5.01 AVATROMBOPAG, Tablet 20 mg, Doptelet®, Swedish Orphan Biovitrum Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 Highly Specialised Drugs (S100 HSD) Authority Required (Written) listing for avatrombopag for the treatment of severe thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and intravenous immunoglobulin (IVIg).

1.2 Listing was requested based on a cost-minimisation approach (CMA) versus eltrombopag; a comparison with romiplostim was presented as a secondary comparator. Table 1 summarises the components of the overall clinical claim addressed by the submission.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with chronic ITP who have had an inadequate response to or are intolerant to corticosteroids and immunoglobulins.
Intervention	Avatrombopag; recommended starting dose 20 mg QD orally. Dose adjustments based on platelet count response, with maintenance dose between 20 mg weekly and 40 mg daily.
Comparator	Primary comparator: eltrombopag; starting dose 50 mg QD orally. Dose adjustments based on platelet count response, with maximum dose 75 mg daily. Secondary comparators: romiplostim, splenectomy.
Outcomes	Durable platelet response Reduction in concomitant ITP medication Bleeding events Bleeding events WHO grade 2-4 Need for rescue therapy Adverse events
Clinical claim	In patients with chronic ITP, avatrombopag is non-inferior to eltrombopag in efficacy (durable platelet response, reduction in concomitant ITP medication, any bleeding event, bleeding event WHO grade 2-4, need for rescue therapy) and non-inferior in safety.

Source: Table ES.1, p1 of the submission.
ITP = Immune thrombocytopenic purpura; QD = every day.

2 Background

Registration status

2.1 Avatrombopag is currently being evaluated by the TGA. The requested indication is for 'the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous

treatment.' A TGA indication is also being sought for thrombocytopenic patients with chronic liver disease.

2.2 The submission provided the TGA Clinical Evaluation Report, the TGA letter setting out proposed dates for decision, and the TGA Risk Management Plan Evaluation Report. The Evaluation Report recommended that avatrombopag be approved for adult patients with ITP. The TGA Delegate's Overview was available prior to the PBAC meeting, with the Delegate being inclined to approve the registration of avatrombopag in ITP, subject to specialist advice and with additional caveats relating to post-market safety data reporting.

2.3 Avatrombopag is registered in the United States and in the European Union for the treatment of ITP.

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	**Dispensed Price for Max. Qty**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
Avatrombopag					
Avatrombopag 20 mg capsule[a] 30	$[redacted][b] (public) $[redacted][b] (private)	2[c]	30	5	Doptelet

[a] The submission specified capsules but the unit of use is a tablet.
[b] The submission used an incorrect dispensing fee of $7.78 instead of $7.82.
[c] The submission requested 2 packs as the maximum quantity whereas the financial estimates assumed the maximum quantity was 1 pack.

Category / Program:	S100 - Highly Specialised Drugs
Prescriber type:	☐ Medical Practitioners
Restriction type:	☐ Authority Required (in writing only via post/HPOS upload)
~~**Administrative Advice:**~~ ***Prescribing Instructions:***	~~The authority application must be made in writing and must include: a completed authority prescription form, a completed Idiopathic Thrombocytopenic Purpura Initial PBS Authority Application - Supporting Information Form, and a platelet count supporting the diagnosis of ITP. The platelet count must be no more than 4 weeks old at the time of application.~~ *The authority application must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail and must include:* *(a) details (date, unique identifying number/code or provider number) of the pathology report supporting the diagnosis of ITP* *(b) current platelet count* *All reports must be documented in the patient's medical records.*
Condition:	Severe thrombocytopenia in patients with chronic ITP
~~**Population criteria:**~~	~~Patient must be aged 18 years or older~~
Treatment Phase:	Initial Treatment

