Application to add rasburicase to WHO Model List of Essential Medicines

As a Medicine for Treatment and prevention of for tumour lysis syndrome

Submitted by:

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Potential conflicts of interest

All the authors declare no conflict of interest

Date: January 2021

General items

1. Summary statement of the proposal for inclusion, change or deletion.

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.

The tumour lysis syndrome is an oncologic emergency characterized by a group of metabolic disturbances including: hyperkalaemia, hyperphosphatemia, hypocalcaemia, and hyperuricemia. In particular, hyperuricemia may lead to renal damage and end-stage renal failure. The incidence of clinical tumour lysis syndrome has been estimated in 4-6%, although it may vary with the underlying malignancy: It is far more frequent in haematological malignancies, although it has been described in solid tumours as well, especially in gastrointestinal and lung cancers.

Rasburicase can quickly reduce plasmatic uric acid levels, much faster than allopurinol, since the latter can only prevent the formation of new uric acid. It also may prevent the appearance of the laboratory abnormalities that define the tumour lysis syndrome (RR 0.51, 95% CI 0.33 - 0.79; very-low certainty evidence).

Treating the complications of tumour lysis syndrome is very resource intensive. Specially hyperuricemia, which may lead to renal complications and the need of renal-replacement therapies. The use of rasburicase is a cost-effective alternative in high risk groups and may even prevent some costs. At the current time, the price of the drug may be an access barrier to low and middle income countries. Shortened schemes of administration and a careful selection of patients may be a reasonable approach to implement rasburicase in those settings.

2. Relevant WHO technical department and focal point.

Department of Health Products Policy and Standards, World Health Organization, Geneva, Switzerland

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International Nonproprietary Name (INN)	Anatomical Therapeutic Chemical (ATC) code
Rasburicase	V03AF07

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Rasburicase: powder for injection 1.5 mg in vial

Manufacturer: Sanofi-Aventis

Trade name: Fasturtec

Hiperuricemia dose: 0.20 mg/kg/day (for children, adolescents and adults)

No dose adjustment is necessary for renally or hepatically impaired patients.

There is no data regarding the use of rasburicase in pregnant women. Results from animal studies cannot be interpreted due to the presence of endogenous urate oxidase in standard animal models. Because teratogenic effects of rasburicase cannot be ruled out, it should only be used during pregnancy if strictly necessary. It is unknown whether rasburicase is excreted in human milk.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

As individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

The recommended dose is 0.20 mg/kg/day a once daily 30 minute intravenous infusion in 50 ml of a sodium chloride 9 mg/ml (0.9%) solution.
The duration of treatment may be up to 7 days, the exact duration should be based upon adequate monitoring of uric acid levels in plasma and clinical judgment.

8. Information supporting the public health relevance.

The tumour lysis syndrome is an oncologic emergency characterized by a group of metabolic disturbances including: hyperkalaemia, hyperphosphatemia, hypocalcaemia, and hyperuricemia. In particular, hyperuricemia may lead to renal damage and end-stage renal failure.
The exact incidence of tumour lysis syndrome is unknown, since its frequency varies with the underlaying malignancy and the specific definition used. Some definitions include only laboratory abnormalities such as plasmatic levels of potassium, phosphate, calcium or uric acid. Under these definitions, the incidence of a laboratory abnormalities can be as high as

45% of patients, as it has been observed in small cohorts of children with acute lymphoblastic leukaemia.[1,2] In broader populations, however, the incidence of a laboratory tumour lysis syndrome has been estimated in around 10-15%.[3,4] Fortunately, only a proportion of patients with laboratory abnormalities ultimately develop symptoms, such as nausea, muscle cramps, weakness or fatigue. The reported incidence of a clinical tumour lysis syndrome is around 4-6%.[3,5,6]

The tumour lysis syndrome is far more frequent in haematological malignancies, although it has been described in solid tumours as well, especially in gastrointestinal and lung cancers.[7] In general, the risk of tumour lysis syndrome is higher in cancers with a high proliferative rate and rapid response to therapy.

Treating the complications of tumour lysis syndrome is very resource intensive. Specially hyperuricemia, which may lead to renal complications and the need of renal-replacement therapies. Therefore, in low and middle income settings the use of rasburicase might result in net savings, especially with shortened regimens.[8-10]

9. Review of benefits: summary of evidence of comparative effectiveness.

Methods

We searched for randomized trials up to December 2020 on MEDLINE and EMBASE, from date of inception and without language limits. Additionally, we searched for up to date systematic reviews in MEDLINE, EMBASE and The Cochrane Library (see appendix).

We used the following inclusion criteria:

1. Study design: Randomized trial
2. Population: Individuals with any malignancy
3. Intervention: Rasburicase
4. Comparison: any other strategy without rasburicase

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool. We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach.

