

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

RASBURICASE

Summary

- Rasburicase is a recombinant urate oxidase produced by genetically modified *Saccharomyces cerevisiae*.
- It is an infusion to be used immediately prior to and during the initiation of chemotherapy for haematological malignancies.
- Use of rasburicase leads to a rapid decline in uric acid levels, which may protect against renal failure.
- It is generally well tolerated, with the commonest side effects including fever, nausea, vomiting and rash.
- Rasburicase is significantly more expensive than allopurinol, however cost savings may result from a decreased incidence of renal impairment requiring dialysis.
- It may be particularly useful in patients with high grade tumours with a high proliferation index who are at risk of significant tumour lysis syndrome.

Date Published: September 2001

Monograph Number: 04/01/09

Marketed; May 2001

Region of origin to whom queries should be directed: Leeds

The information contained in this document will be superseded in due course.

Not to be used for commercial purposes

Copyright MIPG 2001

Web site <http://www.ukdipg.org.uk/stage4.htm>

RASBURICASE

Approved Name:	Rasburicase
Brand Name: (Manufacturer):	Fasturtec (Sanofi Synthelabo)
Presentation:	Powder and solvent for concentrate for solution for infusion. Each vial contains 1.5mg rasburicase.
BNF Therapeutic Class:	Recombinant urate oxidase (BNF 10.1.4)
Licensed 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. For use in adults and children (lowest age in trials was 4 weeks).
Dosage And Administration:	0.2mg/kg/day for 5 to 7 days Administer as a once daily 30 minute infusion in 50ml sodium chloride 0.9%. Rasburicase is to be used immediately prior to and during the initiation of chemotherapy. There is insufficient data to recommend multiple treatment courses.
Sector of Use:	Hospital [Y] Primary Care [N]

Therapeutic Comment:	Rasburicase is a new class of agent for the treatment and prophylaxis of hyperuricaemia due to leukaemia and lymphoma. It is more effective than the current therapy, allopurinol, in reducing uric acid levels. It has a better side effect profile than the unlicensed non-recombinant urate oxidase, Uricozyme®, and is likely to be a significant advance in the management of hyperuricaemia due to tumour lysis syndrome.
-----------------------------	---

Cost and Course Details: (MIMS July 2001)	3 x 1.5mg vial £120.00 Cost for 7 days treatment at 0.2mg/kg/day: 30kg patient £1,120 60kg patient £2,240
--	--

Treatment Alternatives:	Non-recombinant urate oxidase (Uricozyme®): previously used on a named-patient basis, free of charge. Now no longer available. Allopurinol 100mg x 28 £0.91 300mg x 28 £2.17 Cost for 7 days treatment at 10mg/kg/day: 30kg patient £0.54 60kg patient £1.08
--------------------------------	---

INTRODUCTION

Hyperuricaemia is a well-recognised complication of leukaemia and lymphoma and their treatment [1]. In patients with myeloproliferative diseases or haematopoietic malignancies, nucleic acids are catabolised as a result of an increased turnover of the malignant cell population. This results in an increase in purine metabolism, leading to hyperuricaemia. Aggressive cancer regimens cause an increase in cell lysis and release of purine metabolites. Tumour lysis syndrome is characterised by severe hyperuricaemia, hyperphosphataemia, hyperkalaemia, hypocalcaemia and acute renal failure. As a consequence of hyperuricaemia, renal insufficiency develops when urine becomes supersaturated with uric acid, and uric acid crystals form in the renal tubules and distal collecting system [2].

Despite management of metabolic abnormalities to reduce the risk of acute renal failure, 25% of children with advanced stage Burkitt lymphoma and B-cell acute lymphoblastic leukaemia (ALL) still experience acute renal failure at onset of cytoreductive chemotherapy [2].

The standard prophylaxis or treatment of hyperuricaemia consists of allopurinol, urinary alkalinisation, hydration and osmotic diuresis [1]. By inhibiting the enzyme xanthine oxidase, allopurinol blocks uric acid formation but increases the renal load of uric acid precursors (hypoxanthine and xanthine). Unlike hypoxanthine, xanthine is less soluble than uric acid in urine. Occasional cases of xanthine nephropathy and calculi have been reported in patients treated with allopurinol. In addition, patients still need to excrete pre-existing uric acid, which is not affected by allopurinol [1].

