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Supplementary Material for

South Australian Medicines Evaluation Panel in review: providing evidence-based guidance on the use of high-cost medicines in the South Australian public health system

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File S1. Methods details

Summary documents of SAMEP recommendations and evidence were consulted and the following data extracted: name of medicine, patient indication, year of consideration, whether the request was clinician initiated, result of prior or subsequent PBAC consideration if any, best level of available evidence reviewed according to the NHMRC 2009 hierarchy[37], safety considerations, effectiveness considerations, cost-considerations, cost per patient per course, number of anticipated patients per annum, outcome of SAMEP review and formulary listing details with any restrictions. Projected costs per annum were calculated as the cost per patient per course or year multiplied by the estimated number of patients who would be eligible in any given time period.

Table S1. High cost medicines not recommended for listing on formulary

Medicine **Year** **Indication**	**Clinician initiated**	**PBAC Outcome (at the time of SAMEP review)**	**Level of best available evidence**	**Safety** **Effectiveness**	**Cost considerations[1]** **Projected drug acquisition cost per annum**
Adalimumab 2015 Hidradenitis supurativa	✓	Rejected (subsequently achieved listing)	Not progressed-PBAC assessment published	NA NA	NA NA
Alemtuzumab 2012 B-cell Chronic Lymphocytic Leukaemia	×	Not yet considered	I (Cochrane review)	Increased risk of viral reactivation (e.g. CMV) or opportunistic infection relative to other treatments Increased efficacy on secondary measures relative to ≥ 1 current therapy[2]	Uncertain effect size therefore not possible to estimate cost effectiveness ≈$200,000
Arsenic trioxide 2014 Induction of remission and consolidation in patients with newly diagnosed acute promyelocytic leukemia	✓	Subsequently considered/listed	II	Favourable acute safety profile, concerns about long term safety[3] Non-inferior to standard care	Not cost-effective ≈$100,000 per adverse event avoided[4] ≈$130,000
Bendamustine 2013 Relapsed or refractory non-Hodgkin's lymphoma	✓	Not yet considered (listed for similar indications)	I	Increased side effects relative to best supportive care No evidence of gains in PFS or QoL	Uncertain benefit therefore not possible to estimate ≈$27,000–$160,000

Medicine **Year** **Indication**	**Clinician initiated**	**PBAC Outcome (at the time of SAMEP review)**	**Level of best available evidence**	**Safety** **Effectiveness**	**Cost considerations**[1] **Projected drug acquisition cost per annum**
Bevacizumab 2014 Recurrent glioblastoma multiforme	✓	Rejected, 1 new RCT since (currently being considered)	II	Some side effects, particularly hypertension No evidence of gains in OS or QoL relative to other treatments	Uncertain benefit therefore not cost effective[5] ≈$70–$350,000
Defibrotide 2012 & 2018 Veno-occlusive disease in adults	×	Not yet considered	III-3	Risk of bleeding Potential survival benefit versus best supportive care. Limitations in evidence reduce confidence.	Uncertain benefit therefore not possible to estimate ≈$900,000
Defibrotide 2018 & 2012 Veno-occlusive disease in children	✓	Not yet considered	III-3	Risk of bleeding Potential survival benefit versus best supportive care. Limitations in evidence reduce confidence.	Uncertain benefit therefore not possible to estimate ≈$50,000
Denosumab 2016–17 Postmenopausal women with early breast cancer	✓	Not yet considered	II	Increased risk of atypical fracture on cessation compared to placebo decreased risk of fracture while on therapy Evidence for survival not yet mature	Uncertain benefit therefore not possible to estimate ≈$120,000
Fampridine 2012 Symptomatic improvement of walking ability in adult patients with multiple sclerosis	✓	Subsequently rejected twice	II	Increased risk of UTI relative to placebo, concerns with long term safety and potential for carcinogenic effects Increased walking speed (25%), clinical relevance uncertain, duration of effect uncertain	ICER >$100,000 per QALY with generous assumptions therefore not cost effective ≈$70,000
Infliximab 2015 Hidradenitis supurativa	✓	Not yet considered	II	Increased Adverse events relative to placebo No evidence of superiority over placebo	No evidence of benefit therefore not cost effective Unknown (population size unknown)
Omalizumab 2014 Severe chronic idiopathic urticaria	✓	Subsequently listed	II	High level of uncertainty with regards to safety (reports of anaphylaxis/other hypersensitivity). Not TGA listed at time of consideration. Increased QoL relative to placebo, no evidence compared to other therapies. Significant transferability issues between studied and proposed population.[6]	Very unlikely that the incremental cost-effectiveness ratio (ICER) is less than $150K per QALY therefore not cost effective ≈$880,000

