a 'gastrostomy tube'
- through a tube that goes through your nose to the stomach - called a 'nasogastric tube'

Take RAVICTI by mouth unless otherwise directed by your doctor.

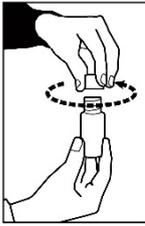
RAVICTI and meals

Take RAVICTI with or straight after a meal. Young children should be given the medicine during or straight after a feeding.

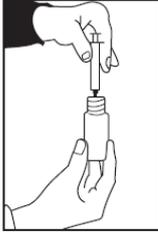
Measuring the dose

- Use an oral syringe to measure your dose.
- You should have the RAVICTI bottle along with an oral syringe to administer the correct amount of RAVICTI.

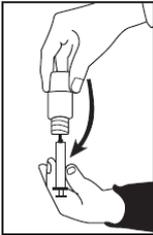
1. Open the bottle of RAVICTI by pushing down on the cap and twisting to the left.



2. Place the tip of the oral syringe into the integrated syringe insert in the bottle.

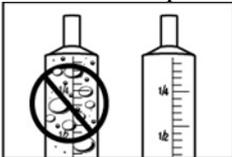


3. Turn the bottle upside down with the oral syringe still inserted.



4. Fill the oral syringe by pulling the plunger back until the syringe is filled with the amount of RAVICTI liquid that your doctor has told you to take.
 - Note: If possible, use the oral syringe ml size that is nearest to (but not smaller than) the recommended dose (for example, if the dose is 0.8 ml, use a 1 ml oral syringe).

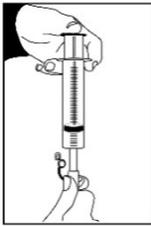
5. Tap the oral syringe to remove air bubbles, making sure you have filled it with the correct amount of liquid.



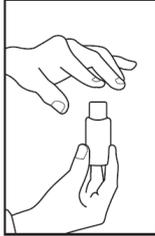
6. Swallow the liquid from the oral syringe or attach the oral syringe to a gastrostomy or nasogastric tube.



7. **Important note:** Do not add or stir RAVICTI into larger volumes of liquid such as water or juice as RAVICTI is heavier than most liquids. Mixing RAVICTI with large volumes of liquid may result in you not getting the full dose.
8. RAVICTI can be added to a small amount of soft foods, such as ketchup, medical formulas, apple sauce or squash puree.
9. If the volume of your oral syringe is smaller than your prescribed dose, you will have to repeat these steps to get your full dose. Use one oral syringe for all doses taken each day.
10. After you take your full dose, have a drink of water to make sure no medicine is left in your mouth, or flush the gastrostomy or nasogastric tube with 10 ml of water using a new oral syringe. The syringe used to flush the gastrostomy or nasogastric tube shall not be used for measuring the dose of RAVICTI to avoid introduction of water into the medicine.



11. Close the bottle by screwing on the cap.



12. **Important note:** Do not rinse the oral syringe between daily doses as the introduction of water causes RAVICTI to degrade. If RAVICTI gets in contact with water, the liquid will become cloudy in appearance. Store bottle and oral syringe in a clean, dry place between doses.

13. Discard the oral syringe after the last dose of the day. Do not re-use the oral syringe for measuring the dose of RAVICTI on another day.

14. Remaining unused syringes should be kept for use with another bottle. Each bottle should be discarded after 14 days.

If you take more RAVICTI than you should

If you take more of this medicine than you should, talk to a doctor.

If you notice any of the following signs, talk to a doctor or go to a hospital straight away as these may be signs of overdose or high ammonia:

- feeling sleepy, tired, light-headed or sometimes confused
- headache
- changes in taste
- problems hearing
- feeling disorientated
- less able to remember things
- existing neurological conditions may get worse

If you forget to take RAVICTI

If you forget a dose, take the missed dose as soon as you remember. However, for adults, if the next dose is in less than 2 hours, then skip it and take your next dose as normal.

For children: if the next dose is in less than 30 minutes, then skip it and give the next dose as normal.

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

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

If you stop taking RAVICTI

You will need to take this medicine and follow a special low protein diet throughout your life. Do not stop taking RAVICTI without talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist if you notice any side effects.

The following side effects may happen with this medicine:

Common: may affect up to 1 in 10 people

- stomach bloating or pain, constipation, diarrhoea, heartburn, wind, vomiting, feeling sick (nausea), pain in the mouth, retching
- swelling of the hands or feet, feeling tired
- feeling dizzy, headache or tremor
- decreased or increased appetite
- not wanting to eat some foods
- bleeding between menstrual periods
- acne, skin smells abnormal
- tests show increased liver enzyme levels, imbalance of salts in the blood, low levels of a type of white blood cell ('lymphocytes') or low levels of vitamin D

Uncommon: may affect up to 1 in 100 people

- dry mouth, burping, stomach ache or discomfort, changes in your stools such as being oily, urgent need for bowel movements, painful bowel movements, inflammation of mouth and lips
- feeling hungry, increased temperature
- hot flushes
- gallbladder pain
- bladder pain
- back pain, joint swelling, muscle spasms, pain in the arms or legs, heel spur
- viral infection in the gut
- feeling of pins and needles, feeling very restless, sleepiness, feeling drowsy, problems with speech, feeling confused, feeling depressed, alteration of taste
- menstrual periods stop or are irregular
- voice disorder, nosebleeds, stuffy nose, sore or painful throat
- hair loss, sweating more than usual, itchy rash,
- uneven heartbeat
- reduced thyroid function
- weight loss or weight gain
- tests show higher or lower potassium in your blood
- tests show higher levels of triglycerides, low density lipo-protein or white cells in your blood
- tests show abnormal ECG ('electrocardiogram')
- tests show prothrombin time is longer
- tests show low albumin in your blood

Side effects in children less than 2 months of age

The following side effects have been observed in a clinical study including 16 patients less than 2 months of age:

- diarrhoea, constipation, wind, reflux of stomach contents, poor feeding
- rash
- reduced number of red blood cells
- increased number of platelets (may cause blood clot)
- increased liver enzymes
- decreased amino acid levels

Side effects in children 2 months to less than 2 years of age

- diarrhoea, constipation
- eczema, nail ridging, rash

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RAVICTI

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

Do not use RAVICTI after the expiry date which is stated on the carton and the bottle label after the letters "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions. Once the bottle is open, you must use your medicine within 14 days of opening. The bottle should be discarded even if it is not empty.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What RAVICTI contains

- The active substance is glycerol phenylbutyrate.
- Each ml of liquid contains 1.1 g of glycerol phenylbutyrate. This corresponds to a density of 1.1 g/ml.
- There are no other ingredients.

What RAVICTI looks like and contents of the pack

The liquid is filled into a 25 ml clear glass bottle and capped with a plastic, child-resistant cap. In order to ensure correct dosing of RAVICTI, CE-marked oral syringes with suitable size for the dose and compatible with the syringe insert can be obtained from the pharmacy. Ask your doctor or pharmacist which type of syringes you need to obtain based on the prescribed dose volume.

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This leaflet was last revised in 10/2022