~~**Clinical criteria:**~~	~~Patient must have failed to achieve an adequate response to both corticosteroid therapy and immunoglobulin therapy (inadequate response = platelet count ≤ 20 x 10^9/L, or 20-30 x 10^9/L and clinically significant bleeding or a history of clinically significant bleeding with platelet counts in this range)~~ Patient must have failed to achieve an adequate response to, *or be intolerant to*, immunoglobulin therapy AND Patient must have failed to achieve an adequate response to, *or be intolerant to*, corticosteroid therapy *for at least 4 weeks* AND The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist *(TRA)* for this condition.
s	
Treatment Phase:	First Continuing treatment or Re-initiation of interrupted continuing treatment
Clinical criteria:	Patient must have demonstrated a sustained platelet response ~~(= use of rescue medication (corticosteroids or immunoglobulins) on no more than one occasion during the initial period of~~ PBS-subsidised treatment with this drug *for this condition under the Initial treatment restriction if the patient has not had a treatment break, confirmed through a pathology report from an Approved Pathology Authority*; AND *Patient must have swapped treatment from romiplostim or eltrombopag under the Balance of Supply/Change of Therapy and demonstrated a sustained response, confirmed through a pathology report from and Approved Pathology Authority; or* AND Patient must have demonstrated a sustained platelet response to the most recent PBS-subsidised treatment with this drug for this condition prior to interrupted treatment, AND ~~Patient must not have previously received PBS-subsidised continuing treatment with romiplostim for this condition,~~ AND The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist for this condition.
Prescribing Instructions:	~~*The following criteria indicate failure to achieve an adequate response to corticosteroid and/or immunoglobulin therapy and must be demonstrated at the time of initial application;, (a) a platelet count of less than or equal to 20,000 million per L; OR, (b) a platelet count of 20,000 million to 30,000 million per L, where the patient is experiencing significant bleeding or has a history of significant bleeding in this platelet range.*~~ *For the purposes of this restriction, a sustained response is defined as the patient having the ability to maintain a platelet count sufficient to prevent clinically significant bleeding based on clinical assessment.*
Treatment Phase:	Second or subsequent continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition under first continuing or re-initiation of interrupted continuing treatment restriction, AND Patient must have demonstrated a continuing response (same definition as "sustained response" for first continuing treatment authority) to PBS-subsidised treatment with this drug, AND The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist for this condition.

3.2 The proposed listing was for treatment of adult patients with severe chronic ITP who have had an inadequate response to corticosteroids and immunoglobulins. The

requested TGA indication in the draft PI is for the treatment of 'thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment'. The proposed TGA indication was broader than the requested PBS population, which is for severe thrombocytopenia in patients with chronic ITP who have had an inadequate response to corticosteroids and to immunoglobulins, in terms of the TGA indication referring to 'previous treatment' rather than specific drug classes.

3.3 The submission stated that the requested PBS listing was also for patients who are intolerant to corticosteroids and to immunoglobulins. However, this was not reflected in the clinical criteria for the restriction requested in the submission or in the requested TGA indication. Intolerance to corticosteroids and to immunoglobulins is included in the restrictions (clinical criteria) for both eltrombopag and romiplostim, and in the approved TGA indications for these drugs. The PBAC considered it would be appropriate for the restriction to include access for patients who are 'intolerant to corticosteroids and to immunoglobulins', to align the listing with that for eltrombopag.

3.4 At the May 2022 Intracycle meeting of the PBAC, the Committee recommended the following changes to the current restrictions for eltrombopag and romiplostim[1]:

- switching between eltrombopag and romiplostim be allowed at any time and wording in the restriction about switching within 24 weeks be removed to mitigate any confusion among prescribers;
- the wording in the restriction regarding prior splenectomy or contraindication to splenectomy be removed;
- children be included in the updated restrictions by removing age limits;
- restrictions on platelet count specified in continuing treatment be removed, and treatment be allowed to continue if the patient can maintain platelet count sufficient to prevent clinically significant bleeding;
- the requirement to stipulate toxicity to corticosteroid and immunoglobulin be removed.

3.5 The Pre-Sub-Committee Response (PSCR) stated that the Sponsor agrees with the proposed changes made by the Secretariat to align the avatrombopag restriction criteria to the proposed criteria for eltrombopag at the May 2022 PBAC intracycle meeting. This involves the following:

- The Secretariat proposed an amendment to the assessment of response proposed in the submission to align the clinical criteria ('patient must have failed to achieve an adequate response to both corticosteroid therapy and immunoglobulin

1 PBAC Meeting Outcomes, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-05/May-2022-PBAC-Web-Outcomes.pdf

therapy') with that recommended for eltrombopag at the May 2022 PBAC intracycle meeting. The amendment stipulated that inadequate response to corticosteroid therapy should be defined as inadequate response, or intolerance, to corticosteroid therapy for at least 4 weeks (section 6 – recommended listing, eltrombopag and romiplostim Public Summary Document [PSD], May 2022). The PBAC noted that intolerance to corticosteroids and immunoglobulins was not included in the requested TGA indication for avatrombopag (paragraph 3.3), but considered this request was reasonable.

