Package leaflet: Information for the user

Trecondi 1 g powder for solution for infusion
Trecondi 5 g powder for solution for infusion
treosulfan

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trecondi is and what it is used for

Trecondi contains the active substance treosulfan, which belongs to a group of medicines called alkylating agents. Treosulfan is used to prepare patients for bone marrow transplant (haematopoietic stem cell transplantation). Treosulfan destroys the bone marrow cells and enables the transplant of new bone marrow cells which leads to the production of healthy blood cells.

Trecondi is used as a **treatment before blood stem cell transplantation** in adults with cancer and non-cancerous disorders, and in adolescents and children older than one month with cancer.

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

Do not use Trecondi
- if you are allergic to treosulfan,
- if you suffer from an active uncontrolled infection,
- if you suffer from severe heart, lung, liver or kidney diseases,
- if you suffer from hereditary DNA repair disorder, a condition that reduces the ability to repair DNA (which carries your genetic information),
- if you are pregnant, or think you may be pregnant.

Warnings and precautions
Trecondi is a cell-killing (cytotoxic) medicine that is used to decrease the number of blood cells. At the recommended dose, this is the desired effect. You will have regular blood tests during treatment to check your blood cell counts do not fall too low.

In order to prevent and treat infections, you will be given medicines, such as antibiotics, antifungals or antivirals.

Trecondi may increase the risk of having another cancer in the future.

Since inflammation of the oral mucosa is a common side effect of this medicine, you should pay attention to adequate oral hygiene. Prophylactic use of mouthwashes (e.g. with barrier protectants, antimicrobials) or application of ice within the oral cavity (lessens blood flow to the oral mucosa and reduces the amount of treosulfan reaching the cell) is recommended.

You must not receive live vaccines during treatment with treosulfan.

Trecondi may cause symptoms of the menopause (absence of menstrual periods).

Children and adolescents
Fits (seizures) may occur very rarely in infants of less than 4 months of age. Children younger than 1 year may have more severe side effects that affect breathing than older ones. Your child will be monitored for signs of side effects affecting nerves and breathing problems.

Nappy rash with ulceration of the area around the anus (perianal) may occur in infants, toddlers and children wearing nappies because treosulfan passed out in the urine can damage the skin. Therefore, nappies should be changed frequently during 6–8 hours after each dose of this medicine.

There is not sufficient information on the use of treosulfan in children aged less than 1 month.

Other medicines and Trecondi
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility
You must not get pregnant during treatment with this medicine and up to 6 months after treatment. Use an effective method of contraception when either you or your partner is receiving this medicine.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you receive this medicine.

You should stop breast-feeding before starting treatment with this medicine.

If you are a man treated with this medicine, you should not father a child during and up to 6 months after treatment.

This medicine may make you infertile and it may not be possible for you to get pregnant after treatment with it. If you are concerned about having children, you should discuss this with your doctor before treatment. Men should seek advice about the possibility of sperm preservation before starting therapy.

Driving and using machines
This medicine can cause nausea, vomiting and dizziness which may reduce your ability to drive or use machines. If you are affected, do not drive or use machines.

3. How to use Trecondi

Use in adults
This medicine is used in combination with fludarabine.
The recommended dose is 10–14 g/m² body surface area (calculated using your height and weight).

Use in children and adolescents

This medicine is used in combination with fludarabine and in most cases also with thiotepa. The recommended dose is 10–14 g/m² body surface area.

How Trecondi is given
This medicine will be given to you by your doctor. It is given by drip (infusion) into a vein over 2 hours for 3 days before blood stem cell infusion.

If you were given more Trecondi than you should
Because this medicine is given by a doctor, you will be given the correct dose. However, if you think you have received more of this medicine than you should, tell your doctor or nurse as soon as possible.

4. Possible side effects

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

Serious side effects
The most serious side effects of treosulfan therapy or the transplant procedure include:
- decrease in blood cell counts which is the intended effect of the medicine to prepare you for your transplant infusion (all patients: very common)
- infections caused by bacteria, viruses and fungi (adults: common; children and adolescents: very common)
- blocking of a vein into the liver (adults: uncommon; children and adolescents: not known)
- inflammation of the lung (pneumonitis) (adults: uncommon)

Your doctor will monitor your blood counts and liver enzymes regularly to detect and manage these events.

