For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated. Please read carefully before using a new pack.

Rasburicase 1.5 mg/ml powder and solvent for concentrate for solution for infusion.
FASTURTEC®

COMPOSITION
After reconstitution, 1 ml of Fasturtec concentrate contains 1.5 mg rasburicase.

Fasturtec is a recombinant urate-oxidase enzyme produced by genetically modified *Saccharomyces cerevisiae* strain. Rasburicase is a tetrameric protein with identical subunits of a molecular mass of about 34 kDa.

1 mg corresponds to 18.2 EAU*.
*One enzyme activity unit (EAU) corresponds to the enzyme activity that converts 1 μmol of uric acid into allantoin per minute under the operating conditions described: +30 °C ± 1 °C TEA pH 8.9 buffer.

INDICATIONS
Treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in patients with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy.

DOSAGE AND ADMINISTRATION
Fasturtec should be administered under the supervision of a physician trained in chemotherapy of haematological malignancies.

Fasturtec is to be used immediately prior to and during the initiation of chemotherapy only, as at the present, there is insufficient data to recommend multiple treatment courses.

The recommended dose for Fasturtec is 0.20mg/kg/day. Fasturtec is administered as a once daily 30 minute intravenous infusion in 50ml of a sodium chloride 9 mg/ml (0.9%) solution

The duration of treatment with Fasturtec may be up to 7 days, the exact duration should be based upon adequate monitoring of uric acid levels in plasma and clinical judgment.

Administration of rasburicase does not require any change in the timing or schedule of initiation of cytoreductive chemotherapy.

Rasburicase solution should be infused over 30 minutes. Rasburicase solution should be infused through a different line than that used for infusion of chemotherapeutic agents to prevent any possible drug incompatibility. If use of a separate line is not possible, the line should be flushed out with saline solution between infusion of chemotherapeutic agents and rasburicase. Because rasburicase may degrade uric acid in vitro, special precautions must be used during sample handling for plasma uric acid measurements.

Additional information on special populations
Renally or hepatically impaired patients: No dose adjustment is necessary.

Paediatric patients: As no adjustment is necessary, the recommended dose is 0.20 mg/kg/day.

CONTRAINDICATIONS
- Hypersensitivity to uricases or any of the excipients

- G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia**.**

WARNINGS

- Rasburicase like other proteins, has the potential to induce allergic responses in humans**,** including anaphylaxis and/or anaphylactic shock with potential fatal outcome. Clinical experience with rasburicase demonstrates that patients should be closely monitored for the onset of anaphylactic reactions (see section Adverse Events). In case of severe allergic reaction, treatment should be immediately and permanently discontinued and appropriate therapy initiated.
- At present, there is insufficient data available on patients being re-treated to recommend multiple treatment courses. Anti-rasburicase antibodies have been detected in treated patients and healthy volunteers administered rasburicase.
- Methemoglobinemia has been reported in patients receiving rasburicase. It is not known whether patients with deficiency of methemoglobin reductase or of other enzymes with antioxidant activity are at increased risk of methemoglobinemia. Rasburicase should be immediately and permanently discontinued in patients having developed methemoglobinemia, and appropriate measures initiated.
- Hemolysis has been reported in patients receiving rasburicase. In such case, treatment should be immediately and permanently discontinued and appropriate measures initiated.

PRECAUTIONS

Caution should be used in patients with a history of atopic allergies.

INTERACTIONS

In humans, no metabolism studies have been carried out. Rasburicase, being an enzyme itself, would be an unlikely candidate for drug-drug interactions.

PREGNANCY

No clinical data on exposed pregnancies are available. Rasburicase has been shown to be teratogenic in rabbits given doses of 10, 50 and 100 times the human dose and in rats given doses 250 times the human dose. Animal studies with respect to effects on parturition and postnatal development have not been performed. The potential risk for humans is unknown. Rasburicase should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

LACTATION

It is unknown whether rasburicase is excreted in human milk, therefore, it should not be used in breast-feeding women.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

No studies on the effect on the ability to drive and use machines have been performed.