PHARMACOLOGY

Rasburicase is a recombinant urate oxidase enzyme produced from genetically modified strain of *Saccharomyces cerevisiae* cloned with DNA from a strain of *Aspergillus flavus* [3]. Urate oxidase acts as a catalyst in the enzymatic oxidation of uric acid to allantoin, a readily excreted metabolite that is 5-10 times more soluble than uric acid. It is an endogenous enzyme in most mammals, but not in humans. A non-recombinant form of urate oxidase (Uricozyme®, Sanofi Synthelabo, France) purified from cultures of *Aspergillus flavus*, has been shown to be a more effective agent than allopurinol in correcting hyperuricaemia. However, this product is associated with an approximately 5% rate of acute hypersensitivity reactions, including bronchospasm and hypoxaemia, even in patients without a history of allergy, and with methaemoglobinaemia or haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency [1].

PHARMACOKINETICS

After infusion of rasburicase, at a dose of 0.2mg/kg/day, steady state is achieved at day 2-3. The elimination half-life in patients is about 19 hours. Clearance is increased in children and adolescents compared with adults [4]. For further details, consult the SPC. No dosage adjustment is required in renal or hepatic impairment [4]. Rasburicase is able to lower uric acid concentrations below 2-3mg/dL within 24 hours after the start of the first infusion in patients with high plasma levels of uric acid [3]. Time to first confirmation of normal levels of uric acid in hyperuricaemic patients is 4 hours for rasburicase and 24 hours for allopurinol [4]. Low uric acid levels are generally maintained during the dosing period. A second, transient increase in uric acid levels may occur during or shortly after chemotherapy [3].

EFFICACY

Published data on the clinical efficacy of rasburicase are limited. The European Public Assessment Report (EPAR) contains safety and efficacy data for rasburicase in 375 subjects (265 children and 110 adults) [3]. Two of the studies included in the EPAR are reported in the literature [1,2]. Other data are published in abstract form only [5].

Pui et al enrolled 131 patients, under 21 years of age, who had hyperuricaemia due to leukaemia or lymphoma or were judged to be at high risk for this complication onto a multicentre, open label, non-randomised, uncontrolled study [1, 3]. The study included a dose validation phase, to determine the effective dose, and an accrual phase, to confirm efficacy and safety [1].

The starting dose in the first phase was 0.15mg/kg/day, based on results of volunteer studies and the equivalent effective dose of non-recombinant urate oxidase. The dose was then increased by increments of 0.05mg/kg. Once the validated dose was identified the accrual phase began, and no further dose escalations were allowed [1]. Further details are given in Table 1.

Of the 131 patients (88 boys and 43 girls) who were treated, each had a massive tumour burden as indicated by high serum lactate dehydrogenase concentrations or hyperleukocytosis. Rasburicase, administered at 0.15mg/kg, effectively corrected or prevented hyperuricaemia in the first 11 patients treated. However, the 12th patient, a 13 year old boy with stage III small noncleaved non-Hodgkin's lymphoma (NHL) and a presenting uric acid level of 21.1 mg/dL had a transient increase in uric acid concentration at 48 hours. According to the study design, the dose was increased to 0.2mg/kg, which proved effective in 14 subsequently treated patients and hence was used in the accrual phase [1].

During the accrual phase, 2 patients had hyperuricaemia at 48 hours, which resolved 24 hours later. Beyond 48 hours there were 2 cases of treatment hyperuricaemia, neither lasting more than 24 hours.

At either dose, rasburicase produced dramatic decreases in uric acid concentrations in all 131 patients, regardless of whether they presented with hyperuricaemia. Despite intensive chemotherapy, the median uric acid concentration remained at or near 0.5mg/dL in both groups throughout the treatment course [1].

Similar results were reported by Lascombes et al who conducted a multicentre, open-label trial in 107 newly diagnosed patients with NHL, ALL or acute non-lymphoid leukaemia (ANL) at risk of developing hyperuricaemia. Rasburicase 0.15mg/kg/day was administered to 17 adults and 90 children during induction chemotherapy [5]. Further details are reported in Table 1.

Goldman et al conducted an open-labelled, randomised, multicentre, comparative trial of rasburicase versus allopurinol. Fifty-two paediatric patients (age range 0.3 to 17 years) with leukaemia or lymphoma were enrolled. Randomisation was stratified according to presenting uric acid level (<8mg/dL or ≥8mg/dL) and disease (leukaemia or lymphoma) [2, 3].

Patients treated with rasburicase had a more rapid decline and maintained lower plasma uric acid levels throughout induction chemotherapy. They also, on average, experienced a 2.6 fold lower exposure to uric acid during the first 96 hours of therapy, as calculated from the mean area under the curve (AUC) [2].