- At the May 2022 PBAC intracycle meeting, the PBAC recommended the requirement for written assessment for eltrombopag and romiplostim be changed to telephone/electronic assessment for First Continuing treatment or Re-initiation of interrupted continuing treatment (section 6 – recommended listing, eltrombopag and romiplostim PSD, May 2022). The Secretariat proposed flowing on these changes to avatrombopag, requiring written assessment for the Initial treatment and Grandfather treatment restrictions, and telephone/electronic assessment for First Continuing treatment or Re-initiation of interrupted continuing treatment. The PBAC considered the listing of avatrombopag should reflect its recommendations for changes to the TPO-RA listings recommended at its May 2022 intracycle meeting.

3.6 The evaluation noted that there was inconsistency in the number of packs proposed for listing; the submission showed 2 packs as the maximum quantity whereas the financial estimates used 1 pack. The PSCR did not clarify this inconsistency. The PBAC considered that a maximum quantity of 1 pack was appropriate, with an allowance for prescribers to apply for an additional pack.

3.7 The submission proposed a Special Pricing Arrangement: 'should avatrombopag be recommended by the PBAC, the sponsor is willing, in principle, to be listed with a confidential special pricing arrangement (SPA) which includes a rebate on the published AEMP such that the cost-minimisation claim is realised once the confidential eltrombopag price in chronic ITP is incorporated'.

3.8 The definition of 'sustained response' (and 'continuing response') is different to that defined in the current PBS Authority restrictions for eltrombopag,[2] but consistent with the recommendation at the May 2022 intracycle meeting that restrictions on platelet count specified in continuing treatment be removed, and treatment be allowed to continue if the patient can maintain platelet count sufficient to prevent clinically significant bleeding (paragraph 3.4). The PBAC agreed with the ESC that consistency with the May 2022 intracycle meeting is appropriate in this regard.

For more detail on PBAC's view, see section 7 PBAC outcome.

2 https://www.pbs.gov.au/medicine/item/5827Q, accessed 19 July, 2022.

4 Population and disease

4.1 Immune thrombocytopenia (ITP, also called idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura) is caused by autoantibodies against platelet antigens, most often platelet membrane glycoproteins. Antibody-coated platelets are removed by the spleen, but also in other tissues. Inadequate platelet numbers lead to bleeding in many but not all patients; bleeding can be severe or fatal. The incidence of ITP is of the order of 3/100,000 person-years; the prevalence is several times greater. ITP is customarily divided into primary ITP, in which there is no apparent underlying cause, and secondary, in which there is an identified inciting factor (such as *H. pylori* infection, systemic lupus erythematosus, etc), but the proportion of primary cases depends on the state of medical knowledge and the diligence with which secondary causes are sought. Secondary ITP, defined by the investigators' routine practice, was an exclusion criterion in the studies considered in the submission.

4.2 A review of experience from a single Australian teaching hospital identified 54 new cases of primary ITP over 5 years; median age was 56 years and 56% were female. There were 72 cases of secondary ITP in the same period. About half the new primary ITP patients required treatment at presentation (28/54), in most cases steroids were used (23/28); about half the patients later required non-steroid treatment. Thrombopoietin-receptor agonists (TPO-RAs) were used only in clinical trials.[3]

4.3 Most treatment decisions in ITP are based on limited evidence; recent Australian consensus guidelines noted that 'Most recommendations are made with low Levels of Evidence'.[4]

4.4 Avatrombopag is a small-molecule TPO-RA. The submission stated that it does not require dietary restrictions or routine monitoring.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated eltrombopag as the main comparator and romiplostim as a secondary comparator; both are PBS-listed for treatment of ITP. The submission also presented an evaluation of splenectomy. The ESC and the PBAC considered that overall, the choice of comparator was reasonable.

