PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting Held via Videoconference

Held on 18 June 2020

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PTAC members:

Present:

Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Brian Anderson
Bruce King
Giles Newton Howes
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Stephen Munn
Tim Stokes

Apologies

Alan Fraser
Simon Wynn Thomas

1. The role of PTAC, PTAC Subcommittees and meeting records

1.1. This meeting record of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and PTAC Subcommittees.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. PTAC and PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from PTAC Subcommittees', including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC Subcommittees may, at times, make recommendations that differ from PTAC's, or from other PTAC Subcommittees', when considering the same evidence.

PHARMAC considers the recommendations provided by both PTAC and PTAC Subcommittees when assessing applications.

2. Febuxostat for the prevention of tumour lysis syndrome in allopurinol-intolerant patients scheduled to receive cancer therapy that carries an intermediate or high tumour lysis syndrome risk

Application

2.1. The Committee reviewed the application to widen access to febuxostat for the prevention of tumour lysis syndrome in allopurinol-intolerant patients scheduled to receive cancer therapy that carries an intermediate or high tumour lysis syndrome risk.

2.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

2.3. The Committee **recommended** that access to febuxostat for the prevention of tumour lysis syndrome in allopurinol-intolerant patients scheduled to receive cancer therapy that carries an intermediate or high tumour lysis syndrome risk be widened with a high priority due to:

- The high health need of patients who develop tumour lysis syndrome
- The similar efficacy between allopurinol and febuxostat
- Oral febuxostat being a more suitable alternative for those intolerant of allopurinol than intravenous rasburicase, the current allopurinol alternative
- The favourable cost differential between febuxostat and rasburicase

2.4. The Committee considered that PHARMAC could seek subsequent advice from cancer haematologists on the Cancer Treatments Subcommittee (CaTSoP) regarding the size of the patient population and how to define the Special Authority criteria appropriately, to inform the economic analysis.

Discussion

2.5. The Committee noted that tumour lysis syndrome (TLS) is an infrequent but potentially severe complication of cancer therapy, usually chemotherapy, which occurs from the rapid and extensive lysis of cancer cells leading to the release of metabolites such as uric acid, phosphate and potassium into the extracellular space. The Committee noted that cell lysis can occur quickly following cancer treatment, particularly in high cell-dividing cancers, such as Burkitt's lymphoma, resulting in rapid and extremely high serum urate, hence there is a need for prophylaxis. The Committee noted that TLS can be a fatal side effect of cancer treatment or can result in complications including sepsis, acute kidney injury requiring dialysis and acute respiratory failure (Durani et al. Oncologist. 2017;22:1506-9). The Committee noted that TLS can be categorised into two groups – clinical TLS and laboratory TLS, as defined by the expert opinion-based Cairo-Bishop definitions (Cairo and Bishop. Br J Haematol. 2004;127:3-11).

2.6. The Committee noted that TLS risk is stratified by tumour type and burden, baseline renal function, baseline uric acid level, and chemotherapy agent received. The Committee noted that a number of haematologic cancers including acute lymphoblastic leukaemia, acute myeloid leukaemia and aggressive lymphoma carry intermediate to high risk of TLS. The Committee noted that while haematological malignancies are most commonly associated with TLS risk, solid tumours including neuroblastoma, germ cell tumours and small cell lung cancer are associated with an intermediate risk of TLS (Durani et al. Br J Haematol. 2020;188:494-500).

2.7. The Committee noted that currently patients undergoing cancer treatment with a low TLS risk are managed with hyperhydration, those with an intermediate/high risk are managed with allopurinol (treatment initiated two days prior to cancer treatment, for a total of approximately nine days), and those with particularly high TLS risk are managed with intravenous (IV) rasburicase (3 mg per day for approximately 3-5 days). The Committee noted that patients with an intermediate/high risk of TLS who are allopurinol-intolerant are often managed with IV rasburicase.

2.8. The Committee noted that while the incidence of TLS with currently available treatments is low, the health need of patients who develop TLS is high. The Committee noted a study, in which TLS-attributable mortality occurred in approximately 2% of patients with acute myeloid leukaemia, treated with intensive chemotherapy and receiving standard prophylactic measures such as hyperhydration and allopurinol (Montesinos et al. Haematologica 2008;93:67-74).