For patients randomised to rasburicase there was an

RASBURICASE

86% reduction in plasma uric acid concentrations 4 hours after the first dose compared to 12% for allopurinol. In addition, patients hyperuricaemic at baseline who received rasburicase (n=10) all achieved a uric acid concentration of less than 5mg/dL in less than 4 hours. In contrast no patient hyperuricaemic at the start of allopurinol treatment achieved a uric acid level of less than 8mg/dL [2].

Both published studies reported the changes in renal function during rasburicase treatment. Pui et al reported that a steady improvement in renal function was seen in both the hyperuricaemic and nonhyperuricaemic groups. Renal function was within the normal range in all patients by day 6 of treatment. None of the patients required dialysis after the start of rasburicase therapy, despite 25 patients having malignancies associated with a high rate of renal complications [1].

Goldman et al reported that one patient who received allopurinol, required haemodialysis during the study period. In contrast, a patient in the rasburicase group who presented with renal insufficiency and hyperuricaemia improved during therapy without the need for dialysis. The authors attempted to examine the relationship of renal function to treatment arm by studying creatinine levels in the hyperuricaemic patients over the first 96 hours of therapy. Hyperuricaemic patients who received rasburicase had a steady decline in age-adjusted creatinine levels, whilst the hyperuricaemic allopurinol group had increasing creatinine levels [2]. However, the sample size was too small to determine a difference in the incidence of renal failure or need for renal support between the two groups.

ADVERSE EFFECTS

Rasburicase appears to be generally well tolerated. The manufacturers list the following adverse effects and their incidence in the SPC [4]:

Fever	6.8%
Nausea	1.7%
Vomiting	1.4%
Rash	1.4%
Diarrhoea	0.9%
Headache	0.9%
Allergic reactions	0.6%

Enzymatic uric acid oxidation by rasburicase leads to the formation of allantoin and hydrogen peroxide.

Excess hydrogen peroxide can cause haemolytic anaemia in certain at risk groups, including those with G-6-PD deficiency. In trials 0.9% of subjects developed haemolytic anaemia; one of these subjects was documented to have G-6-PD deficiency [4].

Rasburicase is a protein and therefore can induce antibody formation. There is concern that subsequent administration could enhance hypersensitisation or limit the clinical effect. However, most patients who have received a course of rasburicase will be able to take allopurinol with subsequent courses of chemotherapy. Rasburicase antibodies were detected by Piu et al [1] in 14% of the 121 patients tested, and in none of the 23 patients tested by Goldman et al [2].

CONTRAINDICATIONS AND PRECAUTIONS

Rasburicase is contraindicated in patients with hypersensitivity to uricases or any of the excipients, and in patients with G-6-PD deficiency or other cellular metabolic disorders. There is no information about the effects of rasburicase in human pregnancy, and no animal studies have been carried out. Rasburicase should not be used during pregnancy or breast-feeding [4].

Rasburicase should be used with caution in patients with a history of atopic allergies [4].

No metabolism studies have been carried out. However, rasburicase is considered unlikely to interact with any drugs [4].

References

1. Pui CH et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricaemia in patients with leukemia or lymphoma. *J Clin Oncol* 2001; **19(3)**: 697-704.
2. Goldman SC et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumour lysis. *Blood* 2001; **97(10)**: 2998-3003.
3. Committee for Proprietary Medicinal Products. Fasturtec. European Public Assessment Report (EPAR), The European Agency for the Evaluation of Medicinal Products, November 2000.
4. Sanofi-Synthelabo. Fasturtec. Summary of Product Characteristics, February 2001.
5. Lascombes F et al. High efficacy of recombinant urate oxidase in prevention of renal failure related to tumour lysis syndrome. 40th Annual Meeting of the American Society of Hematology, Miami Beach, Florida, USA, 4-8 December 1998. *Blood* 1998; **92(10 suppl 1)**: 237B (Abstract 4019).