5.2 Eltrombopag is administered orally, while romiplostim is given as weekly subcutaneous injections. The submission suggested that avatrombopag 'is likely to

3 Choi P, Gordon J, Harvey M, Chong B. Presentation and outcome of idiopathic thrombocytopenic purpura in a single Australian centre. *Internal Med J* 2012; 42:841-845.

4 Choi P, Merriman E, Bennet A, et al. Consensus guidelines for the management of adult immune thrombocytopenia in Australia and New Zealand. *Med J Aust* 2022; 216 (1): 43-52.

mostly replace [eltrombopag] in clinical practice', while 'low substitution from romiplostim is expected'. The evaluation considered it reasonable to claim that eltrombopag will be the main therapy for which avatrombopag will be substituted, and that romiplostim could be significantly impacted if the number of patients unable to use eltrombopag because of hepatotoxicity or unwillingness to adhere to dietary restrictions (which the submission states to be 'small') is greater than estimated, or if clinicians switch between TPO-RAs for other reasons. The PBAC noted the advice from the sponsor hearing and considered that dietary restrictions would be the most likely reason to switch from eltrombopag to avatrombopag, and that patients may switch from romiplostim to avatrombopag (over eltrombopag) if they have liver issues or require assistance with romiplostim injections. For the requested population, splenectomy may be considered an alternative therapy when the requirement for patients to have undergone splenectomy for access to TPO-RAs is removed (paragraph 3.4). This is implied by the treatment algorithm presented in the submission. There have been no randomised controlled trials of splenectomy for ITP, and it was stated in the submission that for this reason 'an indirect treatment comparison with avatrombopag was unable to be performed'.

5.3 If treatment with avatrombopag is substantially more costly than any of the alternative therapies (eltrombopag and romiplostim), the PBAC could only recommend listing avatrombopag if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapies (*National Health Act 1953*, Section 101(3B)). The PBAC advised that the cost minimisation should be performed against the least costly comparator, eltrombopag, so that it is not more costly than any of the alternative therapies.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the risk factors and manifestations of severe thrombocytopenia due to chronic ITP and outlined that treatment goals in practice are patient centred, i.e., to reduce the risk of bleeding events while minimising treatment related toxicities. Current TPO-RA therapies, romiplostim and eltrombopag were discussed. The clinician characterised the treatment challenges with each of these agents, including the dexterity required to self-administer romiplostim, and the severe dietary and mealtime restrictions associated with use of daily oral eltrombopag. The clinician noted avatrombopag has simple administration requirements without dietary restrictions and was of the view that some patients may switch to avatrombopag because of the more convenient dosing and administration requirements.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (8) and healthcare professionals (1) via the Consumer Comments facility on the PBS website. The comments from individuals described the impact of living with ITP and treatment regimens, including risk of bleeding, side effects and administration challenges of currently available TPO-RA therapies and the impact of splenectomy. The input from the health professional highlighted the need for early access to TPO-RAs and the need for additional therapeutic options, as non-response to one agent is not typically predictive of response to other therapies. The health professional described avatrombopag as being the least likely of the three TPO-RAs to impact adversely on lifestyle due to tolerability concerns, administration challenges of romiplostim (as an injected therapy), and dietary and mealtime restrictions associated with treatment with eltrombopag. The health professional also considered that definition of response to treatment is broader than just platelet counts and stated the patient experience and actual purpose of treatment was important to consider when determining appropriate PBS criteria for the TPO-RAs.

Clinical trials

6.3 The primary analysis in the submission was based on an indirect treatment comparison using one trial of avatrombopag vs placebo (Study 302) and one trial of eltrombopag vs placebo (RAISE). A secondary indirect comparison was presented of avatrombopag vs placebo (Study 302) and romiplostim vs placebo (Kuter 2008).

6.4 The literature search presented in the submission was a standard literature search of appropriate databases. However, the evaluation considered that the decision to exclude some studies that contain potentially relevant data was not adequately justified, either for the comparison with eltrombopag or for the secondary comparison with romiplostim. The PSCR maintained that Study 302, RAISE and Kuter 2008 inform the pivotal and most applicable Phase III evidence for avatrombopag, eltrombopag and romiplostim, respectively. The PSCR stated that the ongoing NICE evaluation of avatrombopag concluded that additional data do not meaningfully alter the effect estimates with new data. However, a principal reason given by the evaluation for finding the exclusions unsatisfactory related to the estimation of equi-effective doses.

