

**6.05 ELTROMBOPAG,
Tablet 25 mg,
Tablet 50 mg,
Revolade[®],
Haematology Society of Australia and New Zealand.**

1 Purpose of submission

- 1.1 The submission requested Section 100, Highly Specialised Drugs Program listing for eltrombopag for the treatment of severe aplastic anaemia (sAA), as first-line treatment in combination with immunosuppressive therapy (IST, consisting of horse anti-thymocyte globulin, hATG, and ciclosporin A, CsA), and as a second-line treatment in patients with an inadequate response or intolerance to IST¹.
- 1.2 The submission stated that “eltrombopag is registered in Australia for sAA for first-line treatment in combination with IST, and for those with an insufficient response to IST, however, is not reimbursed by the PBS. Eltrombopag is reimbursed for immune thrombocytopenia. As such, Australian patients are unable to access eltrombopag as standard of care [for sAA] and will inevitably achieve inferior clinical outcomes. Eltrombopag is standard of care and reimbursed in Europe, USA and New Zealand and most developed countries.”
- 1.3 The submission stated in the covering letter that “severe aplastic anaemia is a rare bone marrow failure disorder (orphan disease) and does not represent a commercial priority for Novartis, the Australian manufacturer of Eltrombopag.” The PBAC noted the cover letter provided by HSA NZ stated that the submission was supported by Novartis.

¹ Rabbit anti-thymocyte globulin is available, but hATG was found in a randomised controlled trial (Scheinberg 2011) to be superior, and it is therefore the standard of care.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	<p><u>First-line treatment</u> Adults and children with severe aplastic anaemia</p> <p><u>Second-line treatment</u> Adults with severe aplastic anaemia who have had an insufficient response to IST</p>
Intervention	<p><u>First-line treatment</u> Adults and adolescents: 150 mg per day. Children 6 to 11 years: 75 mg per day. Children 2 to 5 years: 2.5mg/kg per day. Patients of East-/ Southeast Asian ancestry are treated with half the recommended dose. All patients treated for 6 months. In combination with IST.</p> <p><u>Second-line treatment</u> Adults: 50 mg daily, titrated up to 150 mg per day depending on haematological response. Patients of East-/ Southeast Asian ancestry are treated with half the recommended dose.</p>
Comparator	<p><u>First-line treatment</u> hATG + ciclosporin A</p> <p><u>Second-line treatment</u> No comparator nominated; comparator might be 'standard of care' including treatment of infections and transfusion</p>
Outcomes	Haematological response, survival, clonal evolution, haemolytic paroxysmal nocturnal haemoglobinuria, discontinuation of IST, quality of life, transfusion requirements
Clinical claim	<p>Eltrombopag in combination with IST is superior to IST alone for the first-line treatment of patients with sAA in terms of the number of patients who achieve a complete response and time to response, with similar safety.</p> <p>In patients with an insufficient response to IST, eltrombopag provides a significant clinical benefit in terms of haematologic response and transfusion independence, with an acceptable safety profile.</p>

Source: Constructed during the evaluation. The submission did not define a clinical claim, and the evaluation has used the "clinical conclusion" on p21 of the submission for this purpose.

hATG = horse anti-thymocyte globulin; IST = immunosuppressive therapy

2 Background

Registration status

2.1 The TGA-registered indications for eltrombopag in aplastic anaemia are:

- severe aplastic anaemia (sAA) in combination with standard immunosuppressive therapy for the first-line treatment of adult and paediatric patients 2 years and older;
- adult patients with sAA who have had an insufficient response to immunosuppressive therapy.

2.2 The indication for adult patients with an insufficient response to IST was registered in 2015². The indication for patients 2 years and older in combination with IST for first-line treatment was registered in 2019³.

² <https://www.tga.gov.au/sites/default/files/auspar-eltrombopag-160330.pdf>, accessed 25 July, 2023.

³ <https://www.tga.gov.au/resources/prescription-medicines-registrations/revolade-novartis-pharmaceuticals-australia-pty-ltd>, accessed 5 September 2023

Previous PBAC consideration

- 2.3 The PBAC has not previously considered eltrombopag for the treatment of severe aplastic anaemia.
- 2.4 Eltrombopag was listed on the PBS on 1 November 2011 for severe chronic idiopathic thrombocytopenic purpura (ITP), with amendments to the restriction criteria recommended in May 2022⁴.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

First line setting

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ELTROMBOPAG					
Eltrombopag 25 mg tablet, 28	\$3,684.36 published price, public hospital \$3,732.73 published price, private hospital	3	84	5	Revolade
Eltrombopag 50 mg tablet, 28	\$7,368.72 published price, public hospital \$7,417.09 published price, private hospital	3	84	5	Revolade

Source: 3b. Impact – proposed (pub) worksheet in UCM-Release-3-Workbook-Eltrombopag-sAA.xls. Calculated using 3 x current PBS listing for one pack of 28 tablets.

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – (in writing only via post/HPOS upload)
Indication: Severe aplastic anaemia
Clinical criteria: The condition must be severe aplastic anaemia
AND
Clinical criteria: Patient must not have received treatment with prior immunosuppressive therapy <i>for this condition</i>
AND
Clinical criteria: The treatment must be administered in combination with standard immunosuppressive therapy <i>as defined in the Product Information for this medicine</i>
AND
Clinical criteria: Patient must be considered ineligible for haemopoietic stem cell transplant

⁴ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-05/eltrombopag-and-romiplostim-eltrombopag-tablet-25-mg-50mg-as-olamine-tablet>

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Clinical criteria:
<i>Patient must not receive more than 24 weeks of treatment under this restriction</i>
Prescribing Instructions: If the authority application is submitted through HPOS form upload or mail, must be made in writing and it must include: (1) a completed authority prescription form, (2) a completed <i>authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)</i> severe aplastic anaemia PBS Authority Application – Supporting Information Form
Administrative Advice: Duration of treatment must not exceed 6 months
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements Apply.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m.-Monday to Friday)., Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au , Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos , Or mailed to:, Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001

Second-line setting

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ELTROMBOPAG					
Eltrombopag 25 mg tablet, 28	\$3,684.36 published price, public hospital \$3,732.73 published price, private hospital	3	84	3	Revolade
Eltrombopag 50 mg tablet, 28	\$7,368.72 published price, public hospital \$7,417.09 published price, private hospital	3	84	3	Revolade

Source: 3b. Impact – proposed (pub) worksheet in UCM-Release-3-Workbook-Eltrombopag-sAA.xls. Calculated using 3 x current PBS listing for one pack of 28 tablets.

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – (in writing only via post/HPOS upload)
Indication: Severe aplastic anaemia
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be severe aplastic anaemia
AND
Clinical criteria:
Patient must have <i>failed to achieve an inadequate response or intolerance</i> to prior immunosuppressive therapy <i>including anti-thymocyte antibody and ciclosporin</i> OR
<i>Patient must have a documented intolerance of a severity necessitating permanent treatment withdrawal of immunosuppressive therapy</i>
AND
Clinical criteria:
Prescribing Instructions: Patient must not receive more than 16 weeks Duration of treatment must not exceed 4 months <i>Patient must not receive more than 24 weeks under this restriction.</i>

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<p>Prescribing Instructions: <i>The authority application must be made via the online PBS Authorities (real time assessment), or in writing via HPOS form upload or mail and must include:</i> <i>(a) prior immunosuppressive therapy, including dates of treatment; and</i> <i>(b) if applicable, details of the intolerance to immunosuppressive therapy</i></p>
<p>Prescribing Instructions: <i>If the application is submitted through HPOS form upload or mail, it must include:</i> <i>(a) a completed authority prescription form</i> <i>(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</i></p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: Special Pricing Arrangements Apply.</p>
<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m.-Monday to Friday)., Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, Or mailed to:, Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001</p>

<p>Category / Program: Section 100 – Highly Specialised Drugs Program</p>
<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
<p>Restriction type: <input checked="" type="checkbox"/> Authority Required –(Telephone/electronic)</p>
<p>Indication: Severe aplastic anaemia</p>
<p>Treatment Phase: Continuing treatment</p>
<p>Clinical criteria:</p>
<p>The condition must be severe aplastic anaemia</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>under the initial treatment restriction</i></p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must have demonstrated a sustained response to PBS-subsidised treatment with this drug</p>
<p>Prescribing Instructions: For the purposes of this restriction, a sustained response is defined as platelet count > 50 x 10⁹/L, haemoglobin > 100 g/L in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC) > 1 x 10⁹/L for more than 8 weeks.</p>
<p>Prescribing Instructions: Platelet, haemoglobin and neutrophil counts must be no more than 4 weeks old at the time of application and must be documented in the patient's medical records</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: Special Pricing Arrangements Apply.</p>
<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>