Adults

A list of all other side effects is set out below according to how common they are.

Very common (may affect more than 1 in 10 people)
- decreased counts of white blood cells with fever (febrile neutropenia)
- inflammation of the lining of various parts of the body, especially in the mouth (which can cause ulcers), diarrhoea, nausea, vomiting
- tiredness
- increased blood level of bilirubin (a liver pigment, often a sign of liver problems)

Common (may affect up to 1 in 10 people)
- bloodstream infection (sepsis)
- allergic reactions
- decreased appetite
- problems sleeping (insomnia)
- headache, dizziness
- changes and abnormalities in heart rhythm (heartbeat is irregular, too fast or too slow)
- high or low blood pressure, flushing
- difficulty breathing, nosebleeds
- mouth pain, inflammation of the stomach, upset stomach, belly (abdominal) pain, constipation, difficulty in swallowing, gullet or stomach pain
- a type of rash with flat or raised red bumps on the skin (maculopapular rash), red spots on the skin (purpura), redness of skin (erythema), hand and foot syndrome (palms of the hands or soles of the feet tingle, become numb, painfully swollen, or red), itching, hair loss
- pain in arms or legs, back pain, bone pain, joint pain

- sudden decrease of kidney function, blood in the urine
- retention of fluid in the body causing swelling (oedema), fever, chills
- increased liver enzymes, increased C-reactive protein (a marker of inflammation in the body), weight gain, weight loss

Uncommon (may affect up to 1 in 100 people)
- abnormal control of blood sugar level including high or low blood sugar level
- confusion
- bleeding in the brain, problems in the nerves of the arms or legs with symptoms such as numbness, reduced or increased sensitivity, tingling, burning pain (peripheral sensory neuropathy)
- a spinning sensation (vertigo)
- bruising
- fluid around the lung (pleural effusion), inflammation of throat, inflammation of or pain in voice box, hiccups
- bleeding in the mouth, feeling bloated, dry mouth
- a type of rash with red spots and sometimes with purple or blistered areas in the centre (erythema multiforme), acne, rash, dry skin
- muscle pain
- pain of the urinary tract
- chest pain not related to heart problems, pain
- increased blood level of alkaline phosphatase (your doctor will check for this)

Not known (frequency cannot be estimated from the available data)
- life-threatening condition after bloodstream infection (septic shock)
- different cancer caused by chemotherapeutic treatment (second malignancy)
- increased acidity in the blood
- abnormal brain function (encephalopathy), restless, repetitive, or involuntary movements and rapid speech (extrapyramidal disorder), fainting, sensation of tingling, pricking or numbness (paraesthesia)
- dry eye
- heart not pumping enough blood for the body's needs (heart failure), heart attack, fluid in the sac around the heart (pericardial effusion)
- blockage of a blood vessel (embolism)
- throat pain, hoarseness, cough
- gastrointestinal bleeding, inflammation of the colon, inflammation of the gullet, inflammation of the anus
- liver injury caused by medicines, enlarged liver
- inflammation of skin (dermatitis), death of skin tissue, skin ulcer, bronze pigmentation of skin
- kidney failure, inflammation of the urinary bladder with bleeding (haemorrhagic cystitis), pain on passing urine (dysuria)
- increased blood level of lactate dehydrogenase (a substance that indicates tissue or cellular damage)

Children and adolescents

A list of all other side effects is set out below according to how common they are.

Very common (may affect more than 1 in 10 people)
- inflammation of the mucosa especially in the mouth (with ulcers), diarrhoea, nausea, vomiting, abdominal pain
- itching
- fever

Common (may affect up to 1 in 10 people)
- throat pain, nosebleeds
- difficulty in swallowing, mouth pain
- reddening and flaking of most of the skin of the body (dermatitis exfoliative), a type of rash with flat or raised red bumps on the skin (maculopapular rash), rash, redness of skin (erythema), skin pain, bronze pigmentation of skin, hair loss
- increased liver enzymes, increased blood level of bilirubin (a liver pigment, often a sign of liver problems)