6.5 The PBAC noted the submission did not perform any further clinical analysis of avatrombopag and splenectomy as no randomised trials of splenectomy in ITP have been undertaken and this was considered reasonable.

6.6 The evaluation noted that the most important omission was NCT01433978 (also referred to as Study 305), a head-to-head randomised comparison of avatrombopag with eltrombopag; the study was terminated by the sponsor after 23 patients were randomised, and only one patient completed the trial, but relevant results are available, and the trial was included in the TGA dossier. This study was listed twice in Table 2-4 of the submission, under 'Applicability Issues' and also as 'No published data

available'. The submission stated that this study 'was discontinued due to significant enrolment challenges owing to a preclinical finding in rodents which indicated a protocol change to include an endoscopy procedure which likely discouraged patient enrolment. The preclinical finding was later found not to affect humans. Therefore, this study was excluded from the analysis due to the lack of published data available'. Data relevant to the submission are provided in the Clinicaltrials.gov listing; however, the PSCR clarified that only limited safety data is available with no efficacy results reported.

6.7 In addition, three randomised controlled trials comparing eltrombopag and placebo and one comparing romiplostim and placebo were excluded. One reason given for this exclusion was that the patients in the excluded trials were Japanese or Chinese, which raised applicability issues. The eltrombopag PI states that for a given dose, East Asian patients have higher area-under-the-curve (AUC) than non-East Asian patients. This effect is clinically important since the recommended starting dose of eltrombopag is halved for East Asian patients. Because doses of eltrombopag are likely to be lower in East Asian patients, the ESC noted that exclusion of data from those patients results in a higher relative eltrombopag dose, and therefore the estimated equi-effective dose and cost-minimised price of avatrombopag may be higher than if the data were included. In the 2021 Australian Census, 5.5% of respondents reported that they had Chinese ancestry[5]. The Pre-PBAC Response argued the exclusion of the studies in East Asian patients was justified as only a small proportion of Australian residents identify as having Chinese or Japanese ancestry and stated the mean dose in those trials was unlikely to be reflective of Australian practice.

6.8 The ESC considered that there was unjustified exclusion of trials that could add data to a very small evidence base. The PBAC considered it was appropriate to exclude Study 305 due to the very limited results available and since the reason for exclusion did not indicate a problem with avatrombopag. Further, the PBAC did not consider the exclusion of trials conducted in exclusively East Asian patients to be inappropriate.

6.9 Details of the trials presented in the submission are provided in Table 2.

5 https://www.abs.gov.au/statistics/people/people-and-communities/cultural-diversity-census/2021 accessed 28 July, 2022.

Table 2: Trials of avatrombopag, eltrombopag and romiplostim versus placebo presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
E5501-G000-302 NCT01438840 (Study 302)	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Plus Standard Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia.	2018 Br J Haematol.183(3):479-490
RAISE	Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study.	2011 Lancet 377: 393–402
NCT00102323 and NCT00102336	Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial.	Kuter et al. 2008 Lancet 371:395-403

Source: generated during the evaluation from Table 2,3, pp36-38 of the submission.

6.10 Key features of the indirect comparison of avatrombopag and romiplostim are presented in the section entitled 'Indirect comparison of avatrombopag and romiplostim – comparative effectiveness and comparative harms'.

Indirect comparison of avatrombopag with eltrombopag

6.11 Table 3 presents the key features of the included trials for the avatrombopag versus eltrombopag comparison.

Table 3: Key features of the included evidence – indirect comparison avatrombopag vs eltrombopag