- 3.2 The Haematology Society of Australia and New Zealand were aware that a Special Pricing Arrangement applies to eltrombopag but did not have access to the effective prices.
- 3.3 The submission proposed three restrictions: one for first-line treatment, for 6 months only, and two for second-line treatment – an initial and a continuing treatment restriction.
- 3.4 The first-line treatment restriction requires that “Patient must not have received treatment with prior immunosuppressive therapy” and the second-line treatment restriction requires that “Patient must have inadequate response or intolerance to prior immunosuppressive therapy”. This means that eltrombopag + IST cannot be used for re-treatment of patients who have previously responded to IST (with or without eltrombopag), but then relapsed. The Economics Sub-Committee (ESC) advised the second line restriction should be amended to ‘Patient must have inadequate response to or have relapsed following prior immunosuppressive therapy’. The ESC considered reference to intolerance may allow use in a broader population than was included in the clinical trials i.e., the elderly who are unable to tolerate IST. The ESC considered there would be a small population of patients who may have relapsed after previously receiving IST (with or without eltrombopag) who may benefit from retreatment with eltrombopag in the second line setting and advised the restriction should allow these patients to be treated.
- 3.5 The proposed restrictions do not align with the clinical data submitted. No definition of severe aplastic anaemia was proposed similar to that used in the published studies, and there was no specification of age of the patients in the requested restriction. The ESC considered the definition of Severe and Very Severe Aplastic Anaemia are standard international definitions and it is sufficient to define by name as these patients will be managed by specialised haematologists. The ESC considered it was appropriate to exclude reference to age in the restriction.
- 3.6 The ESC considered IST should be defined as ATG + CsA within the first line restriction to prevent use in older patients unfit for ATG + CsA who may only receive CsA as part of their first line regimen.

4 Population and disease

- 4.1 Aplastic anaemia (AA) is characterised by pancytopenia (too few red cells, neutrophils and platelets) in association with bone marrow aplasia and loss of haematopoietic stem cells.
- 4.2 AA is a rare disease, with an incidence of the order of 2 per million per year. Incidence is higher in Asia, but whether people of Asian descent living outside Asia are also at higher risk is unknown. Because of the high risk of severe infections and bleeding, untreated patients have a poor outlook. Current supportive treatment (prophylaxis of opportunistic infection and transfusion) improves the outlook substantially, but sAA remains a life-threatening illness, with reported 3-5 year survival of the order of 85-

- 90%. The ESC noted patients with AA typically die of infections or bleeding complications.
- 4.3 The loss of haematopoietic stem cells is caused by autoimmune destruction. Some cases are clearly preceded by exposure to a drug or virus, but it is believed that in these cases also the mechanism of destruction of stem cells is autoimmune.
 - 4.4 AA can evolve into disorders characterised by acquired genetic abnormalities (“clonal evolution”): paroxysmal nocturnal haemoglobinuria, myelodysplasia, and acute myeloid leukaemia. It has been suggested that because eltrombopag stimulates proliferation of haematopoietic stem cells it may increase the risk of clonal evolution.
 - 4.5 The term “severe AA” (sAA) is used when there is hypocellular bone marrow and at least two of: absolute neutrophil count in peripheral blood $< 0.5 \times 10^9/L$; platelet count in peripheral blood $< 20 \times 10^9/L$; reticulocyte (immature red cell) count in peripheral blood $< 60 \times 10^9/L$. Very severe AA (vsAA) fulfills the same criteria as sAA but with an absolute neutrophil count of $< 0.2 \times 10^9/L$.
 - 4.6 In patients unsuitable for bone marrow transplant or lacking a donor, treatment is immunosuppressive therapy (IST). Standard practice is to give anti-thymocyte globulin from horses (hATG), ciclosporin A (CsA), and eltrombopag. This use of eltrombopag is consistent with the TGA-approved indications.
 - 4.7 Patients who have failed IST with CsA and hATG without eltrombopag, can be given eltrombopag as a single agent. This use is consistent with the TGA-approved indications.
 - 4.8 The ESC noted AA is typically the same condition in the first-line and refractory settings with the same level of transfusion dependence and risk of infection but cumulative issues arising with a longer duration of disease i.e., platelet refractoriness, iron overload and recurrent more difficult to treat infections.
 - 4.9 Eltrombopag is a non-peptide agonist of the thrombopoietin receptor. Thrombopoietin is an important regulator of stem cell survival, but thrombopoietin levels are elevated in aplastic anaemia, and the mechanism by which eltrombopag acts in aplastic anaemia is not clear.
 - 4.10 The principal adverse events associated with eltrombopag in trials for idiopathic thrombocytopenic purpura have been thrombo-embolic events associated with exuberant platelet responses, and elevation of transaminases and bilirubin, mostly mild and without hepatic functional impairment.

5 Comparator

- 5.1 The submission nominated hATG + CsA as the comparator for treatment-naïve patients with sAA. The ESC considered this was the appropriate comparator, noting that eltrombopag is given in combination with hATG and CsA.

- 5.2 No comparator was nominated for patients receiving eltrombopag as second-line treatment. The submission stated that there are no effective, established standard-of-care treatments available for sAA with an insufficient response to IST and ineligible for HSCT, other than infection treatment and transfusion support.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC acknowledged the significant work by HSANZ in bringing this request to the PBAC.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (11) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with eltrombopag including the increased overall and complete response rates, reduced need for platelet transfusions, and resulting decrease in complications. The comments described the potential side effects of eltrombopag as manageable, with the benefits outweighing the risks. Comments described the significant impacts of sAA on quality of life, as well as the effects of current treatment options and long hospital stays, and the complications resulting from both. Input noted the improvements to quality of life observed for an individual undergoing eltrombopag treatment, including fewer blood tests, fewer trips to the hospital, and fewer transfusions. Comments noted the significant cost of eltrombopag but noted the rarity of the disease, as well as the reduction in other resources, such as blood products, and resources associated with hospital admissions. Some comments noted that inclusion of eltrombopag on the PBS for sAA would improve equity of access.
- 6.3 The National Paediatric Medicines Forum outlined the experience of Children's Hospitals in using eltrombopag in paediatric patients and stated the availability of eltrombopag for sAA would improve equity of access and clinical outcomes for paediatric patients with sAA.

Clinical studies

- 6.4 For first-line treatment, the submission presented one open-label randomised trial comparing hATG + CsA + eltrombopag to hATG + CsA. For second-line treatment, the submission presented a single case series. These studies are listed in Table 2.
- 6.5 A number of additional studies were identified during the evaluation, including a randomised controlled study in children, and two recent systematic reviews, one a systematic review and meta-analysis of data in adults and children (Zhang 2023) and one a systematic review of data in children (Marrapodi, 2023).

6.6 The studies not presented in the submission but considered relevant are listed in Table 3.

Table 2: Clinical studies included in the submission

Trial ID	Protocol title/ Publication title	Publication citation
RACE NCT02099747	de Latour RP, Kulasekararaj A, Iacobelli S et al. Eltrombopag added to immunosuppression in severe aplastic anemia.	<i>N Engl J Med</i> 2022; 386: 11 – 23.
NCT00922883	Olnes MJ, Scheinberg P, Calvo KR et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. Desmond R, Townsley DM, Dumitriu B et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug.	<i>N Engl J Med</i> 2012; 367: 11 – 19. <i>Blood</i> 2014; 123(12): 1818 – 1825.

Source: Table 1, p14 of the submission.

