# AUSTRALIAN PRODUCT INFORMATION – FASTURTEC (RASBURICASE)

## 1 NAME OF THE MEDICINE

Rasburicase

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.5 mg rasburicase.

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

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

For full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

Powder for injection

Crimped, colourless glass vial containing white to off-white pellet.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Rasburicase is indicated for the treatment and prophylaxis of acute hyperuricaemia, in patients with haematological malignancy at risk of a rapid tumour lysis.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

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

In patients who are not hyperuricemic at baseline, chemotherapy regimens should be started within 24 hours of first administration of rasburicase. In patients who are hyperuricemic at baseline, chemotherapy regimens should be started within 48 hours of first administration of rasburicase.

#### Children and adults

The recommended dose for rasburicase is 0.20 mg/kg/day. Rasburicase is administered as a once daily 30 minute intravenous infusion in 50 mL of a 0.9% sodium chloride solution. The

duration of treatment with rasburicase may vary between 5 and 7 days. No dose adjustment is necessary for special populations (renally or hepatically impaired patients). Administration of rasburicase does not require any change in the timing or schedule of initiation of cytoreductive chemotherapy.

### Administration

Do not use an in-line filter. 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 agents infusion and rasburicase. Rasburicase should be administered under the supervision of a trained physician. It contains no antimicrobial agent. Rasburicase is for single use in one patient only. Discard any residue.

### Uric acid analysis

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.

### Preparation

Rasburicase must be reconstituted with the solvent supplied and further diluted only in 0.9% sodium chloride injection. Do not use any glucose intravenous infusion for dilution due to potential incompatibility. This product should not be mixed with other drugs for its infusion.

#### *Reconstitution of the solution*

Under controlled and validated aseptic conditions, add 1 mL of solvent to each vial containing 1.5 mg of rasburicase and mix by swirling very gently. Do not shake. Inspect visually prior to use. Only clear solutions without particles should be used. The solvent contains no preservative, therefore the solution should be reconstituted immediately prior to further dilution, and in no case be stored for longer than 24 hours at 2-8ºC.

#### *Dilution before infusion*

The required quantity of solution (according to the patient's body weight) is to be further diluted with 0.9% sodium chloride injection to make up a total volume of 50 mL. As the reconstituted solution contains no preservative the diluted solution should be infused immediately, and in no case be stored for longer than 24 hours at 2-8ºC.

### Infusion

The final solution should be infused over 30 minutes. Rasburicase solution should be infused through a different line from 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 agents infusions and rasburicase

## 4.3 CONTRAINDICATIONS

Hypersensitivity to rasburicase, other uricases or any of the excipients.

G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia. (Hydrogen peroxide is a by-product of the conversion of uric acid to allantoin. In order to prevent possible haemolytic anaemia induced by hydrogen peroxide, rasburicase is contraindicated in patients with these disorders.)

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administration of rasburicase reduces the uric acid level to below normal levels and by this mechanism reduces the chance of development of renal failure due to precipitation of uric acid crystals in renal tubules as a consequence of hyperuricaemia. Tumour lysis can also result in hyperphosphataemia, hyperkalaemia and hypocalcaemia. Rasburicase is not directly effective in the treatment of these abnormalities. Therefore, patients must be monitored closely.

### Hypersensitivity

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 allergic-type undesirable effects, especially skin allergic reactions, bronchospasm or severe hypersensitivity reactions including anaphylaxis (see Section 4.8 Adverse effects (Undesirable effects). In case of severe allergic reaction, treatment should be immediately and permanently discontinued and appropriate therapy initiated.

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

At the present, there is insufficient data available on patients being retreated to recommend multiple treatment courses. Anti-rasburicase antibodies have been detected in treated patients and healthy volunteers administered rasburicase. In healthy volunteers, 53% subjects receiving rasburicase had anti-rasburicase antibodies one month post last dose. Most of the positive subjects were no longer positive at 1 year.

Methaemoglobinaemia has been reported in patients receiving rasburicase. It is not known whether patients with deficiency of methaemoglobin reductase or of other enzymes with antioxidant activity are at increased risk of methaemoglobinaemia. Rasburicase should be immediately and permanently discontinued in patients having developed methaemoglobinaemia, and appropriate measures initiated.

Haemolysis has been reported in patients receiving rasburicase. In such cases, treatment should be immediately and permanently discontinued and appropriate measures initiated.

Rasburicase has not been investigated in patients with hyperuricaemia in the context of myeloproliferative disorders.

There is no data available to recommend the sequential use of rasburicase and allopurinol.

### Use in the elderly

No data available.