2.9. The Committee noted that in the context of gout, the available epidemiological evidence indicates that allopurinol-intolerance occurs in 3-10% of patients, with local estimates indicating a slightly lower rate of intolerance. The Committee considered an appropriate definition of allopurinol-intolerance in the context of TLS prevention should be "documented intolerance to allopurinol", and that this would likely include patients who had previously been treated for gout. Members considered that this group would likely include patients who experienced a gout flare while on treatment and as such were classed as intolerant, despite true intolerance not being present. The Committee considered that oncologists may not confirm whether true allopurinol-intolerance exists when determining a TLS prophylactic treatment regimen. As such, the Committee considered that there may be the potential for some 'slippage' with diagnostic drift with this definition. However, due to the small patient numbers, this would likely be immaterial.

2.10. The Committee noted that Māori and Pacific people have a higher incidence of gout than non-Māori/non-Pacific and are therefore more likely to have had previous exposure to allopurinol and thus more likely to have experienced allopurinol-intolerance. The Committee noted that for the cancers that often categorise patients as high TLS risk, there are minimal differences in incidence according to ethnicity.

2.11. The Committee noted that there may be some cross reactivity between serious cutaneous adverse reactions associated with allopurinol and adverse reactions to febuxostat, but this would be in very small numbers. The Committee noted that allopurinol-hypersensitivity generally develops after 3-6 weeks of treatment, and therefore considered it would be unlikely patients would develop intolerance during the short treatment window for TLS prophylaxis. The Committee considered that a small number of patients may develop allopurinol intolerance once started on prophylactic treatment for TLS and that patients may be required to change to alternative treatment (which could include febuxostat). However, the Committee considered that if this were to occur it would be uncommon, and that most patients in this situation may receive rasburicase.

2.12. The Committee noted that people who carry the HLA-B*5801 allele are at particularly high risk of severe allopurinol adverse reactions. The Committee considered that while the genetic test for HLA-B*5801 is available in New Zealand, it is not commonly used and would be unlikely to be utilised to confirm a high risk of allopurinol hypersensitivity in the event that funding for febuxostat for allopurinol-intolerant patients for TLS prophylaxis was progressed.

2.13. The Committee considered that the population of allopurinol-intolerant patients at an intermediate/high risk of TLS was difficult to quantify. The Committee further considered that it was difficult to determine what proportion of patients would then receive febuxostat, due to the uncertainty as to whether clinicians would opt to use febuxostat over rasburicase for TLS prophylaxis were febuxostat available for this. As such, the Committee considered that further advice from the cancer haematologists on CaTSoP would be useful to further define the size of this patient population.

2.14. The Committee noted that febuxostat is an oral 2-arylthiazole derivative that is a potent, non-purine selective inhibitor of both oxidised and reduced forms of xanthine oxidase, reducing uric acid levels, which is usually used for the long-term treatment of gout. The Committee noted that one of the approved Medsafe indications for febuxostat was the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of TLS. The Committee noted that the recommended oral dose of febuxostat for the prevention of TLS is 120 mg once daily, initiated two days before the beginning of cytotoxic therapy and continued for a minimum of 7 days; however, treatment may be prolonged up to 9 days according to chemotherapy duration as per clinical judgment (Medsafe. 2019).

2.15. The Committee noted there have been reports of an association between the prolonged use of febuxostat and cardiovascular events. The Committee noted that these outcomes have been observed following a number of years on febuxostat and once treatment was discontinued. The Committee considered that this risk was immaterial for the indication under consideration (TLS prevention) due to the short duration of treatment.

2.16. The Committee noted that rasburicase is a recombinant urate-oxidase enzyme administered intravenously, which requires a hospital visit for administration. The Committee noted rasburicase is used prophylactically in patients with high TLS risk, in allopurinol-intolerant patients at an intermediate/high risk of TLS, as well as a rescue therapy in patients who develop TLS. The Committee noted that adverse events from rasburicase occur in approximately 10% of patients. The Committee noted that rasburicase is relatively expensive compared with both allopurinol and febuxostat.

2.17. The Committee noted that serum urate is used as a biomarker for the reduction of TLS in the literature. The Committee noted that, unlike with gout, there is no evidence-based target serum urate to reduce the risk of TLS.