ADVERSE EVENTS

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥ 1 and <10%; Uncommon ≥ 0.1 and <1%; Rare ≥0.01 and <0.1%; Very rare <0.01%, Unknown (cannot be estimated from available data).

Clinical trials for Registration

Undesirable effects, all grades, possibly attributable to rasburicase:

Nervous system disorders

Very common: headache (Grade 3/4: uncommon)

Gastro-intestinal disorders
Very common: vomiting (Grade 3/4: common), nausea (Grade 3/4: common), diarrhoea (Grade 3/4: uncommon)

General disorders and administration site conditions
***V*ery common**: fever (Grade 3/4: common),

POST-MARKETING REPORTS:

Blood and lymphatic system disorders
Uncommon: hemolysis which could be related to G6PD deficiency, methemoglobinemia.

Immune system disorders
Common: allergic reactions. These mainly include rash and urticaria.
Cases of rhinitis, bronchospasm, hypotension, anaphylaxis and/ or anaphylactic shock with potential fatal outcome have been reported.

Nervous system disorders
Uncommon: convulsion*.
Frequency not known: muscle contractions involuntary.

*Frequency estimated from pivotal clinical trials .

OVERDOSE
Signs and Symptoms
In view of the mechanism of action of rasburicase, an overdose will lead to low or undetectable plasma uric acid concentrations and increased production of hydrogen peroxide.

Management
Thus patients suspected of receiving an overdose should be monitored for haemolysis, and general supportive measures should be initiated as no specific antidote for rasburicase has been identified.

INTERFERENCE WITH LABORATORY AND DIAGNOSTIC TESTS
Because rasburicase may degrade uric acid *in vitro*, special precautions must be used during sample handling for plasma uric acid measurements.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Rasburicase must be reconstituted with the entire volume of the supplied solvent ampoule (1.5 mg rasburicase vial to be reconstituted with the 1 ml solvent ampoule). Reconstitution results in a solution with a concentration of 1.5 mg/ml rasburicase to be further diluted with sodium chloride 9 mg/ml (0.9%) intravenous solution.

Reconstitution of the solution:
Add the content of one ampoule of solvent to one vial containing rasburicase and mix by swirling very gently under controlled and validated aseptic conditions.

Do not shake.

Inspect visually prior to use. Only clear and colorless solutions without particles should be used.

For single-use only, any unused solution should be discarded. The solvent contains no preservative. Therefore the reconstituted solution should be diluted under controlled and validated aseptic conditions.

Dilution before infusion:
The required volume of the reconstituted solution depends on the patient's body weight. The use of several vials may be necessary to obtain the quantity of rasburicase required for one administration. The required volume of the reconstituted solution, taken from one or more vials, is to be further diluted with sodium chloride 9 mg/ml (0.9%) solution to make a total volume of 50 ml. The concentration of rasburicase in the final solution for infusion depends on the patient's body weight.

The reconstituted solution contains no preservative. Therefore the diluted solution should be infused immediately.

Infusion:
The final solution should be infused over 30 minutes.

Sample handling:
If it is necessary to monitor a patient's uric acid level, a strict sample-handling procedure must be followed to minimise *ex vivo* degradation of the analyte. Blood must be collected into pre-chilled tubes containing heparin anticoagulant. Samples must be immersed in an ice/water bath. Plasma samples should immediately be prepared by centrifugation in a pre-cooled centrifuge (4 °C). Finally, plasma must be maintained in an ice/water bath and analysed for uric acid within 4 hours.

INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products except those mentioned in Special Precautions for Disposal and Other Handling Section.

Rasburicase solution should be infused through a different line than that used for infusion of chemotherapeutic agents to prevent any possible drug incompatibility. If use of a separate line is not possible, the line should be flushed out with saline solution between chemotherapeutic agent infusions and rasburicase.

No filter should be used for infusion.

Do not use any glucose solution for dilution due to potential incompatibility.

SHELF LIFE
36 months.
After reconstitution or dilution an immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours between +2°C and 8°C.

SPECIAL PRECAUTIONS FOR STORAGE
Powder in vial: store in a refrigerator (2 °C - 8 °C). Do not freeze. Store in the original package in order to protect from light.

After reconstitution or dilution an immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours between +2°C and 8°C

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