### Paediatric use

No data available.

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

*In vivo* drug-drug interaction studies have not been conducted. In rats and baboons, rasburicase did not appear to induce or inhibit hepatic cytochrome P450 isoforms. *In vitro*, rasburicase did not metabolise 6-mercaptopurine monohydrate, cyarabine or methotrexate.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

No adverse effects on fertility were observed in male and female rats at intravenous doses up to 10 mg/kg/day at which systemic exposure (plasma AUC) was about 12 times greater than that in humans at the maximum recommended dose. The interpretation of the preclinical studies is hampered due to the presence of endogenous urate oxidase in standard animal models.

### Use in pregnancy – Pregnancy Category B2

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 foetus.

### Use in lactation

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Because rasburicase is concomitantly administered as supportive care to cytoreductive chemotherapy of advanced malignancies, a significant burden of adverse events is expected from the underlying disease state and its treatment.

Undesirable effects possibly attributable to rasburicase reported in clinical trials involving 347 subjects:

**Table 1**

| Adverse events | Incidence in pooled studies (grade 3 or 4) |
|---|---|
| Common: | |
| Fever | 6.8% |
| Vomiting | 1.4% |
| Nausea | 1.7% |
| Uncommon: | |
| Diarrhoea | 0.9% |
| Headache | 0.9% |
| Allergic reactions: | 0.6% |
| bronchospasm | 1 grade 4 |
| allergic reaction | 1 grade 3 |

The most significant drug related adverse events were allergic reactions, mainly rashes (1.4%) and urticaria. Cases of rhinitis, hypotension, bronchospasm (<1%) and severe hypersensitivity reactions including anaphylaxis (<1%) have also been attributed to rasburicase.

Because the enzymatic conversion of uric acid to allantoin by rasburicase produces hydrogen peroxide, haemolytic anaemia and methaemoglobinaemia have been observed in certain at risk populations such as those with G6PD deficiency. In trials, 0.9% subjects developed haemolytic anaemia, one of these subjects was documented to have G6PD deficiency.

### Post-marketing data

Adverse reactions reported during the post-marketing period are detailed below. These reactions are classified within body system categories using the following definitions:

| | |
|---|---|
| *very common* | ≥ 1/10 (≥ 10%) |
| *common* | ≥ 1/100 and < 1/10 (≥ 1% and <10%) |
| *uncommon* | ≥1/1000 and < 1/100 (≥ 0.1% and <1.0%) |
| *rare* | ≥1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%) |
| *very rare* | < 1/10,000 (< 0.01%) |
| *not known* | frequency cannot be estimated from available data |

#### *Nervous system disorders*

*uncommon*: convulsion
*Frequency not known*: muscle contractions involuntary

#### *Blood and lymphatic system disorders*

*uncommon*: haemolysis 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.

#### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

### 4.9 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC code: V03AF07.

## Mechanism of action

In humans, uric acid is the final step in the catabolic pathway of purines. The acute increase in plasma levels of uric acid subsequent to the lysis of large numbers of malignant cells and during cytoreductive chemotherapy may lead to degradation of renal function and renal failure which results from the precipitation of crystals of uric acid in renal tubules. Rasburicase is a potent uricolytic agent that catalyses enzymatic oxidation of uric acid into allantoin, a water soluble product, more easily excreted by the kidney in the urine. The enzymatic oxidation of uric acid leads to stoichiometric formation of hydrogen peroxide. The increase of hydrogen peroxide over ambient levels can be eliminated by endogenous antioxidants and the only increased risk for haemolysis is in G6PD deficient and inherited anaemia patients.

In healthy volunteers, a marked dose-related decrease in plasma uric acid levels was observed across the dose range 0.05 mg/kg to 0.20 mg/kg of rasburicase. This dose related decrease in plasma uric acid levels was seen within four hours post first dose and remained for up to 24 hours post last dose of rasburicase.

## Clinical trials

ACT2511 (n=107) and ACT2694 (n=131) were phase II, open-label, multicentre studies of rasburicase used as uricolytic therapy for the prophylaxis and treatment of hyperuricaemia in patients with leukemia or lymphoma. Patients in ACT2511 received 0.15 mg/kg, while those in ACT2694 received either 0.15 mg/kg (n=12) or 0.20 mg/kg (n=119). Primary endpoint was plasma uric acid concentrations over time. Overall, plasma uric acid fell rapidly after the first dose, and remained several-fold below the mean baseline value during rasburicase treatment. The mean percentage reduction (±SD) in uric acid four hours after the first dose was 88% ± 12% in ACT2511 and 84.9% ± 12.6% in ACT2694.