Medicine **Year** **Indication**	**Clinician initiated**	**PBAC Outcome (at the time of SAMEP review)**	**Level of best available evidence**	**Safety** **Effectiveness**	**Cost considerations[1]** **Projected drug acquisition cost per annum**
Palivizumab 2015 Prevention of lower respiratory tract disease in infants	✓	Rejected three times	I	Very rare risk of anaphylaxis, no of adverse events similar to placebo No evidence of decreased risk of RSV infection or mortality. NNT to prevent one hospitalisation of 1-2 days is 17.	Cost of one avoided hospitalisation ≈ $250,000 therefore Not cost-effective ≈$30–1,000,000
Pertuzumab 2017 HER2-positive locally advanced/inflammatory breast cancer	✓	Not yet considered	II	Slightly increased cardiotoxicity relative to standard care Increase in pathological complete response in the breast. No evidence of improved survival.	No evidence of survival benefit therefore not cost effective ≈$300,000
Trastuzumab emtansine 2014 HER2-positive metastatic breast cancer	×	Rejected, subsequently listed	II	Better safety profile than comparators Increased PFS relative to lapatinib and capecitabine	ICER = $249,000 per QALY (comparator at no cost to SA Health) therefore not cost effective ≈$1,050,000

Abbreviations: PBAC = Pharmaceutical Benefits Advisory Committee; CMV= Cytomegalovirus; RCT = randomised controlled trial; OS = overall survival; QoL = quality of life; UTI = urinary tract infection; ICER= incremental cost effectiveness ratio; QALY = quality adjusted life year; RSV = Respiratory syncytial virus; NNT = number needed to treat; PFS = progression free survival; HER 2 = human epidermal growth factor receptor 2.

[1] With respect to cost-effectiveness evaluation the SAMEPSAMEP: whenever possible considers the ICER using QALYs as a measure. However, shortcomings in the available data often prohibit cost-effectiveness analysis. Hence, the SAMEPSAMEP, when the ICER cannot be calculated, also considers other approaches to quantifying benefit per dollar spent. For example, the SAMEPSAMEP may consider cost per cancer recurrence avoided. The term cost considerations in this table reflects, in broad terms, the approach available to the SAMEP with each consideration.

[2] Increased PFS relative to chlorambucil, OS outcomes not mature, No evidence vs fludarabine Inferior or equivalent to rituximab.

[3] Potentially lower acute toxicity profile acceptable relative to ATRA + chemotherapy, long term safety profile uncertain (risk of secondary malignancy of concern). Risk to providers from exposure identified.

[4] no proven reduction in bed days or superior effectiveness.

[5] Previously estimated ICER from PBAC (>$200,000 per QALY).

[6] None of the published trials directly reflect the proposed patient population (refractory to high dose antihistamines), therefore it is unclear if the quality of life improvements seen in the trials would be reflected in the proposed population given the severity of the disease.

I = systematic review; II = randomised controlled trial; III-3 = non randomised comparative trial; IV = case series

Table S2. High cost medicines recommended for listing on formulary

	Clinician initiated	Level of best available evidence	Safety Effectiveness	Cost considerations[1] Projected drug acquisition cost per annum	Outcome
Anagrelide 2014 Third line treatment for essential thrombocythaemia	✓	II, no evidence in refractory patients	Increased toxicity relative to hydroxyurea No evidence compared to IFNα (both have adverse events) Inferior efficacy relative to hydroxyurea, no evidence compared to IFNα (available on PBS), likely superior to no treatment	Judged likely to be cost-effective as 3rd line treatment only ≈$40,000	Recommended with evidence collection *2016 review indicated costs and outcomes as predicted*
Botulinum toxin 2012 Focal spasticity	✓	Mixed (I to IV) dependent on patient population	QUM issue with multiple brands available Limited published evidence for decreased spasticity[1]	Not possible to estimate therefore Uncertain *But* access arrangements increase likelihood of cost offsets and maximise benefit ≈$200,000	Recommended with evidence collection
Eltrombopag 2017 Severe aplastic anaemia (children)	✓	III-3	Risk of liver enzyme elevation, otherwise well tolerated Increased Rate of haematological response Potential to delay or avoid HSCT (NNT=4.8)	Not possible to estimate therefore uncertain *But* cost per patient including potential offsets in HSCT avoided = $35–37,000 + uncaptured benefits to donors, families and patients[2] ≈$60,000	Recommended with evidence collection
Eltrombopag 2017 Immune thrombocytopenia (children)	✓	II	Risk of liver enzyme elevation, risk of new or worsening cataract. Otherwise well tolerated Increased rate of sustained response Potential to avoid or delay the need for splenectomy/other salvage treatments	Lack of evidence comparing eltrombopag to other salvage treatments therefore Uncertain *But* likely to avoid cost associated with splenectomy and downstream complications ≈$160,000	Recommended with evidence collection
Infliximab 2012 Acute colitis (Crohn's, indeterminate or ulcerative refractory to steroids)	✓	I	Increased toxicity relative to comparators Increased rates of remission relative to placebo Similar efficacy to cyclosporin	Not possible to estimate therefore uncertain Likely to be cost saving if colectomy is avoided, 1 in 5 would need to respond to realise savings. ≈$140,000	Recommended with evidence collection

