

Data Sheet

Fasturtec®

NAME OF THE MEDICINE

Non-proprietary Name

Rasburicase rys for injection

CAS Number

134774-45-1

DESCRIPTION

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

The excipients contained in the Fasturtec 1.5mg and 7.5 mg vials are: alanine, mannitol, sodium phosphate-dibasic dihydrate, disodium phosphate-monobasic, sodium phosphate-dibasic dodecahydrate. The solvent contains poloxamer and water for injections.

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

PHARMACOLOGY

Pharmacological Action

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. 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.

Pharmacokinetics

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.

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 (\pm SD) in uric acid four hours after the first dose was 88% \pm 12% in ACT2511 and 84.9% \pm 12.6% in ACT2694.

TABLE 1: SUMMARY OF EFFICACY RESULTS FOR THE TREATMENT INDICATION

Efficacy Criteria	EFC2975		ACT2511	ACT2694		Total Rasburicase n=77
	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	
Mean plasma UA concentration at baseline (T0h) (μ mol/L)	571 \pm 161	619 \pm 95	690 \pm 500	583 \pm 387	702 \pm 321	684 \pm 333
[mg/dL]	[9.6 \pm 2.7]	[10.4 \pm 1.6]	[11.6 \pm 8.4]	[9.8 \pm 6.5]	[11.8 \pm 5.4]	[11.5 \pm 5.6]
Mean reduction in UA at 4 hours post first dose	9.3%	85.7%	83.9%	59.2%	84.1%	82.8%
Mean plasma UA concentration at 4 hours post first dose (μ mol/L)	523 \pm 171	80 \pm 62	222 \pm 488	261 \pm 253	132 \pm 178	146 \pm 238
[mg/dL]	[8.80 \pm 2.88]	[1.35 \pm 1.05]	[3.73 \pm 8.20]	[4.38 \pm 4.25]	[2.22 \pm 3.0]	[2.45 \pm 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 AUC ₀₋₉₆ (μ mol.hr/L)	26171	9660	12753	14162	9350	10231
[mg.hr/dL]	[440.0]	[162.4]	[214.4]	[238.1]	[157.2]	[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 \pm 7.0%) compared to that for the allopurinol group (12.1 \pm 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 2: SUMMARY OF EFFICACY RESULTS FOR THE PROPHYLAXIS INDICATION

Efficacy Criteria	EFC2975		ACT2511	ACT2694		Total Rasburicase n=188
	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	
Mean plasma UA concentration at baseline (T0h) (µmol/L)	274 ± 54	309 ± 71	238 ± 83	291 ± 59	268 ± 71	262 ± 77
[mg/dL]	[4.6 ± 0.9]	[5.2 ± 1.2]	[4.0 ± 1.4]	[4.9 ± 1.0]	[4.5 ± 1.2]	[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%
Mean plasma UA concentration at 4 hours post first dose (µmol/L)	234 ± 57	46 ± 24	26 ± 29	42 ± 18	34 ± 24	32 ± 27
[mg/dL]	[3.93 ± 0.95]	[0.78 ± 0.40]	[0.44 ± 0.48]	[0.70 ± 0.31]	[0.57 ± 0.41]	[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 AUC ₀₋₉₆ (µmol.hr/L)	15816	6418	4800	6388	5942	5425
[mg.hr/dL]	[265.9]	[107.9]	[80.7]	[107.4]	[99.9]	[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

UA = uric acid

^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 evaluable patients.

INDICATIONS

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

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.)

PRECAUTIONS

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. 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 '**ADVERSE EFFECTS**'). In such cases, 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.

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.

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.

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

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.

Carcinogenicity

Long-term animal studies on carcinogenicity are not available. 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.

Interactions with other Medicines

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, cytarabine or methotrexate.

ADVERSE 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 3:

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.

DOSAGE AND 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

1.5mg Vials

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 2-8°C.

7.5mg Vials

Under controlled and validated aseptic conditions, add 5 mL of solvent to each vial containing 7.5 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 2-8°C.

Dilution before infusion

1.5mg Vials

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 2-8°C.

7.5mg Vials

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 2-8°C.

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.

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

1.5mg Vials

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

Strength: each vial contains 1.5 mg rasburicase rys.

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

7.5 Vials

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

Strength: each vial contains 7.5 mg rasburicase rys.

Package size: 1 vial of rasburicase and 1 ampoule of solvent per box.

MEDICINE CLASSIFICATION

Prescription medicine

FURTHER INFORMATION

Rasburicase has provisional consent under Section 23 of the Medicines Act 1981.

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