**Table 2 Summary of efficacy results for the treatment indication**

| | **EFC2975** | | **ACT2511** | **ACT2694** | | |
|---|---|---|---|---|---|---|
| Efficacy Criteria | Allopurinol n=9 | Rasburicase (0.20mg/kg) n=10 | Rasburicase (0.15mg/kg) n=12 | Rasburicase (0.15mg/kg) n=5 | Rasburicase (0.20mg/kg) n=50 | Total Rasburicase n=77 |
| Mean plasma UA concentration at baseline (T0h) (µmol/L) [mg/dL] | 571 ± 161 [9.6 ± 2.7] | 619 ± 95 [10.4 ± 1.6] | 690 ± 500 [11.6 ± 8.4] | 583 ± 387 [9.8 ± 6.5] | 702 ± 321 [11.8 ± 5.4] | 684 ± 333 [11.5 ± 5.6] |
| Mean reduction in UA at 4 hours post first dose | 9.3% | 85.7% | 83.9% | 59.2% | 84.1% | 82.8% |

| | EFC2975 | | ACT2511 | ACT2694 | | |
|---|---|---|---|---|---|---|
| Mean plasma UA concentration at 4 hours post first dose (µmol/L) [mg/dL] | 523 ± 171 [8.80 ± 2.88] | 80 ± 62 [1.35 ± 1.05] | 222 ± 488 [3.73 ± 8.20] | 261 ± 253 [4.38 ± 4.25] | 132 ± 178 [2.22 ± 3.0] | 146 ± 238 [2.45 ± 4.0] |
| Mean time to first confirmation of control of UA[a] | 19.2 hours (n=5) | 4.1 hours (n=10) | 4.2 hours (n=7) | 10.9 hours (n=3) | 6.2 hours (n=43) | 5.9 hours (n=63) |
| No. of patients with uric acid rebound >8 mg/dL following start of chemotherapy | 0 | 1 | 1 | 1 | 7 | 10 |
| Mean plasma uric acid AUC0-96 (µmol.hr/L) [mg.hr/dL] | 26171 [440.0] | 9660 [162.4] | 12753 [214.4] | 14162 [238.1] | 9350 [157.2] | 10231 [172.0] |
| Response rate[b] | 100% (n=3)[c] | 75% (n=8)[c] | 100% (n=11)[c] | 80% (n=5)[c] | 90% (n=42)[c] | 89% (n=66)[c] |

EFC2975 was a randomised, multicentre open-label phase III study, comparing rasburicase (n=27) 0.20 mg/kg versus allopurinol (n=25) for the treatment and prophylaxis of hyperuricaemic patients with leukemia and lymphoma. At 4 hours after the first dose, there was a significant difference ($p<0.0001$) in the mean percent reduction from baseline plasma uric acid concentration in the rasburicase group (86.0 ± 7.0%) compared to that for the allopurinol group (12.1 ± 13.3%). Time to first confirmation of normal levels of uric acid in hyperuricaemic patients is four hours for rasburicase and 24 hours for allopurinol. Rasburicase induced excretion of the serum phosphate load prevented further deterioration of renal function from calcium/phosphorus precipitation.

**Table 3 Summary of efficacy results for the prophylaxis indication**

| | EFC2975 | | ACT2511 | ACT2694 | | |
|---|---|---|---|---|---|---|
| Efficacy Criteria | Allopurinol n=16 | Rasburicase (0.20mg/kg) n=17 | Rasburicase (0.15mg/kg) n=95 | Rasburicase (0.15mg/kg) n=7 | Rasburicase (0.20mg/kg) n=69 | Total Rasburicase n=188 |
| Mean plasma UA concentration at baseline (T0h) (µmol/L) [mg/dL] | 274 ± 54 [4.6 ± 0.9] | 309 ± 71 [5.2 ± 1.2] | 238 ± 83 [4.0 ± 1.4] | 291 ± 59 [4.9 ± 1.0] | 268 ± 71 [4.5 ± 1.2] | 262 ± 77 [4.4 ± 1.3] |
| Mean reduction in UA at 4 hours post first dose | 13.2% | 85.1% | 88.6% | 85.0% | 87.4% | 87.7% |

