

Rasburicase injection

Powder for reconstitution, 1.5mg -

Guidance for Individual Patient Approval

Note: The Queensland Health Medicines Advisory Committee (QHMAC) considers that rasburicase has a specific role in therapy and, for children, supports its availability on the Queensland Health List of Approved Medicines (LAM) in line with the dosing guidance in this document. For adult use, the committee has taken the position that rasburicase should not be added to the LAM but appreciates that there may be specific cases where individual patient approval (IPA) is appropriate. **This guide has been drafted to assist medical superintendents (or delegates) and local medicines committees in their consideration of IPA requests for adult use of rasburicase;** and to guide clinicians in the most cost-effective dosing of this agent in all age groups.

Rasburicase is included on the List of Approved Medicines (LAM) with the restriction:

- A. For use in paediatric patients on the advice of a haematologist or paediatric oncologist, to prevent and treat hyperuricaemia manifestations of tumour lysis syndrome.
- B. For use in adult patients, this medicine is not LAM listed—individual patient approval is required.

Rationale for rasburicase use

Rasburicase is a recombinant urate-oxidase enzyme. It has TGA approval for treatment and prophylaxis of acute hyperuricaemia, in patients with haematological malignancy at risk of a rapid tumour lysis⁽¹⁾.

The acute increase in plasma levels of uric acid following the lysis of large numbers of malignant cells and during cytoreductive chemotherapy may lead to 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.

Role in therapy

QHMAC considers that rasburicase is an efficacious and quick-acting parenteral therapy which can be used for treatment (and, rarely, for prophylaxis) of hyperuricaemia associated with tumour lysis syndrome (TLS). However, this medicine has a very specific role in therapy. Evidence is available which supports using more cost effective, lower dosing regimens than those stated in the product information. The aim is to lower uric acid to within the normal range, rather than achieve a zero-plasma level with the TGA approved dose.

The criteria for use of rasburicase must be assessed by either a haematologist or a paediatric oncologist at an appropriate facility. Rasburicase is to be used immediately prior to, and during the initiation of chemotherapy. The use of rasburicase is proposed for patients at high risk of tumour lysis and will only treat the hyperuricaemia manifestations of TLS. Rasburicase has no

effect on the non-hyperuricaemia related electrolyte disturbances and/or clotting abnormalities which complicate TLS. Consequently, there is no rationale for using rasburicase to treat electrolyte disturbances when serum urate is suppressed.

Use of rasburicase should always be in combination with therapies to correct additional manifestations of TLS and should include: adequate IV hydration to maintain urine flow, reduction of urate production, correction of other electrolyte and/or bleeding disturbances, and reduction of tumour bulk.

Safety

Hydrogen peroxide is a byproduct 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 G-6-PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia.

Clinicians should note that evidence supports lower dosing regimens which are not TGA-approved. (Refer to dosing guidance below.) The normal processes which apply to off-label use should be adopted as necessary. Guidance on off-label use can be found in the introductory pages of the LAM and the *CATAG guiding principles for the quality use of off-label medicines* (www.catag.org.au).

Cost estimates

Rasburicase powder for injection 1.5mg costs approximately \$200 per vial.

A. Guidance for paediatric use

In the paediatric setting, it is expected that this medicine will predominantly be used where treatment is required urgently and oral allopurinol is inappropriate. A significant number of paediatric patients who are administered oral allopurinol require temporary renal dialysis, vascaths and ICU admission. The need to dialyse these patients is lessened when rasburicase is used. Additionally, the rapid fall of urate allows earlier administration of chemotherapy, which is particularly important in those patients with airway compromise from T-cell disease.

QHMAC recommends use of rasburicase for the following paediatric diseases at risk of TLS where oral allopurinol is unsuitable or inappropriate:

- B-cell lymphoma where there is life-threatening mass disease which requires urgent treatment (e.g. airway obstruction)
- B-cell acute lymphoblastic leukaemia (ALL), where oral allopurinol cannot be used
- T-cell lymphoma or leukaemia with WCC > 100,000 or urate > 0.5 at presentation or relapse (if plan to treat relapse aggressively)
- other acute leukaemias with WCC > 200,000 or urate > 0.5 at presentation or relapse (if plan to treat relapse aggressively)
- any malignancy with evidence of TLS at presentation (e.g. urate > 0.5 and disturbance of calcium/phosphate and with expectation of rapid response to chemotherapy). (NOTE: Not

many solid tumours will fall into this category but large volume or metastatic germ-cell tumours would.)

Paediatric dosing

Based on available evidence QHMAC recommends the following alternate regimen to TGA-approved dosing ^(1,2,3,4,5,6,7)

For children, administer 0.15-0.2mg/kg/day (to a maximum of 6mg)^(5, 6) as a once daily intravenous infusion. Most patients will require only one dose. Further doses can be given at the discretion of the consultant if the uric acid level increases. Some lymphoma patients (Burkitt's Lymphoma with bulky disease) or other very high risk patients may require up to twice daily dosing at the consultant's discretion. Dose adjustment⁽¹⁾ is not required in patients with renal or hepatic impairment. (Round dose up to nearest 1.5mg for vial size.)

B. Guidance for adult use

It is anticipated that the use of rasburicase will be infrequent as timely use of oral allopurinol is effective in the majority of patients. It takes 24-72 hours for allopurinol to effectively inhibit de novo uric acid production.

QHMAC recommends use of rasburicase for the following clinical scenarios and adult diseases at risk of TLS where oral allopurinol is unsuitable or inappropriate:

- Burkitt's and Burkitt-like NHL
- other aggressive NHL (DLCL; ALCL etc.) with bulky disease (tumour masses >10cm) and significantly elevated LDH (>500 U/L)
- acute leukaemia associated with significantly elevated WCC:
 - AML WCC >50-100 x10⁹/L;
 - ALL WCC >100-200 x10⁹/L.
- Initiation of venetoclax (and other BCL-2 inhibitors) in patients with a high tumour burden

Approval of new anti-tumour agents over the next 5-10 years will require some flexibility in applying this guideline.

Adult dosing

Based on the available evidence, QHMAC recommends a more cost-effective approach—lower doses and shorter duration of treatment than is approved by the TGA, with re-dosing as required ^(1,2,3,4,5,6,7,8,9,10):

Administer 3mg (i.e. 2 x 1.5mg vials) as a single dose. This dose should bring uric acid into the normal range but can be repeated if necessary. Patients should be monitored and may require a repeat dose every 2-3 days if serum

urate returns to greater than normal. If considered clinically appropriate, allopurinol can be given after treatment with rasburicase has ceased.

Acknowledgments

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Version Control

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