Table 3: Additional relevant clinical studies

Trial ID	Protocol title/ Publication title	Publication citation
First-line treatment		
NCT01624805	Assi R, Garcia-Manero G, Ravandi F, et al. Addition of eltrombopag to immunosuppressive therapy in patients with newly diagnosed aplastic anemia.	<i>Cancer</i> 2018; 124:4192-4201.
NCT03413306	Goronkova O, Novichkova G, Salimova T, et al. Efficacy of combined immunosuppression with or without eltrombopag in children with newly diagnosed aplastic anemia.	<i>Blood Adv</i> 2023; 7(6):953-962.
NCT01623167	Townsley D, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia .	<i>N Engl J Med</i> 2017; 376:1540-50.
	Patel BA, Groarke EM, Lotter J, et al. Long-term outcomes in patients with severe aplastic anemia treated with immunosuppression and eltrombopag: a phase 2 study .	<i>Blood</i> 2022; 139:34-43.
	Groarke E, Patel B, Gutierrez-Rodriguez F, et al. Eltrombopag added to immunosuppression for children with treatment-naive severe aplastic anaemia.	<i>Br J Haematol</i> 2021; 192:605-614.
NR	Fang M, Song H, Zhang J et al. Efficacy and safety of immunosuppressive therapy with or without eltrombopag in pediatric patients with acquired aplastic anemia: A Chinese retrospective study.	<i>Pediatr Hematol Oncol</i> 2021; 38:633-646.
NR	Lesmana H, Jacobs T, Boals M, et al. Eltrombopag in children with severe aplastic anemia.	<i>Pediatr Blood Cancer</i> 2021; 68:e29066.
NR	Jie M, Fu L, Li S, et al. Efficacy and safety of eltrombopag in the first-line therapy of severe aplastic anemia in children.	<i>Pediatr Hematol Oncol</i> 2021; 38:647-657.
NR	Filippidou M, Avgerinou G, Tsiou H, et al. Longitudinal evaluation of eltrombopag in paediatric acquired severe aplastic anaemia.	<i>Br J Haematol</i> 2020; 190:e157-e159.
NR	Su MY, Chang HH, Chou SW, et al. Role of eltrombopag in severe aplastic anemia treatment in children.	<i>Pediatr Neonatol</i> 2021; 62:655-657.
Systematic reviews		
NR	Zhang S, Wang Q, Cui K et al. Efficacy of eltrombopag with immunosuppressive therapy versus immunosuppressive therapy alone on severe aplastic anaemia: A systematic review and meta-analysis.	<i>Clin Drug Investig</i> 2023; 43:315–324.
NR	Marrapodi MM, Mascolo A, Robert D, et al. The efficacy and safety of eltrombopag in pediatric patients with severe aplastic anemia: a systematic review.	<i>Front Pediatr</i> , 2023; 11:1149718.

Source: Constructed during the evaluation.

NR = None reported

- 6.7 The key features of the relevant studies, both those included in the submission and those identified during the evaluation, are presented in Table 4 (first-line treatment) and Table 5 (second-line treatment).
- 6.8 The evaluation considered the evidence in relation to first-line treatment was of moderate to poor quality, with unclear or high risk of bias. Of note, in de Latour (2022) red cell and platelet transfusions were given at the investigators' discretion, and, since the definitions of response excluded transfused patients, achieving a response could be influenced by an investigator's belief that patients receiving eltrombopag were more likely to respond. It could be argued that for this reason the trial should be classified as at high risk of bias, and in that case the overall quality of evidence would be low. The ESC acknowledged the de Latour (2022) trial was a large randomised, controlled clinical trial for a rare condition. The ESC noted that whilst red cell and platelet transfusions were at the discretion of the investigator, there are clear international standards for transfusion. Additionally, the ESC considered it was very unlikely that blood products were given more or less often based on investigators knowledge of which arm the patient was in and a guiding principle of any haematology practice is to minimise blood product use in all patients.
- 6.9 Although the submission proposed listing of eltrombopag for all age groups, the randomised controlled trial and the case series identified during the evaluation as specifically relevant to use in children were not presented in the submission; those studies suggest that in children the advantage of regimens containing eltrombopag is highly uncertain, but may be less than in adults.
- 6.10 The evaluation considered the evidence in relation to second-line treatment was of low quality. It should be noted that the results are not directly comparable to those for first-line treatment because the definition of response used in the Olnes (2012) and Desmond (2014) study were less stringent than that used in studies of first-line treatment. The ESC noted only single arm studies are available due to the nature of the condition and considered use in the second line setting will likely become rare after the first 12 – 24 months with patients accessing eltrombopag in first line.

Table 4: Key features of the evidence relating to first-line treatment

Study	N	Design/ duration	Risk of bias	Patient population	Primary outcome
Randomised studies					
de Latour 2022	197	R, OL, MC, 24 months; hATG + CsA vs hATG + CsA + ELT	Unclear	Age ≥ 15; newly diagnosed sAA or vsAA, not eligible for HSCT	CR at 3 months = Hb > 100 g/L and ANC > 1 x 10 ⁹ /L and platelet count > 100 X 10 ⁹ /L excluding patients receiving transfusions
Goronkova 2023	98	OL, R, MC, hATG + CsA vs hATG + CsA + ELT; after 4 months non-responders crossed over to the other group	Unclear	Ages 2-18, newly diagnosed sAA, no matched sibling donor	CR + PR at 4 months; CR = ANC ≥1.0 x 10 ⁹ /L and Hb ≥100 g/L, and platelet count ≥100 x 10 ⁹ /L (not clear but probably excludes patients receiving transfusion); PR = transfusion independence and ANC ≥0.5 x 10 ⁹ /L, Hb ≥85 g/dL and platelet count ≥30 x 10 ⁹ /L

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Study	N	Design/ duration	Risk of bias	Patient population	Primary outcome
Non-randomised studies					
Assi 2018	38	OL, non-randomised, sequential cohorts (unclear if consecutive patients): 1 st cohort hATG + CsA + G-CSF; 2 nd cohort hATG + CsA + ELT	High	Newly diagnosed sAA (no limit on age), adequate renal and liver function, ECOG status ≤ 2	CR at any time, median follow-up 21 months (range 3-49); CR = < 5% myeloblasts in BM with normal maturation and no dysplasia and Hb > 100 g/L and ANC > 1 x 10 ⁹ /L and platelet count > 100 X 10 ⁹ /L
Townsley 2017	92	OL, non-randomised, sequential cohorts of consecutive patients; all patients received hATG + CsA; 1 st cohort + ELT day 14-6 months; 2 nd cohort + ELT day 14-3 months; 3 rd cohort + ELT day 1-6 months	High	Age ≥ 2 yr; newly diagnosed sAA	CR at 6 months; CR = ANC ≥ 1.0 x 10 ⁹ /L and Hb ≥ 100 g/L, and platelet count ≥ 100 x 10 ⁹ /L
Patel 2022	178	Extension of Townsley 2017, with 86 additional patients receiving same treatment as 3 rd cohort; 102 historical controls treated with hATG + CsA from previous trials NCT00061360 and NCT00260689	High	Age ≥ 2 yr; sAA “not definitively treated with ATG-based IST” and not eligible for HSCT	CR at 6 months; CR = ANC ≥ 1.0 x 10 ⁹ /L and Hb ≥ 100 g/L, and platelet count ≥ 100 x 10 ⁹ /L
Groarke 2021	127	Sub-group analysis of Patel 2022	High	Age < 18.	Same as Patel 2022
Fang 2021	57	Retrospective consecutive cohort, 2012 to 2018; 2012-2016, 39 patients received hATG + CsA, 2017-2018, 17 patients received hATG + CsA + ELT	High	≤ 16 years; newly diagnosed, treatment-naive sAA	CR (ANC ≥ 1.5 x 10 ⁹ /L, Hb ≥ 110 g/L, platelet ≥ 100 x 10 ⁹ /L); PR (ANC ≥ 0.5 x 10 ⁹ /L, Hb ≥ 80 g/L, platelet ≥ 20 x 10 ⁹ /L); not stated whether regardless of transfusion.
Lesmana 2021	25	Retrospective review of consecutive patients 2000-2018; 16 treated before 2015 received hATG + CsA, 9 treated after 2015 received hATG + CsA + ELT (2 after failed hATG + CsA)	High	≤ 18 years, sAA with > 12 months follow-up	CR, PR, CR + PR (same definitions as de Latour 2022).
Jie 2021	14	Case series, retrospective record review, not clear whether consecutive cases but only patients seen March – September 2017. Data for a “historical cohort” is provided but no information about how, when or where these patients were treated is given.	High	Age < 18, sAA; IST was rabbit ATG + CsA.	CR and PR at 3, 6, 12 and 24 months; CR = BM < 5% myeloblasts, normal maturation, no dysplasia and ANC > 1 x 10 ⁹ /L, Hb > 100 g/L, platelet count > 100 x 10 ⁹ /L. PR = transfusion independence, no G-CSF ANC > 0.5 x 10 ⁹ /L, Hb > 80 g/L, platelet count > 20 x 10 ⁹ /L. Transfusion independence for RBC = “lowest Hb > 60 g/L after the last blood transfusion; for platelets = lowest platelet count > 10 x 10 ⁹ /L after the last platelet transfusion; for G-CSF = lowest ANC > 0.5 x 10 ⁹ /L after the last G-CSF”.
Filippidou 2020	11 ^b	Case series, not clear whether prospective or retrospective or whether consecutive cases.	High	Age < 18, sAA	CR and PR, but no definition provided.