| | EFC2975 | | ACT2511 | ACT2694 | | |
|---|---|---|---|---|---|---|
| Mean plasma UA concentration at 4 hours post first dose (µmol/L) [mg/dL] | 234 ± 57 [3.93 ± 0.95] | 46 ± 24 [0.78 ± 0.40] | 26 ± 29 [0.44 ± 0.48] | 42 ± 18 [0.70 ± 0.31] | 34 ± 24 [0.57 ± 0.41] | 32 ± 27 [0.53 ± 0.45] |
| No. of patients with uric acid rebound >8 mg/dL following start of chemotherapy | 0 | 0 | 2 | 0 | 0 | 2 |
| Mean plasma uric acid AUC0-96 (µmol.hr/L) [mg.hr/dL] | 15816 [265.9] | 6418 [107.9] | 4800 [80.7] | 6388 [107.4] | 5942 [99.9] | 5425 [91.2] |
| Response rate[b] | 91% (n=11)[c] | 100% (n=15)[c] | 99% (n=93)[c] | 100% (n=7)[c] | 98.5% (n=65)[c] | 99% (n=180)[c] |

a Time from the first dose of study drug to the first sampling time at which a plasma uric acid concentration <476 µmol/L (<8.0 mg/dL) was achieved in the subgroup of treatment indication patients with hyperuricemia (plasma uric acid ≥476 µmol/L or ≥8 mg/dL) immediately prior to the first dose of study drug.

b Response defined as:
- The uric acid endpoint (≤387 µmol/L or ≤6.5 mg/dL in patients <13 years old or ≤446 µmol/L or ≤7.5mg/dL in patients ≥13 years old) is reached by T48 ± 2h and maintained until 24 hours after the last administration of rasburicase.
- Another hypouricemic agent (to control hyperuricemia) is not required because of failure to achieve the uric acid endpoint.

c Number of available patients.

## 5.2 PHARMACOKINETIC PROPERTIES

After infusion of rasburicase at a dose of 0.20 mg/kg/day, steady state is achieved at day 2 3. No unexpected accumulation of rasburicase was observed. In patients, the volume of distribution ranged from 110 - 127 mL/kg, which is comparable to the physiological vascular volume. Clearance of rasburicase was ca. 3.5 mL/h/kg and the elimination half-life ca. 19 hours. The patients included in the pharmacokinetic studies were mainly children and adolescents. Based upon these limited data, it seems that clearance is increased (ca. 35%) in children and adolescents compared to adults, resulting in a lower systemic exposure.

Rasburicase is a protein, and therefore: 1) not expected to bind to proteins, 2) expected that metabolic degradation will follow the pathways of other proteins, i.e. peptide hydrolysis, 3) unlikely to be candidate for drug-drug interactions.

Renal elimination of rasburicase is considered to be a minor pathway for rasburicase clearance. As metabolism is expected to occur by peptide hydrolysis, impaired liver function is not expected to affect the pharmacokinetics.

### 5.3 PRECLINICAL SAFETY DATA

#### Genotoxicity

Assays for gene mutations (histidine reversion in *S. typhimurium* and mouse lymphoma gene mutation assay), chromosomal damage (cytogenetics in human peripheral blood lymphocytes *in vitro* and micronucleus test in rats *in vivo*) and DNA damage (*in vitro* rat hepatocyte assay) did not provide any evidence of a genotoxic potential.

#### Carcinogenicity

Long-term animal studies on carcinogenicity are not available.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

The excipients contained in the Fasturtec 1.5 mg vials are: alanine, mannitol, dibasic sodium phosphate dihydrate, monobasic sodium phosphate, dibasic sodium phosphate dodecahydrate. The solvent contains poloxamer and water for injections.

### 6.2 INCOMPATIBILITIES

Rasburicase solution should be infused through a different line from 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 agents infusions and rasburicase.

Do not use any glucose intravenous infusion for dilution due to potential incompatibility. This product should not be mixed with other drugs for its infusion.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2ºC to 8ºC (Refrigerate. Do not freeze).

#### Reconstituted solution

The solvent contains no preservative, therefore the solution should be reconstituted immediately prior to further dilution, and in no case be stored for longer than 24 hours at 2-8ºC.

### Diluted solution

As the reconstituted solution contains no preservative the diluted solution should be infused immediately, and in no case be stored for longer than 24 hours at 2-8ºC.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Fasturtec is a sterile powder supplied in a stoppered clear glass vial, accompanied by a solvent in a clear glass ampoule.

Package size: 3 vials of rasburicase and 3 ampoules of solvent per box.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical structure

No data available.

#### CAS number

134774-45-1

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

## 8 SPONSOR

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300 Barangaroo Avenue
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## 9 DATE OF FIRST APPROVAL

19 March 2003

## 10 DATE OF REVISION

03 June 2026

## SUMMARY TABLE OF CHANGES

| Sections Changed | Summary of new information |
|---|---|
| **8** | Sponsor address updated |