Rasburicase

Table 1: Efficacy studies for rasburicase

Ref No	Design of Study (Publication Type)	Treatments Assessed	Primary Outcome Measures	Results and Comments
1, 3	Multicentre, open-label, non-randomised, uncontrolled trial. Age range: 1month to 20 years. <u>Inclusion criteria:</u> Recent diagnosis of B-cell ALL. ALL with an initial leukocyte count of at least $50 \times 10^9/L$ or a lymphomatous presentation and a large tumour burden. Stage III or IV small noncleaved-cell (B-cell) or NHL with a large tumour burden. Any leukaemia or NHL with a plasma uric acid concentration of at least 8mg/dL and either a serum creatinine or lactate dehydrogenase concentration exceeding twice the upper limit of normal. <u>Exclusion criteria:</u> Age 21 years or older. History of clinically significant atopic allergy, bronchial asthma or glucose-6-phosphate dehydrogenase deficiency. A dose of allopurinol within 24 hours or 2+ doses within the preceding 7 days. Pregnancy and breast-feeding.	<u>Dose validation phase:</u> (n=34) Rasburicase 0.15mg/kg/day for 5-7 days. The dose was increased by increments of 0.05mg/kg to one that corrected hyperuricaemia within 48 ± 2 hours after the start of treatment and prevented hyperuricaemia for up to 24 hours in at least 14 consecutive pts. <u>Dose accrual phase:</u> (n=97) Rasburicase 0.20mg/kg/day for 5-7 days (the dose identified by the validation phase).	Response rate according to the following criteria: <ul style="list-style-type: none"> uric acid endpoint (≤ 6.5mg/dL in pts <13 years old or ≤ 7.5mg/dL in pts ≥ 13 years old) reached by 48 ± 2 hours and maintained until 24 hours after last dose of rasburicase no other hypouricaemic agent required to control uric acid concentrations. Uric acid concentration reduction at 4 hours after rasburicase treatment. 24 hour urinary allantoin concentrations.	Hyperuricaemia present at diagnosis in 65 (50%) pts and renal impairment in 28 (21%). Rasburicase 0.20mg/kg/day controlled or normalised uric acid concentrations in 95% of pts. The median level of 5.7mg/dL (range 2.6 to 33.8) at diagnosis, decreased to 0.5mg/dL (range 0.08 to 15.4) at 48 hours after the first dose (n=131, $p < 0.0001$). In the 65 hyperuricaemic pts the median level decreased from 9.7 to 1mg/dL ($p = 0.0001$). The median level in the remaining 66 pts decreased from 4.3 to 0.5mg/dL ($p = 0.0001$)
5,3 (Abs)	Multicentre, open-label trial Age range: 1-72 years. <u>Inclusion criteria:</u> Newly diagnosed NHL, ALL or ANL with risk of hyperuricaemia. Scheduled for treatment with cytotoxic chemotherapy within 48 hours. <u>Exclusion criteria:</u> Current or recent use of allopurinol.	Dose validation (n=20) and accrual phases (n=87): Rasburicase 0.15mg/kg/day for 5-7 days, during induction chemotherapy.	As above.	18 (17%) pts hyperuricaemic at baseline. Rasburicase 0.15mg/kg/day normalised uric acid levels in 99% of pts by 48 hours after the first dose. Uric acid levels reduced by at least 25% (mean $88 \pm 12\%$) in all pts with a 4 hour value (101/107).
2, 3	Multicentre, open-label, randomised, comparative trial. Age range: 3½ months to 17 years. <u>Inclusion criteria:</u> Murphy stage III or IV NHL, ALL with a peripheral WBC count of 25,000/iL or higher, or any childhood lymphoma or leukaemia with a uric acid level ≥ 8 mg/dL. Minimum life expectancy of 4 weeks. ECOG performance scale of ≤ 3 or a Karnofsky scale of $\geq 30\%$. <u>Exclusion criteria:</u> Previous treatment with rasburicase or Uricozyme Treatment with allopurinol within 7 days. Documented asthma, atopy, or G-6-PD deficiency.	Rasburicase 0.20mg/kg/day (n=27) or allopurinol 300mg/m ² (or 10mg/kg) in 3 divided doses (n=25) for 5-7 days. All pts received hydration (~3L/m ² daily). Intravenous sodium bicarbonate at investigators discretion.	Area under the serial plasma uric acid concentration curves from the start of study drug until 96 hours (AUC ₀₋₉₆). Percent reduction of uric acid at 4 hours after the first dose of uric acid-lowering therapy (i.e. prior to chemotherapy).	Comparison of AUC ₀₋₉₆ indicated that pts receiving rasburicase had an average 2.6 (95% CI 2.0-3.4) fold lower exposure to uric acid. 4 hours after the first dose of rasburicase, 86% serum uric acid was eliminated vs 12% in pts on allopurinol ($p < 0.0001$). Median time to achieve uric acid <8mg/dL: 4 hrs for rasburicase and 23.9 hrs for allopurinol. Renal failure requiring dialysis: no rasburicase pts, 1 allopurinol pt.

Abbreviations: ALL - acute lymphoblastic leukaemia, NHL - non-Hodgkins lymphoma, Abs – abstract, ANL - acute non-lymphoid leukaemia, WBC – white blood cell, ECOG – Eastern Cooperative Oncology Group, G-6-PD – glucose-6-phosphate dehydrogenase.