A.27	Rasburicase – tumor lysis syndrome (TLS)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Rasburicase is a drug use for the prevention and treatment of tumor lysis Syndrome (TLS). It is caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation. TLS most often occurs after the initiation of cytotoxic therapy in patients with clinically aggressive and highly aggressive lymphomas (particularly the Burkitt subtype) and T-cell acute lymphoblastic leukemia (ALL). However, it can occur spontaneously and with other tumor types that have a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy. The emergence of effective targeted anticancer drugs, used alone or in combination with conventional cytotoxic agents, has led to an increase in the frequency and severity of TLS in hematologic cancers that previously were rarely associated with this complication.
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.	Excessive purine catabolism results in the production of hypoxanthine and xanthine, which are metabolized to uric acid trough the enzyme xanthine oxidase (XO). Two drugs (allopurinol and febuxostat) inhibit XO activity. After two or three days the effect of both drugs result in both excretion of hypoxanthine (which is more soluble than uric acid) and xanthine (less soluble than acid uric). Preformed uric acid is not altered by the action of both drugs. By contrast when urate oxidase (UO), which is present in most mammals but not in humans , is given exogenously (such as Rasburicase) serum and urine levels markedly decrease within few hours. This rapid reduction in serum uric acid is in contrast to the effect of allopurinol and febuxostat which decrease uric acid formation and therefore does not acutely reduce the serum uric acid concentration.
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). Few controlled clinical studies are available on the use of rasburicase for prophylaxis or treatment of TLS in adults. A systematic review (which included four controlled trials, only one of which(Cortes J et al.) had a non-rasburicase containing arm) and 17 observational studies concluded that rasburicase was effective in reducing serum uric acid levels in adults with or at risk for TLS, but that evidence was currently lacking to know whether clinical outcomes were improved compared with other therapeutic alternatives. 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 for prevention and treatment of TLS in children with cancer included one randomized trial (Goldman SC *et al* 2001) and five controlled (but not randomized) studies comparing outcomes in patients treated with allopurinol vs urate oxidase (Cheuk DK *et al* 2017). In the controlled trial (Rasburicase therapy was associated with a much greater reduction in serum uric acid four hours after the first dose . Serum creatinine levels steadily declined in patients treated with rasburicase, while they increased over the four days of therapy in the allopurinol group. No patient receiving rasburicase required dialysis, compared with one in the allopurinol group. Severe hemolysis developed in one rasburicase-treated patient who had no evidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency. In addition to the randomized trials, the pooled results of five controlled clinical trials also showed significantly lower uric acid levels at days 2 to 4 after urate oxidase treatment. Overall available data provide clear evidence supporting the use of rasburicase rather than allopurinol for children with high-risk conditions. However in the only controlled randomized study although urate oxidase is effective in reducing serum uric acid, its impact in reducing clinical TLS, acute kidney injury, or mortality was not evident even due to the small sample size, but evident in the comparison of the five controlled trials.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Rasburicase is well-tolerated. The Application provides adequate information about the risks of hemolysis, hemoglobinuria, methemoglobinemia, interference with serum uric acid measurements, and anaphylaxis

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Rasburicase should not be given to patients with G6PD deficiency because hydrogen peroxide, a byproduct of uric acid breakdown, can cause severe hemolysis in this setting. Males , history of prior drug-induced hemolytic anemia and/or a racial/ethnic background associated with G6PD deficiency,(eg, African-American, Mediterranean, or Southeast Asian descent)should undergo enzyme assay. If administration of rasburicase is needed in an emergency situation and the results of G6PD testing are not available, rasburicase should be given at a single low dose (eg, 0.02 to 0.05 mg/kg and no more than 3 mg), and hemodialysis should be readily available in the event of significant hemolysis.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Tumor lysis syndrome (TLS) is an oncologic emergency that is caused by massive tumor cell lysis and the release of large amounts of potassium, phosphate, and uric acid into the systemic circulation. TLS is associated with high risk of kidney failure and increased mortality. The best treatment is prevention. Guidelines for prevention and management, based on a disease-specific estimated risk of TLS is currently available. Although the evidence is stronger for use of rasburicase in children with high-risk conditions than in adults, rasburicase has been approved for use in both children and adults by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Evidences are moderate but overall there is a strong consensus that the use of rasburicase in high-risk patients, can prevent serious complication (kidney failure) and mortality. It is mandatory to refer to the international TLS consensus expert panel of pediatric and adult oncologists, for the proper definition of low, intermediate and high risk TLS classification, associated TLS prophylaxis recommendations and accordingly for the correct use of rasburicase.
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: Rasburicase should **not** be given to patients with G6PD deficiency.
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.	1. The price of drug may be an access barrier to LMIC; 2. Shortened dose of administration may be a reasonable approach. The efficacy and cost of a single dose of rasburicase compared with daily dosing was addressed in a meta-analysis of 10 studies (eight retrospective and two prospective).Overall, the pooled response rate to single-dose therapy was not significantly different from that of daily administration. Single-dose administration generated significant cost savings, approximately $4500 versus $36,000 for drug treatment.
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.	Addition of rasburicase, considering: 1. Treating the complications of TLS is very resource intensive; 2. Stronger advice for children with high–risk conditions more than in adults; 3. The price of drug may be an access barrier to LMIC; 4. Shortened dose of administration may be a reasonable approach.
References (if required)	1. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008; 26:2767. 2. Howard SC, Trifilio S, Gregory TK, et al. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. Ann Hematol 2016; 95:563. 3. Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor Lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone--results of a multicenter phase III study. J Clin Oncol 2010; 28:4207. 4. Lopez-Olivo MA, Pratt G, Palla SL, Salahudeen A. Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. Am J Kidney Dis 2013; 62:481. 5. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001; 97:2998. 6. Cheuk DK, Chiang AK, Chan GC, Ha SY. Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer. Cochrane Database Syst Rev 2017; 3:CD006945.

	7. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011; 364:1844. 8. Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol 2010; 149:578. 9. Feng X, Dong K, Pham D, et al. Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: a meta-analysis. J Clin Pharm Ther 2013; 38:301.