Study	N	Design/ duration	Risk of bias	Patient population	Primary outcome
Su 2021	5 ^a	Case series, retrospective record review, 2016-2020	High	Age <18, sAA; IST was rabbit ATG + CsA	CR = ANC > 1 X 10 ⁹ /L + Hb > 100 g/L + platelet count > 100 x 10 ⁹ /L; Robust response = same except platelet count > 50 x 10 ⁹ /L but less than 100 x 10 ⁹ /L; No response = “still in SAA status”; PR = neither no response nor complete response nor robust response.

Source: Constructed during the evaluation.

ANC = absolute neutrophil count; BM = bone marrow; CR = complete response; CsA = ciclosporin A; ELT = eltrombopag; hATG = horse anti-thymocyte globulin; HSCT = haematopoietic stem cell transplant; IST = immunosuppressive therapy; MC = multi-centre; OL = open label; PR = partial response; R = randomised; sAA = severe aplastic anaemia; vsAA = very severe aplastic anaemia; yr = year

^a Three additional patients were included who received eltrombopag as second-line treatment.

^b Only four patients received eltrombopag from the start of IST; the others started eltrombopag 1-8 weeks after IST began.

- 6.11 Although the rates of complete and partial response were outcomes in all of the studies, the definitions of complete and partial responses were variable and in several studies were unclear. The ESC noted that transfusion independence was defined in the de Latour (2022) study as no red cell or platelet transfusions for two weeks prior to response assessment.
- 6.12 A partial response was defined in de Latour (2022) as “transfusion independence (both red cells and platelets), with a blood lineage that did not meet the criteria of severe aplastic anaemia but was insufficient for a complete response [i.e., Hb > 80 g/L but < 100 g/L, ANC > 0.5 x 10⁹/L but < 1 x 10⁹/L, and platelet count > 20 x 10⁹/L but < 100 x 10⁹/L]”. The ESC noted it was defined in the protocol that response assessment must be completed at least 2 weeks after the last transfusion and any platelet transfusions given purely to facilitate an invasive procedure did not impact on response assessment.
- 6.13 An alternative definition of partial response, using the same blood count criteria but not including transfusion independence, is referred to in de Latour (2022) as the NIH criteria. Response rates using this definition are materially different. The ESC noted the De Latour response criteria are more rigorous than the NIH criteria as it required a minimum of 3 determinations over a period of at least 2 weeks starting a least 2 weeks after last transfusion i.e., required transfusion independence.
- 6.14 In the case series of Olnes (2012) and Desmond (2014) and in the case series of Jie (2021) there were definitions of response that allowed some transfusions to be given, but in other studies the definition was unclear.

Table 5: Key features of the evidence relating to second-line treatment

Study	N	Design/ duration	Risk of bias	Patient population	Primary outcome
Olnes 2012	25	OL, non-randomised, consecutive case series, ELT +/- CsA	High	Adults, sAA and platelet count $\leq 30 \times 10^9/L$ and at least one course of ATG + CsA > 6 months before	Response at 12 weeks = one or more of: Hb increased ≥ 15 g/L or reduction in RBC transfusions of at least 4 units over 8 consecutive weeks, compared with the pre-treatment number in the previous 8 weeks; ANC increase $> 0.5 \times 10^9/L$ or $\geq 100\%$ increase if pre-treatment ANC $< 0.5 \times 10^9/L$; Platelet count $20 \times 10^9/L$ above pre-treatment or stable platelet counts with transfusion independence for a minimum of 8 weeks if platelet transfusion dependent pre-treatment.
Desmond 2014	43	Extension of Olnes, 2012, with 18 additional patients	High	Age ≥ 12 ; sAA and platelet count $< 30 \times 10^9/L$ and at least one course of ATG-based IST begun > 6 months before; patients responding to initial IST but then relapsing and refractory to re-treatment were eligible	Response at 3-4 months = same as Olnes, 2012

Source: Constructed during the evaluation.

ANC = absolute neutrophil count; CsA = ciclosporin A; ELT = eltrombopag; hATG = horse anti-thymocyte globulin; Hb = haemoglobin; IST = immunosuppressive therapy; OL = open label; sAA = severe aplastic anaemia.

Comparative effectiveness

First line treatment

6.15 Results from the two randomised, open-label studies are summarised in Table 6 and results from the remaining case series studies are summarised in Table 7.

Table 6: Results of randomised, open label studies of eltrombopag in first-line treatment

de Latour 2022	hATG + CsA N = 101	hATG + CsA + eltrombopag N = 96	Comparison (95% CI)
Response at 3 months n (%)			
Complete response	10 (9.9%)	21 (21.9%)	RR 2.21 (1.10, 4.45)^a
Partial response	21 (20.8%)	36 (37.5%)	NR
Complete + partial response	31 (30.7%)	57 (59.4%)	RR 1.97 (1.44, 2.69)
Complete response in patients with vsAA	0/34	4/34 (11.8%)	NR
Partial response in patients with vsAA	4/34 (11.8%)	9/34 (26.5%)	NR
Response at 6 months n (%)			
Complete response	20 (19.8%)	30 (31.2%)	RR 1.68 (1.05, 2.68)
Partial response	21 (20.8%)	35 (36.5%)	NR
Complete + partial response	41 (40.6%)	65 (67.7%)	RR 1.71 (1.33, 2.21)
Other outcomes			
Overall survival ^c % (95% CI)			
At 6 months	93.1% (88.1, 98.0)	96.9% (93.4, 100)	NR
At 12 months	88.9% (82.8, 95.1)	95.7% (91.6, 99.8)	
At 24 months	85.0% (77.7, 92.4)	89.5% (82.4, 96.6)	
Deaths	14 (13.9%)	8 (8.3%)	HR 0.57 (0.24, 1.37)
Due to infection	9 (8.9%)	4 (4.2%)	NR
Due to bleeding	2 (2.0%)	0	NR
Patients with no infections Grade 3 or higher	72 (72.0%)	73 (76.0%)	NR
Incidence rate of infections Grade 3 or higher, n/person year	1.000	0.969	RR 0.97 (0.63, 1.49)
HSCT	12 (11.9%)	11 (11.5%)	NR
HSCT in patients with vsAA	8/34 (23.5%)	8/34 (23.5%)	NR
Goronkova 2023			
n (%)	hATG + CsA N = 49	hATG + CsA + eltrombopag N = 49	Comparison (95% CI)
Complete + partial response at 4 months	26 (53.1%)	32 (65.3%)	p = 0.218 ^b
Complete response at 4 months	6 (12.2%)	15 (30.6%)	p = 0.027^b
Overall survival at 3 years	91%	89%	p = 0.673 ^b
Relapse after response	5/26 (19.2%)	8/32 (25.0%)	p = 0.590 ^b

Source: Constructed during the evaluation from published reports.

CsA = ciclosporin A; hATG = horse anti-thymocyte globulin; HR = hazard ratio; HSCT = haematopoietic stem cell transplant; NR = not reported; RR = relative risk; sAA = severe aplastic anaemia; vsAA = very severe aplastic anaemia; statistically significant results are in **bold**.

^a Adjusted for age, severity of aplastic anaemia, and study centre.

^b Chi-square test.

^c Kaplan-Meier.

