A.27	Rasburicase – treatment and prevention of tumour lysis syndrome
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: This application proposes to add rasburicase to the list of WHO Essential Medicine as treatment for individuals with tumour lysis syndrome and as prevention in individuals at high risk of tumour lysis syndrome
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Rasburicase 1,5 mg powder (FASTURTEC©) is a recombinant urate oxidase enzyme that catalyzes the oxidation of uric acid into allontoin, highly soluble metabolite easily eliminated via the kidneys. It is indicated to treat and prevent tumor lysis syndrome (TLS), a life-threatening complication of cancer therapy, especially while treating high proliferative cancers, mainly hematological malignancies or solid organ malignancies who are receiving anticancer therapy expected to cause tumor lysis and subsequent elevation of PUA levels. Acute kidney injury represents one of the most serious consequences of TLS and predicts mortality. Rasburicase efficacy is evaluated comparing to allopurinol, a xanthine oxidase inhibitor that prevent new uric acid formation by inhibiting xanthine oxidase whereas rasburicase converts preexisting uric acid to allantoin. Rasburicase is dramatically effective in lowering plasma uric acid levels, however its impact in preventing and treating hard outcomes, TLS, renal complications and mortality needs more demonstration.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Two randomized clinical trials (RCTs) tested uric acid levels (trials endpoint), comparing receiving rasburicase or allopurinol- rasburicase to receiving only allopurinol. The treatment was given during 5 days after chemotherapy. One trial was including adults, and the second was including children, all affected by hematological malignancies (Leukemia, lymphoma). Both trials have found a significant reduction of plasmatic uric acid level with rasburicase. Only one trial estimated the effect of rasburicase in hard clinical outcome, incidence of clinical TLS, incidence of laboratory TLS and acute renal failure. the benefit of rasburicase was clear only with the endpoint laboratory TLS (RR:0,51 CI95% 0,33-0,79). We note that we cannot find which trial the proposal is referring to here, the reference was not mentioned in the proposal and it was not specified if the population included in the trial were adults or children or both. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Cochrane review was completed for Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer, and concluded that urate oxidase might be effective in reducing serum uric acid. However, it is unclear whether it reduces clinical TLS, renal failure, or mortality, and the adverse effects might be more common for urate oxidase compared with allopurinol. Therefore, Clinicians should weigh the potential benefits of reducing uric acid and uncertain benefits of preventing mortality or renal failure from TLS against the potential risk of adverse effects. Lower doses of rasburicase have been tested, 0,15 mg/kg /day, comparing to 0,20 mg/kg /day, and no significant difference has been found in reducing plasmatic uric acid, Ref1 (Study not reported by the proposal).
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Hypersensitivity reactions need monitoring, generally mild: skin rash, urticaria or bronchospasm. Rasburicase should not be given to patients with known G6PD deficiency, particular attention therefore should be paid in G6PD endemic populations (Africans, Mediterranean's), Ref2.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable for limited and specific indications, when a high risk of TLS is evaluated by treating doctors. Vigorous Hydration with allopurinol remains the first line of management of TLS.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Evidences are low to moderate, regarding a lack of evidence in the assessment of rasburicase effect in hard clinical outcomes (mortality, renal failure).
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: -Monitoring of Acid uric level -Excluding G6PD deficiency affected patients. -Monitoring of hypersensitivity reactions.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☐ No ☐ Not applicable Comments:

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	The treatment is costly and that may limit low and middle-income countries access to rasburicase. Indeed, an assessment of a lower doses exist and should had been reported in the proposal for potential use and reduction in the cost of the treatment. Evaluated ICER was highly variable depending on the input parameters considered in the study (indication: prevention of TLS or treatment, population: children versus adults/ Time horizon, etc…..). The reported high ICERs may limit rasburicase efficiency, particularly in countries with middle and low-income.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Rasburicase may be indicated in specific and precise indications and doses, following further elaboration of the proposal that could have included more information about the specific indications approved in different countries, the report of tested doses and regimen (daily versus one dose) of Rasburicase that might be considered in patients treatment, Ref3.
References (if required)	Ref1. Kikuchi A, Kigasawa H, Tsurusawa M, et al. A study of rasburicase for the management of hyperuricemia in pediatric patients with newly diag- nosed hematologic malignancies at high risk for tumor lysis syndrome. Int J Hematol. 2009;90(4):492–500. Ref2. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844–1854. Ref3. Rasburicase in the management of tumor lysis: an evidence-based review of its place in therapy