2.18. The Committee noted the results of the FLORENCE trial, a randomised double-blind phase III trial, which investigated the use of febuxostat or allopurinol in adult patients with haematologic malignancies at intermediate to high TLS risk grade (Spina et al. Ann

Oncol. 2015;26:2155-61). The Committee noted that patients were treated with allopurinol 200 mg, 300 mg or 600 mg based on investigator's choice, or 120 mg febuxostat, initiated two days prior to chemotherapy and continued for 7-9 days. The Committee noted that the study stated all patients received hydration therapy; however, this was not controlled or documented between groups. The Committee noted that the study population was predominantly European, had low baseline uric acid and had a relatively low incidence of laboratory and clinical TLS compared with other studies. The Committee noted that the mean serum urate area under the curve (AUC) was significantly less for febuxostat than for allopurinol (514.0 vs 708.0; p<0.0001), and that there was no statistically significant difference observed for serum creatinine, treatment responder rate or the incidence of laboratory TLS and clinical TLS. The Committee noted that the reported adverse events were similar between allopurinol and febuxostat groups.

2.19. The Committee noted the results of the Bellos et al. meta-analysis that analysed four studies investigating the use of febuxostat for the prevention of TLS in children and adults with a range of malignancies (Bellos et al. J Clin Pharm Therap. 2019). The Committee noted that the results of the meta-analysis reported that, compared to allopurinol, febuxostat achieved a similar tumour lysis syndrome incidence (odd ratio (OR): 1.01, 95% confidence interval (CI):0.56-1.81), responder rate (OR: 1.39, 95% CI: 0.55-3.51) and serum urate levels (mean difference: -0.21 mg/dL, 95% CI: -1.30-0.88).

2.20. The Committee noted that when considering the dosages of allopurinol and febuxostat, it was likely that even 80 mg febuxostat would reduce serum urate levels more than allopurinol. However, the Committee considered that a 120 mg dose would be appropriate in the setting of intermediate-high TLS risk.

2.21. The Committee noted the results of a phase III study investigating rasburicase 0.2 mg/kg verses allopurinol 300 mg in adults with haematologic malignancies at risk for hyperuricemia and TLS (Cortes et al. J Clin Oncol. 2010;28:4207-13). The Committee noted the trial reported no difference in clinical TLS incidence between rasburicase and allopurinol treatment groups (3% vs 4% respectively), however a difference in laboratory TLS incidence was observed between rasburicase and allopurinol groups (21% vs 41% respectively, p=0.003) and a difference in plasma urate response rate was observed (87% vs 66% respectively).

2.22. The Committee considered that there was no published evidence to suggest that allopurinol-intolerant patients with an intermediate/high risk of TLS would preferably receive febuxostat over rasburicase. The Committee also considered that it was uncertain if patients treated with febuxostat would no longer receive rasburicase in their treatment course.

2.23. The Committee considered that as an oral formulation, febuxostat may be considered more suitable than an IV infusion of rasburicase, which requires a hospital visit for each treatment and is more expensive. However, members considered that patients at high TLS risk would likely have been admitted to hospital for induction chemotherapy at the time TLS prophylactic treatment was started, and therefore the suitability of a take-home oral tablet may be less of a factor for these patients. The Committee considered rasburicase to be the current alternative for those patients prospectively considered intolerant of allopurinol, that febuxostat has similar efficacy to allopurinol, and that febuxostat would be an appropriate alternative to the second line medicant rasburicase.

2.24. The Committee considered that in paediatrics, approximately two thirds of patients are prophylactically treated with allopurinol and the other third with rasburicase. The Committee considered that this practice would be unlikely to change if febuxostat were available.

2.25. The Committee noted that if patients received febuxostat instead of rasburicase, that a reduction in infusion resource may occur. However, the Committee reiterated that there

was no evidence to suggest that patients would no longer receive rasburicase. The Committee considered that rasburicase would still be used as a rescue treatment in patients who develop TLS.

2.26. The Committee recommended further advice be sought from cancer haematologists on CaTSoP on how to define the Special Authority criteria appropriately to ensure that the comparator would be intravenous rasburicase, in the setting of prophylaxis against TLS.