Table 7: Results of cohort studies of eltrombopag in first-line treatment

	hATG + CsA	hATG + CsA + eltrombopag ^d	Comparison
Assi 2018	N = 17	N = 21	
Complete response, n (%)	5 (29%)	8 (38%)	p = 0.71 ^a
HSCT, n (%)	1 (1.0%)	4 (4.2%)	-
Patel 2022	N = 102	N = 178	Comparison
Complete response at 6 months, n (%)	17 (16.8%)	69 (38.8%)	p < 0.001^b
Relapse in patients with complete or partial response after 5 years follow-up, n/N (%)	22/68 (32.4%)	61/145 (42.1%)	p = 0.09 ^b
Overall survival at 4 years %	85%	92.5%	p = 0.41 ^b
Groarke 2021	N = 87	N = 40	Comparison
Complete response at 3 months, n (%)	12 (13.8%)	9 (22.5%)	P = 0.26 ^a
Partial response at 3 months, n (%)	43 (49.4%)	18 (54.0%)	NR
Complete response at 6 months, n (%)	20 (23.0%)	12 (30.0%)	P = 0.42 ^a
Partial response at 6 months, n (%)	43 (49.4%)	16 (40.0%)	NR
Relapse at 1 year, n (%)	5 (5.7%)	7 (17.5%)	NR
Fang 2021	N = 39	N = 18	Comparison
Complete response at 6 months, n (%)	7 (17.9%)	9 (50.0%)	p < 0.05^c
Partial response at 6 months, n (%)	20 (51.2%)	8 (44.4%)	-
Survival at 2 years, n (%)	36 (92.3%)	18 (100%)	-
Lesmana 2021	N = 14	N = 7	Comparison
Complete response at 6 months, n (%)	4 (29%)	2 (29%)	-
Complete response at 12 months, n (%)	7 (50%)	2 (29%)	p = 0.35 ^c
Filippidou 2020		N = 11	
Complete response at 3 months, n (%)	NA	1 (9.1%)	NA
Partial response at 3 months, n (%)		8 (72.7%)	
Su 2021		N = 5	
Complete response at 3 months, n (%)	NA	2 (40.0%)	NA
Partial response at 3 months, n (%)		2 (40.0%)	
Jie 2021	N = 28	N = 14	
Complete response at 3 months, n (%)	3 (10.7%)	1 (7.1%)	NA
Partial response at 3 months, n (%)	15 (53.6%)	4 (28.6%)	
Complete response at 6 months, n (%)	6 (21.4%)	8 (57.1%)	
Partial response at 6 months, n (%)	12 (42.9%)	3 (21.4%)	

Source: constructed during the evaluation from published reports.

CsA = ciclosporin A; hATG = horse anti-thymocyte globulin; HSCT = haematopoietic stem cell transplant; NA = not applicable; NR = not reported; statistically significant results are in **bold**.

^a Chi-square test.

^b Student's t-test.

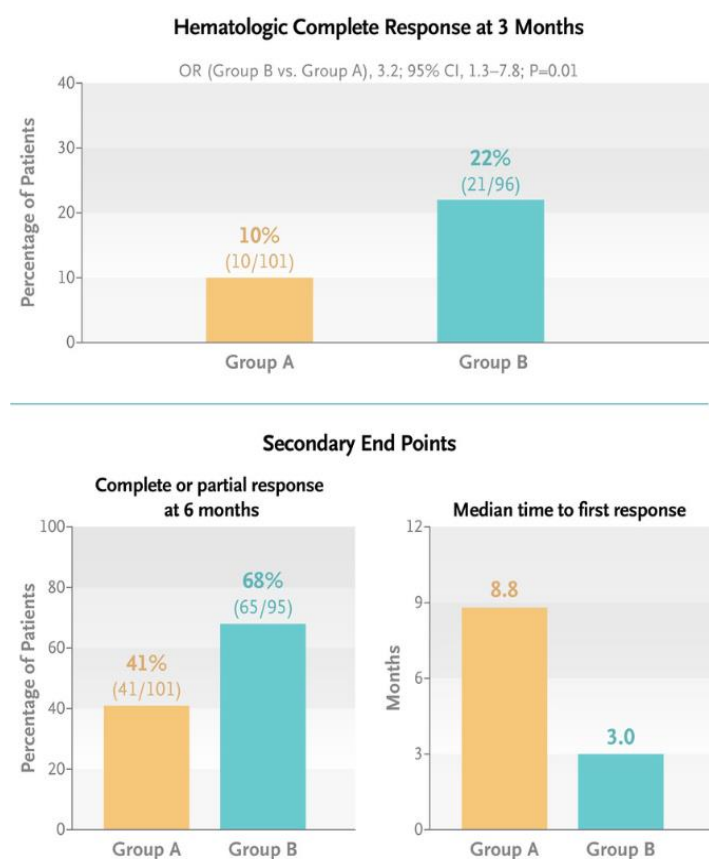
^c Fisher's exact test.

^d Except for Su 2021 and Jie 2021, whose patients received rabbit ATG.

- 6.16 Overall, results for complete haematological responses at 3-6 months with sAA favour hATG + CsA + eltrombopag over hATG + CsA alone. The ESC considered that as a randomised controlled study with objective end points the evidence is likely to be reliable. The ESC considered the outcome measure of haematological response is a clinically meaningful outcome equating to transfusion independence at the level of partial response.
- 6.17 The ESC noted the median time to a first response for patients treated with eltrombopag + IST was 3.0 months and in patients treated with IST was 8.8 months in the de Latour study (Figure 1). The ESC considered an earlier response would be of

benefit to patients with a reduction in transfusion requirements, medical appointments and pathology tests.

Figure 1: Haematologic complete response at 3 months, complete or partial response at 6 months, median time to first response: Group A (yellow) – hATG + CsA, Group B (green) – eltrombopag hATG + CsA



CsA = ciclosporin; hATG = horse antithymocyte globulin.
 Source: de Latour et al. N Engl J Med 2022;386:11-23.

6.18 There was no evidence of a survival benefit from eltrombopag-containing regimens. The submission claimed that “Complete haematologic response is strongly associated with improved survival and long-term outcomes”. This claim seemed to be based on a case series of patients treated between 1989 and 1994, in which death rates from infectious complications were high: 16/122 patients (13.1%) died within 3 months and 2-year survival of the whole cohort was 72%, and of non-responders was 37%.⁵ The applicability of these data to patients receiving modern supportive care is unclear. For example, in the Fang 2021 cohort, 2 year survival for patients with complete response, partial response and no response was 100%, 96.4% and 83.3%, respectively. The ESC considered that a lack of survival benefit reflects that 1) the follow up on the clinical trial was short when considering the natural history of treated AA and 2) patients on

⁵ Rosenfeld SJ, Kimball J, Vining D, Young NS. Intensive immunosuppression with antithymocyte globulin and cyclosporine as treatment for severe acquired aplastic anemia. *Blood* 1995; 85:3058-3065

IST alone in both the de Latour (2022) and the Goronkova (2023) study were allowed to receive eltrombopag at 6 months and 4 months, respectively. The ESC noted Fang 2021 reported a 2 year OS rate for patients with a complete response, partial response and no response as 100%, 96.4% and 83.3%, respectively. The ESC considered historical data is important to demonstrate that haematologic response is related to a better outcome as with current treatments, it is less likely be demonstrated in the timeframe of a clinical trial. The ESC considered that whilst supportive care has improved in the last 30 years there are still limitations to the care of a patient with bone marrow aplasia, who will become refractory to platelet transfusions, develop increasing infectious complications and iron overload with ancillary complications from red cell transfusions. The ESC noted there is evidence to support an OS benefit for eltrombopag at 2 years but considered there is a high level of uncertainty regarding the magnitude of benefit in terms of OS.

- 6.19 There were few HSCTs in the studies reported, and there was no difference in the numbers of HSCT in patients receiving regimens with and without eltrombopag. The ESC considered the follow up in the clinical trials presented was too short to collect meaningful data regarding allograft rates and outcomes. The ESC noted patients who respond to IST +/- eltrombopag will not receive an allograft unless they relapse.
- 6.20 In Goronkova (2023), which enrolled only children, the primary outcome (complete + partial response at 4 months), was not more frequent among patients receiving an eltrombopag-containing regimen. The secondary outcome of the proportion achieving complete response at 4 months was higher among patients receiving an eltrombopag-containing regimen.
- 6.21 The results from Goronkova (2023) were similar to those of Groarke (2021) using historical controls: complete responses were more frequent with eltrombopag-containing regimens, but overall responses (complete + partial) were similar with IST and IST + eltrombopag. Both Goronkova (2023) and Groarke (2021) reported higher relapse rates in patients receiving eltrombopag.
- 6.22 Results from the systematic review and meta-analysis of 6 studies including 699 patients comparing hATG + CsA and hATG + CsA + eltrombopag are shown in Table 8.

Table 8: Results from the systematic review and meta-analysis

Zhang 2023		OR (95%CI) with ELT-containing regimen
Complete response at 6 months	All patients	2.61 (1.82, 3.74)
	Children	2.91 (1.56, 5.41)
Complete response at 3 months	All patients	2.14 (1.09, 4.23)
	Children	1.43 (0.42, 4.94)
Partial response at 6 months	All patients	0.94 (0.49, 1.81)
	Children	0.61 (0.30, 1.24)
Partial response at 3 months	All patients	2.10 (1.21, 3.65)
	Children	1.62 (0.53, 4.98)

Source: Constructed during the evaluation from the published report.

CI = confidence interval; ELT = eltrombopag; OR = odds ratio; statistically significant results are in **bold**.