Not known (frequency cannot be estimated from the available data)
- different cancer caused by chemotherapeutic treatment (second malignancy)
- decreased counts of white blood cells with fever (febrile neutropenia)
- less acid than normal in the blood (alkalosis), abnormal blood level of electrolytes, decreased blood level of magnesium
- headache, sensation of tingling, pricking or numbness (paraesthesia), seizure
- bleeding in the eye, dry eye
- leakage of fluid from the capillaries (small blood vessels), high blood pressure, low blood pressure
- decrease in the oxygen supply to parts of the body (hypoxia)
- inflammation of the colon, inflammation of anus, upset stomach, inflammation of the lining of the rectum, gastrointestinal pain, constipation
- enlarged liver, liver damage
- skin ulcer, a type of rash with red spots and sometimes with purple or blistered areas in the centre (erythema multiforme), hives, skin condition with fluid-filled blisters (dermatitis bullous), acne, hand and foot syndrome (palms of the hands or soles of the feet tingle, become numb, painfully swollen, or red), nappy rash with ulceration in the area surrounding the anus
- pain in arms or legs
- decrease of kidney function, kidney failure, inflammation of the urinary bladder (cystitis)
- redness of scrotal skin
- chills, tiredness, pain
- increased blood level of a liver enzyme (gamma-glutamyl transferase)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: 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 Trecondi

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

Do not use this medicine after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

For storage conditions after reconstitution of the medicine, see the information below for healthcare professionals.

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 Trecondi contains
The active substance is treosulfan. This medicine contains no other ingredients.

Trecondi 1 g powder for solution for infusion
1 vial contains 1 g of treosulfan.

Trecondi 5 g powder for solution for infusion
1 vial contains 5 g of treosulfan.

After reconstitution 1 mL of the solution contains 50 mg treosulfan.

What Trecondi looks like and contents of the pack
White crystalline powder in a glass vial with a rubber stopper and aluminium cap.
Trecondi is available in packs containing 1 or 5 vials (type I glass).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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The following information is intended for healthcare professionals only:

As with all cytotoxic substances, appropriate precautions should be taken when handling treosulfan.

Trained personnel should reconstitute the medicinal product. When handling treosulfan, inhalation, skin contact or contact with mucous membranes should be avoided (the use of adequate protective disposable gloves, goggles, gown and mask is recommended). Contaminated body parts should be carefully rinsed with water and soap, the eyes should be rinsed with sodium chloride 9 mg/mL (0.9%) solution. If possible it is recommended to work on a special safety workbench, equipped with laminar flow, with liquid-impermeable, absorbent disposable foil. Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic medicinal products. Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
Pregnant personnel should be excluded from handling cytotoxics.

Instructions for reconstitution of treosulfan:

1. Treosulfan is reconstituted in its original glass container. Reconstituted solutions of treosulfan may be combined into a larger glass vial, PVC bag or PE bag.
2. To avoid solubility problems, warm the solvent, sodium chloride 4.5 mg/mL (0.45%) solution, to 25 °C - 30 °C (not higher), for example by using a water bath.
3. Remove the treosulfan powder carefully from the inner surface of the vial by shaking. This procedure is very important, because moistening of powder that sticks to the surface results in caking. If this happens, vigorously shake the vial to redissolve the cake.
4. Reconstitute each vial of Trecondi containing 1 g treosulfan in 20 mL of pre-warmed (maximum 30 °C) sodium chloride 4.5 mg/mL (0.45%) solution by shaking.
   Reconstitute each vial of Trecondi containing 5 g treosulfan in 100 mL of pre-warmed (maximum 30 °C) sodium chloride 4.5 mg/mL (0.45%) solution by shaking.

For preparation of sodium chloride 4.5 mg/mL (0.45%) solution equivalent volumes of sodium chloride 9 mg/mL (0.9%) solution and water for injections can be mixed.

Reconstituted solution for infusion

The reconstituted solution contains 50 mg treosulfan per mL and appears as a clear colourless solution. Solutions showing any sign of precipitation should not be used.

After reconstitution with sodium chloride 4.5 mg/mL (0.45%) solution, chemical and physical stability has been demonstrated for 3 days at 25 °C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.
Do not store the reconstituted solution in a refrigerator (2 °C - 8 °C) as this might cause precipitation.

Treosulfan has mutagenic and carcinogenic potential. Remnants of the medicinal product as well as all materials that have been used for reconstitution and administration must be destroyed according to standard procedures applicable to antineoplastic agents, with due regard to current laws related to the disposal of hazardous waste.