	Clinician initiated	Level of best available evidence	Safety Effectiveness	Cost considerations[1] Projected drug acquisition cost per annum	Outcome
Infliximab 2015 Ipilimumab induced steroid refractory colitis	×	IV	Reasonable safety profile Inferred benefit from literature in the colitis population, potentially lifesaving and preferable to colectomy in patients with metastatic melanoma	Not possible to estimate therefore uncertain See above ≈$18–90,000	Recommended
Infliximab 2017 Pyoderma gangrenosum	✓	II (limited value)/IV (more appropriate)	Reasonable safety profile The majority of patients treated with infliximab achieve ulcer healing, even in the setting of long-standing refractory disease	Judged likely to be cost effective in view of QoL gains associated with reduced pain and burden of wound care ≈$34–69,000	Recommended with evidence collection
Plerexifor 2013 For use in combination with chemotherapy and GCSF to mobilise haematopoietic stem cells for collection and subsequent autologous transplantation in patients with lymphoma or multiple myeloma	✓	IV (in failed/poor mobilisers)	Some adverse events Appears to increase the number of patients proceeding to transplantation compared to chemomobilisation	Uncertain effect size therefore not possible to estimate Uncertain	Recommended in compliance with PBS criteria (Rejected x 3, re-assessed after SAMEP consideration and accepted)
Rituximab 2013 ANCA associated vasculitis	✓	I	No increased toxicity relative to cyclophosphamide, long term safety uncertain Non-inferior to cyclophosphamide for induction/relapsed patients Limited evidence in the salvage population (25–100% remission rates)	Judged likely to be cost-effective in patients who are contraindicated to cyclophosphamide ≈$80,000	Recommended
Rituximab 2016 Immune thrombocytopenia	✓	I	Increased toxicity relative to other treatments long term safety uncertain Uncertainty regarding the likelihood of response in steroid refractory patients, potentially delays or avoids splenectomy	Uncertain effect size therefore not possible to estimate. *But* possibly cost saving if splenectomy + associated complications is avoided. ≈$30–260,000	Recommended with evidence collection

	Clinician initiated	Level of best available evidence	Safety Effectiveness	Cost considerations[1] Projected drug acquisition cost per annum	Outcome
Rituximab 2014–15 Autoimmune haemolytic anaemia	✓	II to IV	Increased toxicity relative to other treatments long term safety uncertain Limited evidence to support effectiveness of rituximab, however, relative to IVIG (alternative treatment) the evidence is better	Cost-minimisation assessment versus IVIG favours rituximab $30–220,000	Recommended with evidence collection
Rituximab 2014 Refractory inflammatory myositis	×	II (delayed start group) + local data	Known toxicity, long term safety uncertain Limited evidence to suggest rituximab decreases symptoms and allows weaning of steroids. Uncertain benefit relative to other treatments. Relative to IVIG (alternative treatment) the evidence is similar.	Cost-minimisation assessment versus IVIG suggests cost neutrality or reduced cost with rituximab Uncertain	Recommended with evidence collection *2016 review indicated costs and outcomes as predicted*
Rituximab 2017 Membranous nephropathy	✓	II + local data	Known toxicity, long term safety uncertain Evidence supports higher remission rates with rituximab versus supportive care alone. In patients known to be refractory or contraindicated to standard immunosuppression, local outcome data shows significant reduction in proteinuria (78–98% reduction). NNT to avoid end stage disease = 3.7	Expected to avoid progression to end stage disease and dialysis and therefore be cost saving ≈$40–60,000	Recommended with evidence collection
Zoledronic acid 2016–17 Postmenopausal women with early breast cancer	✓	I	Risk of rare event (osteonecrosis of the jaw) decreased cancer-related mortality vs. no adjuvant treatment decreased rates of distant recurrence vs. no adjuvant treatment	Cost per recurrence avoided ≈$15,000 in women at a high risk of recurrence ≈$80,000	Recommended

Abbreviations: IFNα = Interferon-alpha; PBS = Pharmaceutical Benefits Scheme; QUM = quality use of medicine; HSCT = Hematopoietic stem cell transplantation; NNT = number needed to treat; GCSF = Granulocyte-colony stimulating factor; ANCA = antineutrophil cytoplasmic autoantibodies; IVIG= Intravenous Immunoglobulin. PBAC = Pharmaceutical Benefits Advisory Committee; NA = not applicable;

[1] With respect to cost-effectiveness evaluation the SAMEPSAMEP: whenever possible considers the ICER using QALYs as a measure. However, shortcomings in the available data often prohibit cost-effectiveness analysis. Hence, the SAMEPSAMEP, when the ICER cannot be calculated, also considers other approaches to quantifying benefit per dollar spent. For example the SAMEPSAMEP may consider cost per cancer recurrence avoided. The term cost considerations in this table reflects, in broad terms, the approach available to the SAMEP with each consideration.

Strong advocacy from the statewide rehabilitation network and low likelihood of future research by sponsors.

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