6.23 These results, taken together with those of the systematic review of data in paediatric patients of Marrapodi (2023), support the conclusion that the eltrombopag-containing regimen is more likely to result in complete response, but that the benefit is smaller and less clear in relation to partial responses, and that the benefit is smaller and less clear in children. The ESC considered response in the paediatric population remained uncertain but is likely to be similar to that of adults.

Second line treatment

6.24 Results of the case series of patients refractory to IST treated with eltrombopag alone are shown in Table 9.

Table 9: Results of the study of eltrombopag as second-line treatment

	Eltrombopag N = 43
Desmond 2014	
Response at 3-4 months ^a , n (%)	17 (39.5%) ^b
Patients not meeting criteria for sAA at 6 months ^c , n (%)	9 (20.9%)
Patients receiving platelet transfusions who became platelet transfusion independent, n /N (%)	9/15 (60.0%)

Source: Constructed during the evaluation from the published report.

sAA = severe aplastic anaemia.

^a Response = improvement in red cells or neutrophils or platelets, not all three as in the studies of first-line treatment.

^b Two additional patients are counted as responders by the authors, making a total of 19 (44%), but they had discontinued eltrombopag weeks before haematological parameters improved.

^c At least two of: ANC > 0.5 x 10⁹/L; platelet count > 20 x 10⁹/L; reticulocyte count > 60 x 10⁹/L.

6.25 The evaluation considered the less stringent definition of response in this case series makes it difficult to compare the reported response rate with response rates reported for first-line treatment. The ESC noted transfusion independence can be assumed for PR and whilst the absence of transfusions for 2 weeks in the de Latour study makes that outcome more stringent the outcome criteria in the second line studies remains a reliable outcome.

- 6.26 The ESC considered evidence to support the use of eltrombopag in patients refractory to immunosuppressive therapy (second line) was of poor quality; however, the evidence supported a benefit in haematologic response.

Comparative harms

- 6.27 None of the published studies reported adverse events in the detail normally found in clinical study reports. Several, notably Desmond (2014), reported adverse event data only in the most general terms (“we observed a favorable toxicity profile”).
- 6.28 De Latour (2022) provided the most detailed account of adverse events, but still reported only adverse events aggregated by organ system, adverse events Grade 3 or higher aggregated by organ system, infectious events Grade 3 or higher, and “liver issues” Grade 3 or higher (see Table 6).
- 6.29 For this reason, tables of adverse events have not been prepared and no benefits/harms comparison is presented.
- 6.30 There was no obvious increased risk of clonal evolution, or of karyotypic abnormalities associated with myeloid malignancies in patients given eltrombopag.
- 6.31 Overall, the data reported do not suggest that eltrombopag treatment was associated with more frequent or more severe elevation of transaminases or bilirubin in patients with sAA than previously reported in patients with idiopathic thrombocytopenic purpura, but the limitations of the data make any conclusion uncertain.

Clinical claim

- 6.32 The clinical conclusion in the submission was that eltrombopag in combination with IST is superior to IST alone for the first-line treatment for patients with sAA in terms of the number of patients who achieve a complete response and time to response, with similar safety. In patients who are refractory to IST, eltrombopag provides a significant clinical benefit in terms of haematologic response and transfusion independence, with an acceptable safety profile.
- 6.33 The ESC considered the clinical conclusion for the first line use of eltrombopag was supported by the evidence presented above.
- 6.34 The ESC considered the clinical conclusion for second line treatment is supported by the evidence presented although with a greater degree of uncertainty than first line treatment.
- 6.35 The ESC noted that the safety profile of eltrombopag is well established in ITP and that the TGA and international agencies have supported the tolerable safety of eltrombopag in SAA.
- 6.36 The PBAC considered the claim that eltrombopag in combination with hATG + CsA was of superior comparative effectiveness to hATG + CsA alone for the first line treatment of sAA was reasonable.

- 6.37 The PBAC considered the claim that eltrombopag was of superior comparative effectiveness to standard of care for the second line treatment of sAA was uncertain but, on balance, reasonable.
- 6.38 The PBAC considered the safety of eltrombopag was likely to be consistent with that observed in ITP and was manageable.

Economic analysis

- 6.39 The submission did not present an economic evaluation. The potential cost savings associated with achieving transfusion independence were outlined in the Pre-Sub-Committee Response (PSCR) (see below). The ESC estimated the cost per responder using the drug costs, transfusion costs and response rates.
- 6.40 The ESC noted the majority of use of eltrombopag will be in the first line treatment setting and the cost per patient is estimated to be \$42,886 (Table 11).
- 6.41 The PSCR noted a publication by Lengline⁶ et al reported the median requirement for transfusion-dependant refractory SAA patients was 4U of packed red blood cells (PRBC) and 3U of platelets per month. Based on the National Blood Authority list price for PRBC of \$375 per unit and for platelets of \$257 per unit, the monthly cost for blood products is \$2,271 per patient. The PSCR noted the additional costs of transfusions not accounted for in the cost of blood products, include the cost of hospitalisation, costs associated with the morbidity of the transfusions and clinicals staff costs. The PSCR further noted that published data suggests the actual cost of blood transfusion is approximately twice the cost of the blood products (excluding the cost of potential adverse outcomes)⁷. Based on this the PSCR estimated the monthly cost of blood products for patients with transfusion-dependent sAA is likely to be approximately \$4,500 per month.
- 6.42 The ESC noted the incremental cost per additional responder is \$95,000 to <\$115,000 (Table 10).

⁶ Lengline E, Drenou B, Peterlin P, et al. Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia. *Haematologica*. 2018;103(2):212-220

⁷ Thomson A, Farmer S, Hofmann A, Isbister J, Shander A. Patient blood management - a new paradigm for transfusion medicine? *ISBT Sci Ser*. 2009;4(n2):423-435.

Table 10: Incremental cost per additional responder at 12 months (using the published price of eltrombopag)

	Eltrombopag	SOC	Incremental
Cost of transfusion ^a	\$29,943	\$41,566	-\$11,623
Cost of eltrombopag	\$42,886	-	\$42,886
Total cost	\$72,829	\$41,566	\$31,263
Response rate (at 3 months)	59.4%	30.7%	28.7%
Incremental cost per additional responder over 12 months			\$11

SOC = standard of care

a. Assuming responders receive an average of 3 transfusions and non-responders receive an average of 12 transfusions. Cost per transfusion \$4,500.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

6.43 The ESC noted the benefit of achieving a complete or partial response is becoming transfusion independent. The ESC noted becoming transfusion independent is likely to have a significant beneficial impact on a patient’s quality of life⁸ given the benefits for patients included reduced:

- risk of infections and complications associated with iron overload;
- time spent at a health care facility which can interfere with a patient’s ability to work, and with their social functioning and family life;
- fatigue and tiredness that limits routine physical activities; and
- discomfort (which may be moderate to severe).

6.44 The ESC noted transfusion independence is also associated with a reduction in costs for pathology testing, inpatient hospital stays and outpatient hospital visits, staff time to administer transfusions and managing iron overload (including iron chelating medications, audiology investigations, cardiac MRI etc).

6.45 The ESC considered that, although not strongly supported by the clinical evidence presented, it was likely treatment with eltrombopag would provide a survival benefit in patients with sAA.

6.46 The ESC considered the incremental cost per responder presented in Table 10 was likely to be a conservative estimate of the cost-effectiveness of eltrombopag as it did not take into account a range of additional benefits, including potential impact on survival and quality of life, or any additional costs associated with a patient becoming transfusion independent.

6.47 The PBAC noted that the definition of complete response required a neutrophil count of > 1.0 x 10⁹/L and that reduced duration of severe neutropenia has a significant impact on complications including reducing inpatient admissions, antimicrobial therapy, intensive care requirements and mortality risk.

⁸ Szende A, Schaefer C, Goss TF et al. Valuation of transfusion-free living in MDS: results of health utility interview with patients. Health and Quality of Life Outcomes 2009, 7:81

Drug cost/patient/course

6.48 The cost per patient per course in the first line and second line treatment setting using the published price of eltrombopag is provided in Table 11.

Table 11: Drug cost per patient for eltrombopag applied in financial estimates, 50 mg presentation

	First line treatment	Second line treatment
Dose	150 mg/day	150 mg/day
Mean duration	5.34 months ^a	8.8 months ^b
Mean number of scripts	5.8 ^c	9.6 ^c
Cost/script ^d	\$7,392.91	\$7,392.91
Cost/course	\$42,886.45	\$70,972.89

Source: Excel workbook 'UCM-Release-3-workbook-Eltrombopag-sAA'; de Latour (2022).