We meta-analysed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I2 statistic. All the meta-analyses were conducted using RevMan (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

We identified 3 systematic reviews[11-13] and 2 randomized trials.[14,15] One trial included 280 adults with leukaemia or lymphoma. Participants were randomized to rasburicase, allopurinol or a combination of rasburicase plus allopurinol. All the interventions were given for 5 days after receiving chemotherapy.[15] The other trial included 52 children with leukaemia or lymphoma, who were randomized to rasburicase or allopurinol for 5 to 7 days, also after receiving chemotherapy. Both trials focused on uric acid levels and were not powered to detect differences on patient-important outcomes.

On both trials, the plasmatic uric acid levels were reduced faster with rasburicase: 4 hours after the first dose, uric acid decreased in 86-88% with rasburicase compared with 12-14% with allopurinol. This finding reflects the mechanism of action of the drugs: rasburicase can effectively reduce the uric acid levels while allopurinol can only prevent the formation of new uric acid.

Only one trial reported data to estimate the effect of rasburicase in the incidence of tumour lysis syndrome and patient-important outcomes. Compared to allopurinol, rasburicase may reduce the incidence of laboratory tumour lysis syndrome (RR 0.51, 95% CI from 0.33 to 0.79; 222 fewer events per 1000, 95% CI from 94 to 301 fewer; very-low certainty evidence). However, the evidence of the effect of rasburicase on clinical tumour lysis syndrome or renal failure is less clear (RR 0.74, 95% CI from 0.17 to 3.22; and RR 0.98, 95% CI from 0.14 to 6.87, respectively; both very-low certainty evidence).

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH rasburicase	WITHOUT rasburicase	Difference (CI 95%)	
Clinical tumour lysis syndrome 1 RCT (n=183)	**RR 0.74** (0.17 - 3.22)	**33** Per 1000	**44** Per 1000	**11 fewer** (from 36 fewer to 98 more)	⨁◯◯◯ **VERY-LOW** [a,b]
Laboratory tumour lysis syndrome 1 RCT (n=183)	**RR 0.51** (0.33 - 0.79)	**228** Per 1000	**450** Per 1000	**222 fewer** (from 94 to 301 fewer)	⨁◯◯◯ **VERY-LOW** [a,c]
Acute renal failure 1 RCT (n=183)	**RR 0.98** (0.14 - 6.87)	**22** Per 1000	**22** Per 1000	**0 fewer** (from 19 fewer to 129 more)	⨁◯◯◯ **VERY-LOW** [a,b]

Abbreviations: RR: Risk Ratio. CI: Confidence interval;

a. We rated down the certainty of the evidence due to risk of bias. The study identified was not blinded.
b. We rated down the certainty of the evidence by two levels due to imprecision; given the small sample size and the small number of events observed.
c. We rated down the certainty of the evidence by two levels due to indirectness. There are two sources of indirectness for this outcome: First, the baseline risk of tumour lysis syndrome observed in the control group was extremely high. This is a consequence of the broad definition used in the study. Likely, the incidence observed in usual practice is lower. Second, it is unclear to what extent the correction of laboratory abnormalities may impact on patient-important outcomes.

10. Review of harms and toxicity: summary of evidence of safety.

Compared to allopurinol, rasburicase might increase the risk of adverse events: RR 3.96 95% CI from 0.45 to 34.7; 33 more events per 1000, 95% CI from 6 fewer to 371 more; very-low certainty evidence.

The events observed with rasburicase were mainly hypersensitivity reactions such as rash, arthralgia or injection site irritation. They were generally mild, and only in 1 out of 92 patients lead to a discontinuation of the drug.

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH rasburicase	WITHOUT rasburicase	Difference (CI 95%)	
Adverse events 1 RCT (n=183)	**RR 3.96** (0.45 - 34.7)	**44** Per 1000	**11** Per 1000	**33 more** (from 6 fewer to 371 more)	⨁◯◯◯ **VERY-LOW**

Abbreviations: RR: Risk Ratio. CI: Confidence interval;

a. We rated down the certainty of the evidence due to risk of bias. The study identified was not blinded.
b. We rated down the certainty of the evidence by two levels due to imprecision; given the small sample size and the small number of events observed.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Methods

We searched for economic evaluations up to December 2020 on MEDLINE, EMBASE and the Cochrane library (see appendix). Additionally, we hand-searched the websites of the following agencies and organizations: The National Institute of Health Research, The Center of Review and Dissemination, The Canadian Agency for Drugs and Technologies in Health (CADTH), The National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC) and The International Network of Agencies for Health Technology Assessment (INHATA).

Inclusion/exclusion

Inclusion

We included full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population.

Exclusion

We excluded studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects. Also we excluded abstracts, posters, reviews, letters/editorials, and unpublished studies

Results

We identified four studies: one cost-benefit analysis,[16] two cost-effective analysis[17,18] and one cost consequence.[19]

Three of the four studied identified had very serious limitations and their results were considered unreliable.[16,18,19] None of these 3 studies used an appropriate mathematical model nor a probabilistic sensitivity analysis. Also they have several errors or omissions and some assumptions were not shown or simply not correct.