Assumed 22% of patients receive 3 months of treatment and 78% receive 6 months of treatment

a. Assumes 100% of patients receive 4 months of treatment and 40% of patients receive 12 months of treatment

b. Calculated as $((\text{months}/12) \times 365.25) / 28$

c. Using DPMQ presented in Section 3 and assuming 50% private hospital and 50% public hospital use.

6.49 In the second line setting, the initial dose is 50 mg per day titrated up to 150 mg per day based on haematological response. The financial estimates assumed all patients will be treated with 150 mg per day. The ESC considered assuming all patients in the second line setting would be treated with 150 mg per day is likely to overestimate the cost.

Estimated PBS usage & financial implications

6.50 This submission was not considered by the Drug Utilisation Sub-Committee (DUSC). The submission used an epidemiological approach to calculate the financial estimates. The inputs are summarised in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source
Epidemiology	
	Incidence data: The submission indicated there was no Australian-specific epidemiological data identified. Incidence of 2.34 cases per million was assumed, was based on Montane (2008), which described a Spanish case-control study conducted in Barcelona between 1980 and 2003. This study reported 235 patients with aplastic anaemia and based on study experience of 100,197,224 person-years, gave an incidence of 2.34 per million inhabitants per year. While not current, there does not appear to be an updated incidence source.
	The proportion with sAA (83.8%) was also sourced from Montane (2008), using the same 1980 to 2003 data.
Eligible patients	The submission indicated that a prevalent population was not considered because it was assumed existing patients would currently be treated with IST and therefore ineligible for first-line treatment, and prevalence was not considered for second-line due to poor prognosis for refractory patients. This was reasonable. However, patients requiring re-treatment after relapse were not included, and the evaluation considered this would increase the eligible population substantially. The ESC considered this would be applicable to a small number of patients.
	Eligibility: The submission then calculated all subsequent eligibility estimates based on first and second-line patients. The ESC considered it was likely that with almost all patients using eltrombopag in first-line (80% in Year 1 assumed by the submission; 90% in the following years; see below), there would be very little second-line use in incident patients.

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Parameter	Value applied and source
	<p>First-line patients: Based on the proportion of patients considered ineligible for HSCT. It was assumed 100% of patients aged over 40 years do not proceed to HSCT due to age-associated risks, and 70% under 40 do not have a matched sibling donor. Therefore, it was estimated 84% of patients would be eligible to receive first-line treatment. The PBAC considered this may be an overestimate as more patients may receive HSCT with increased use of partially matched (haploidentical) transplants.</p> <p>Second-line patients: The submission used as the proportion of patients refractory to ISTs the overall response rate for patients treated with hATG+CsA in de Latour (2022), which was 41%. This should have been the non-response rate, 100% - 41% = 59%, and was corrected during the evaluation. Additionally, the estimated number of first-line patients should have been removed from the second-line estimates. Corrected numbers are presented below.</p>
Utilisation	
Uptake and treatment	Uptake: 80% in Year 1, 90% in Year 2 to Year 6; sponsor assumption. For second-line patients it was also assumed that 40% would continue treatment, based on Desmond (2014).
Number of scripts	<p>PBS/RPBS: Script numbers were assumed to be 5.8 for first-line treatment and 4.35 for initial second-line treatment and 13.04 for continuing second-line treatment.</p> <p>Treatment duration: First-line treatment duration was 5.34 months based on de Latour (2022), where 22% of patients were treated for 3 months and 78% were treated for 6 months. Second-line treatment duration was 4 months for initial therapy and 12 months for continuing therapy.</p>
Cost of medicines	
Eltrombopag	25 mg tablet, 28 x 3: published price \$3,684.36 public hospital; \$3,732.73 private hospital 50 mg tablet, 28 x 3: published price \$7,368.72 public hospital; \$7,417.09 private hospital
Substituted medicines	Filgrastim: PBS items 5829T/5830W; \$256.54
Patient co-payment	Patient co-payment was updated to the current \$30.00 for PBS and \$7.30 for RPBS during the evaluation. The submission had calculated average co-payment values of \$17.96 for PBS and \$5.01 for RPBS, which changed to \$14.26 and \$5.54 with the updated co-payment values.
Impact on other medicines	
Filgrastim	The submission stated a small cost offset was applied due to a reduction in G-CSF use (filgrastim), which the submission indicated was used in second-line to manage neutropenia. The cost offset was small, but was not adequately justified.

Source: Table 10, p23-24; Table 11, p24-25 of the submission; Excel workbook 'UCM-Release-3-workbook-Eltrombopag-sAA'.
cont'g = continuing; G-CSF = granulocyte colony stimulating factor; hATG = horse anti-thymocyte globulin; HSCT = haematopoietic stem cell transplant; IST = immunosuppressive therapy; sAA = severe aplastic anaemia

6.51 Table 13 provides estimates of eligible second-line patients, correcting for errors in the submission.

Table 13: Re-calculation of eligible patients

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total incident population	1	1	1	1	1	1
Total sAA population	1	1	1	1	1	1
Submission's estimate of eligible patients						
First-line (incident × 83.8% × 83.97%)	1	1	1	1	1	1
Second-line (incident × 83.8% × 83.97 × 41%)	1	1	1	1	1	1
Total eligible - submission	1	1	1	1	1	1
Re-calculation of eligible patients						
First-line (same as submission)	1	1	1	1	1	1
Second-line - incident with first-line removed (incident × 83.8% × 83.97 × 59%)	1	1	1	1	1	1
Total eligible^b – second-line revised	1	1	1	1	1	1

Source: Table 11, p24-25 of the submission; Excel workbook 'UCM-Release-3-workbook-Eltrombopag-sAA'.

sAA = severe aplastic anaemia

a. Calculated as $(65 - 46) \times 0.838 \times 0.8397 \times 0.59$

b. Totals may be impacted by rounding.

The redacted values correspond to the following ranges:

1 < 500

- 6.52 The submission assumed uptake of 80% in Year 1 and 90% in Years 2 to 6, on the basis of the severity of the disease and the claimed benefit of eltrombopag plus IST. The ESC considered the uptake in the first line and second line setting was likely to be reasonable.
- 6.53 The submission calculated cost offsets due to HSCT procedures based on the claim that the improvement in response rates seen with eltrombopag would lead to a reduction in the number of patients undergoing HSCT. As discussed in paragraph 6.20, there was no evidence from the studies that eltrombopag reduced the need for HSCT. Additionally, HSCT costs represent hospital costs and therefore cannot be considered as an offset in the financials. The ESC noted inclusion of offsets due to HSCT procedures in the financial estimates was not appropriate and this has been removed from the revised estimates.
- 6.54 Table 14 provides the estimated financial implications for the listing of eltrombopag. The revised base case corrects the errors observed in the submission (second-line proportion; double-counting of second-line patients; co-payment values).

Table 14: Estimated use and financial implications (revised during evaluation)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of eltrombopag						
Cost to PBS/RPBS less co-payments - revised	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Estimated financial implications for filgrastim						
Cost to PBS/RPBS less co-payments - revised	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³
Net financial implications						
Net cost to PBS/RPBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²

HSCT = haematopoietic stem cell transplant

^a Assuming 5.34 months of treatment (5.8 scripts), based on de Latour (2022), where 22% of patients were treated for 3 months, and 78% were treated for 6 months. For second-line treatment the submission assumed 4 months of initial treatment (4.35 scripts) and 12 months of continuing treatment (13.04 scripts). The initial treatment was based on the eltrombopag PI, which indicates patients should discontinue if no haematological response after 16 weeks; and 12 months of continuing treatment was based on Desmond (2014) where median time on treatment for responders was 12 months.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

³ net cost saving

6.55 The total cost to the PBS/RPBS of listing eltrombopag was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing using the published prices of eltrombopag.

7 PBAC Outcome

7.1 The PBAC recommended the listing of eltrombopag for the treatment of severe aplastic anaemia (sAA), as first-line treatment in combination with horse anti-thymocyte globulin (hATG) and ciclosporin A (CsA), and as a second-line treatment in patients with an inadequate response to immunosuppressive therapy (IST). The PBAC considered there is a clinical need for effective treatment options for this rare condition. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of eltrombopag would be acceptable at the effective price currently in place for severe chronic idiopathic thrombocytopenic purpura (ITP).

7.2 The PBAC noted the consumer comments highlighted the significant impact of sAA on a patient's quality of life and the clinical need for effective treatment options for this rare condition. The PBAC noted the range of patient relevant benefits of treatment with eltrombopag, including fewer blood transfusions, reduced complications (from other treatments and from transfusions) and fewer hospital visits.

7.3 The PBAC advised the following with respect to the proposed restriction criteria:

- In the first line setting, the clinical criterion 'The treatment must be administered in combination with standard immunosuppressive therapy as defined in the Product Information for this medicine' should be amended to 'The treatment

must be administered in combination with standard immunosuppressive therapy, including anti-thymocyte globulin and ciclosporin' (as discussed in paragraph 3.6).

- In the second line setting, the initial clinical criteria 'Patient must have failed to achieve an inadequate response or intolerance to prior immunosuppressive therapy including anti-thymocyte antibody and ciclosporin; OR Patient must have a documented intolerance of a severity necessitating permanent treatment withdrawal of immunosuppressive therapy' should be amended to 'Patient must not have achieved an adequate response to prior immunosuppressive therapy including anti-thymocyte antibody and ciclosporin; OR Patient must have relapsed following prior immunosuppressive therapy including anti-thymocyte antibody and ciclosporin' (to address the issues raised by the ESC in paragraph 3.4).
- In the second line setting, patients with a response to treatment, with a response defined as no longer meeting the criteria for sAA, should be able to continue treatment. The PBAC advised inclusion of the Prescribing Instruction 'Once platelet count > 50 x 10⁹/L, haemoglobin > 100 g/L in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC) > 1 x 10⁹/L for more than 8 weeks., the dose of eltrombopag should be reduced as per the Product Information' would be appropriate.

7.4 The PBAC considered the clinical positioning of eltrombopag was consistent with the TGA approved indications and supported by international treatment guidelines. The PBAC considered standard of care was the appropriate comparator in the first and second-line treatment setting. The PBAC noted that eltrombopag is used in combination with hATG and CsA in the first line treatment setting and will not replace hATG and CsA.

7.5 The PBAC noted the clinical evidence supporting the use of eltrombopag in the first line treatment setting consisted of an open-label, randomised controlled trial comparing eltrombopag in combination with hATG + CsA to hATG + CsA alone (the RACE trial, n=197). The PBAC noted the relative risk for patients receiving eltrombopag achieving an overall response at 3 months was 1.97 (95% CI: 1.44, 2.69) and at 6 months was 1.71 (1.33, 2.21). The PBAC noted the median time to response was 3 months for patients receiving eltrombopag and 8.8 months for patients receiving hATG + CsA alone. The PBAC considered achieving a partial response (which results in transfusion independence) was also a clinically meaningful outcome for patients, and a higher proportion of patients achieved a partial response with eltrombopag (37.5% vs 20.8% at 3 months). The PBAC noted clinical evidence from another randomised trial in paediatric patients (Goronkova 2023) and a systematic review and meta-analysis of 6 non-randomised studies supported the benefit of eltrombopag in the first line treatment setting.

7.6 The PBAC noted the clinical evidence supporting the use of eltrombopag in the second line treatment setting was of lower quality than in the first line setting but considered

that, overall, patients treated with eltrombopag achieved clinically meaningful haematological responses.

- 7.7 The PBAC considered the claim that eltrombopag is superior in terms of effectiveness to standard of care was supported by the evidence presented in the submission. The PBAC considered the safety of eltrombopag was likely to be consistent with that observed in ITP and was manageable.
- 7.8 The PBAC noted the incremental cost per additional responder at 12 months was \$95,000 to < \$115,000 (based on the published price of eltrombopag, see CIC section using effective price). The PBAC agreed with the ESC that this was likely to be conservative (i.e., an over-estimate) as it did not include a range of additional patient relevant benefits related to becoming transfusion independent. The PBAC considered that the cost per responder was high but was reasonable in the context of a rare condition with a high clinical need. The PBAC noted there was a relatively large randomised controlled trial available which provided some certainty regarding the incremental benefit of eltrombopag.
- 7.9 The PBAC noted the listing of eltrombopag for sAA was estimated to result in < 500 patients treated in Year 1, increasing to < 500 patients in Year 6 with an overall estimated cost to the PBS/ RPBS of \$10 million to < \$20 million (based on the published price of eltrombopag, see CIC section using effective price) over 6 years. The PBAC noted the submission assumed a small cost offset for reduced use of filgrastim in the second line setting to manage neutropenia but considered this was highly uncertain.
- 7.10 The cost per patient, cost per responder and cost to PBS/RPBS using the effective price of eltrombopag is presented in the table below.

Table 15: Cost per patient, cost per responder and cost to PBS/RPBS using the effective price

Effective price	\$ [redacted]	for 3 packs of 25 mg x 28
	\$ [redacted]	for 3 packs of 50 mg x 28
Cost per patient per course	\$ [redacted]	in the first line setting
Cost per responder	\$ [redacted]	
Cost to PBS/RPBS over first 6 years of listing	\$ [redacted]	¹

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

- 7.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for eltrombopag:
- The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over hATG + CsA alone on the basis of haematological response;
 - The treatment is expected to address a high and urgent unmet clinical need due to the limited treatment options available;

- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.12 The PBAC did not recommend that eltrombopag should be treated as interchangeable on an individual patient basis with any other drug.

7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended.

8 Recommended listing

8.1 Add new items:

First line setting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ELTROMBOPAG					
Eltrombopag 25mg tablet, 28	New	3	84	5	Revolade
Eltrombopag 50mg tablet, 28	New	3	84	5	Revolade
Restriction Summary/ Treatment of Concept					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – (in writing-legacy) – Postal/HPOS upload or Online PBS Authorities immediate assessment				
	Indication: Severe aplastic anaemia				
	Clinical criteria:				
	The condition must be severe aplastic anaemia				
	AND				
	Clinical criteria:				
	Patient must not have received treatment with immunosuppressive therapy for this condition				
	AND				
	Clinical criteria:				
	The treatment must be administered in combination with standard immunosuppressive therapy, including anti-thymocyte antibody and ciclosporin				
	AND				
	Clinical criteria:				
	Patient must be considered ineligible for haemopoietic stem cell transplant				
	Clinical criteria:				
	Patient must not receive more than 24 weeks of treatment under this restriction				
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail it must include: (1) a completed authority prescription form,				

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	(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements Apply.
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 888 333.</p> <p>Prescribing information (including Authority Application forms and other relevant documentation is applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)</p> <p>Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826</p>

Second-line setting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ELTROMBOPAG					
Eltrombopag 25mg tablet, 28	New	3	84	3	Revolade
Eltrombopag 50mg tablet, 28	New	3	84	3	Revolade
Restriction Summary/ Treatment of Concept					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – (in writing-legacy) – Postal/HPOS upload or Online PBS Authorities immediate assessment				
	Indication: Severe aplastic anaemia				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The condition must be severe aplastic anaemia				
	AND				
	Clinical criteria:				
	Patient must not have achieved an adequate response to prior immunosuppressive therapy including anti-thymocyte antibody and ciclosporin; OR				
	Patient must have relapsed following prior immunosuppressive therapy including anti-thymocyte antibody and ciclosporin				
	AND				
	Clinical criteria:				
	Patient must not receive more than 16 weeks duration of treatment under this restriction.				
	Prescribing Instructions: The authority application must be made via the online PBS Authorities (real time assessment), or in writing via HPOS form upload or mail and must include: (a) prior immunosuppressive therapy, including dates of treatment;				

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	<p>Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (a) a completed authority prescription form (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements Apply.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 888 333. Prescribing information (including Authority Application forms and other relevant documentation is applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ELTROMBOPAG					
Eltrombopag 25mg tablet, 28	New	3	84	5	Revolade
Eltrombopag 50mg tablet, 28	New	3	84	5	Revolade
Restriction Summary/ Treatment of Concept:					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required –(Telephone/electronic)				
	Indication: Severe aplastic anaemia				
	Treatment Phase: Continuing treatment				
	Clinical criteria:				
	The condition must be severe aplastic anaemia				
	AND				
	Clinical criteria:				
	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the initial treatment restriction				
	AND				
	Clinical criteria:				
	Patient must have demonstrated a response to PBS-subsidised treatment with this drug				
	Prescribing Instructions: Platelet, haemoglobin and neutrophil counts must be no more than 4 weeks old at the time of application and must be documented in the patient's medical records				
	Prescribing Instructions: Once platelet count > 50 x 10 ⁹ /L, haemoglobin > 100 g/L in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC) > 1 x 10 ⁹ /L for more than 8 weeks., the dose of eltrombopag should be reduced as per the Product Information				

	Prescribing Instructions: For the purposes of this restriction, a response is defined as no longer meeting the criteria for severe aplastic anaemia.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements Apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.