Only one study had an acceptable quality. It was a cost-effective study from China, that used a decision tree as the model method, from a perspective of the health care system.[17] The study addressed the use of rasburicase in the prevention and treatment paediatric patients with acute myeloid leukaemia, acute lymphoid leukaemia or non-Hodgkin's lymphoma. The results suggested that rasburicase was cost-effective in most of the scenarios, with an ICER between $991 - $2,031 per QALY for treatment and $ 5,391 - $17,580 per QALY as prophylaxis.

Summary of Economic Evaluations

Study	Limitations	Other comments		Cost-effectiveness (ICER)	Uncertainty
Shaoyan H. 2019 [17]	potentially serious limitations[a]	Model	Decision tree model with a lifetime horizon	For patients with AML, preventive use The ICER was $17,580.05 /QALY. For patients with ALL, prevention with rasburicase vs SOC, The ICER was $5,783.46 /QALY For patients with NHL, prevention with rasburicase vs SOC The ICER was $5,391.00 /QALY Treatment use: For patients with AML, treatment with rasburicase	The uncertainty was measure in a deterministic and probabilistic way. In the tornado diagram, the most important factor was the life expectancy with TLS cured. Based on the WHO recommended WTP threshold, rasburicase is cost-effective vs SOC during for TLS prevention with the probability of 66% for AML and nearly 100% for both ALL and NHL. The PSA results further demonstrated cost-effectiveness of rasburicase is much more pronounced in the treatment-use scenario achieving 100% cost-effective at WTP below 50% per capita GDP The results show a more robust cost-effective result for the treatment with rasburicase
		Population	Paediatric patients with acute myeloid leukaemia, acute lymphoid leukaemia and non-Hodgkin's lymphoma		
		Time horizon	Lifetime		
		Costs	The cost was obtained from a published study, they considered hospitalization costs and possible events		
		Perspective	Healthcare system		
		Others	The study considered a treatment and preventive use, using a threshold of 1-3 GDP of the country ($7,972.90GDP for 2017)		

				vs SOC The ICER was $2,031.18 /QALY. For patients with ALL, treatment with rasburicase vs SOC resulted in The ICER was $1,142.93 /QALY. For patients with NHL, treatment with rasburicase vs SOC The ICER was $990.37/QALY	

Abbreviations: AML: acute myeloid leukaemia, ALL: acute lymphoid leukaemia, NHL: non-Hodgkin's lymphoma, SOC: standard of care

(a) Standard of care is not appropriately described. The evidence use for effectiveness was observational (very-low certainty of evidence)

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

US Food and Drug Administration: Approved

European Medicines Agency: Approved

Australian Government: Approved

Japanese Pharmaceuticals and Medical Devices Agency: Approved

Health Canada: Approved

13. Availability of pharmacopoeial standards

Rasburicase

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

References

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hyperuricaemia and tumour lysis syndrome in haematological cancer patients. *Support Care Cancer.* 2003;11(4):249-257.
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Appendix

Appendix 1: Search strategies

Search strategy for randomized trials in MEDLINE and EMBASE (via OVID)

DATE: December 2020

1. exp Urate Oxidase/
2. rasburicase.mp.
3. exp Tumor Lysis Syndrome/
4. Tumor Lysis Syndrome.mp.
5. randomized controlled trial.pt.
6. random allocation/
7. double-blind method/
8. single-blind method/
9. randomi?ed controlled trial$.mp.
10. Randomi?ed clinical trial$.mp.
11. controlled clinical trial.pt.
12. ((singl$ or double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
13. random$.mp.
14. placebo$.mp.
15. cross-over studies.sh.
16. latin square.tw.
17. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. animals/ not humans/
19. 17 not 18
20. 1 or 2
21. 3 or 4
22. 19 and 20 and 21

Search strategy for systematic reviews in MEDLINE and EMBASE (via OVID)

DATE: December 2020

1. exp Urate Oxidase/
2. rasburicase.mp.
3. exp Tumor Lysis Syndrome/
4. Tumor Lysis Syndrome.mp.
5. systematic review/
6. meta-analysis/
7. (meta analy* or metanaly* or metaanaly*).ti,ab.

8. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.
9. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
10. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
11. cochrane.jw.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 1 or 2
14. 3 or 4
15. 12 and 13 and 14

Search strategy for economic evaluations in MEDLINE (via OVID)

DATE: December 2020

(Rasburicase OR Elitek OR recombinant urate oxidase) AND (Economics[Mesh:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab])

Search strategy for economic evaluations in EMBASE (via OVID)

(tumor lysis syndrome.af. OR tumor lysis syndrome/) AND ((Rasburicase or Elitek or recombinant urate oxidase).af. OR rasburicase/) AND (Cost-effectiveness.mp. or "cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or "cost"/ or "cost effectiveness analysis"/ or QALY.mp. or quality adjusted life year/ or health technology assessment.mp. or biomedical technology assessment/ or economics/ or willingness to pay.mp. or "health care cost"/ or life years gained.mp. or disability-adjusted life years.mp. or disability-adjusted life year/ or Statistical Model/ or economic model*.ab,ti. or Probability/ or markov.ti,ab,kw. or monte carlo method/ or monte carlo.ti,ab. or Decision Theory/ or Decision Tree/)