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in economic evaluation
Avatrombopag vs placebo						
Study 302	49	R, DB 6 months, OL extension up to 24 months	High	Adults with ITP >12 mo, average of two platelet counts <30 x 10^9/L and no count >35 x 10^9/L, at least one successful previous treatment; normal prothrombin time and APTT and no history of thrombo-embolic disease; no history of atrophic gastritis or elevated gastrin.	The proportion of subjects who have at least 6 out of 8 weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of treatment in the absence of rescue therapy; mean cumulative number of weeks with platelet count ≥50 x 10^9/L during the 6-month treatment period; reduction in concomitant medication for ITP, rescue therapy, bleeding events.	Used
Eltrombopag vs placebo						
RAISE	197	R, DB 6 months	Low	Adults with ITP ≥6 mo, baseline platelet count < 30 x 10^9/L, at least one successful previous treatment; exclusion for history of thrombo-embolism only if also two or more of smoking, diabetes, hypercholesterolaemia, or hereditary thrombophilic disorders	Comparable, although designation as primary and secondary outcomes differed.	Used

Source: Table 2-13, pp56-7 of the submission.
APTT = activated partial thromboplastin time; DB = double blind; ITP = immune thrombocytopenia purpura; mo = months; R = randomised.

6.12 Patients were eligible to enter the open-label phase of Study 302 if they had completed the double-blind phase, or had been withdrawn for inadequate therapeutic effect; they were ineligible if there were safety or tolerability concerns, as judged by the investigator, or if they required rituximab, splenectomy or another TPO-RA. The submission did not make use of data from the open-label phase of Study 302 in the comparisons with eltrombopag [or romiplostim].

6.13 The risk of bias for Study 302 was assessed as 'high', because of the very high rate of early withdrawal of placebo-treated patients (16/17), raising the possibility of effective unblinding of the investigators. Inadequate therapeutic effect was the reason for withdrawal in 15/16 patients; one subject withdrew consent. Subjects could be withdrawn at the discretion of investigators for inadequate therapeutic effect, defined as platelet count <30 x 10^9/L for three weeks or for one week if judged clinically hazardous. All 15 placebo-treated patients who withdrew for inadequate therapeutic effect proceeded immediately to the open-label phase. This suggests that withdrawal may have been an alternative to rescue therapy for placebo-treated patients, and this is supported by the high rate of discontinuation for lack of effect but the low rate of use of rescue therapy (15/17 and 2/17, respectively) in the placebo-

treated group of Study 302 compared to placebo-treated patients in RAISE, of whom 55/62 completed 26 weeks treatment but 25/62 received rescue therapy.

6.14 Clearly, nearly all placebo-treated patients who could have been withdrawn for inadequate therapeutic effect were withdrawn. While 7/32 avatrombopag-treated patients were withdrawn for inadequate therapeutic effect, it was not possible to determine from the data provided how many avatrombopag-treated patients actually met the criteria for withdrawal for inadequate therapeutic effect. There was, however, at least one avatrombopag-treated patient who met the criteria for withdrawal for inadequate therapeutic effect but remained in the study. It is stated also that eight patients treated with avatrombopag in the double-blind phase did not continue to the open-label phase, of whom three were the patients who discontinued study drug in the double-blind phase for adverse events and were, therefore, ineligible. It is not possible to determine from the data provided whether the five avatrombopag-treated patients who could have continued to the open-label phase, but did not, were among the seven withdrawn for inadequate therapeutic effect, but no alternative explanation is offered for their not continuing. The difference between withdrawal for inadequate therapeutic effect being followed by entry to the open-label phase in 15/15 placebo-treated patients but 2/7 avatrombopag-treated patients would support the hypothesis of effective unblinding, unless there is an alternative explanation.

6.15 An important issue in the reporting of Study 302 is the grading of bleeding events. The WHO Grading Scale was used in both Study 302 and RAISE. The WHO Grading Scale, as set out in the WHO Handbook for Reporting Results of Cancer Treatment, is Grade 0 = no bleeding, Grade 1 = petechiae, Grade 2 = mild blood loss, Grade 3 = gross blood loss and Grade 4 = debilitating blood loss.[6] The WHO Grading Scale explicitly discourages the use of supplementary descriptors such as 'clinically significant'. In the submission, for reporting efficacy, any bleeding (i.e., Grades 1-4) is distinguished from bleeding Grades 2-4. Grade 2-4 bleeding is referred to as 'clinically significant' for which no criteria are given. For reporting bleeding as an adverse event, bleeding Grades 1-2 are distinguished from bleeding Grades 3-4, so that numbers for bleeding under efficacy and adverse events need not be the same.

6.16 The dosing procedures for avatrombopag during the study were unclear. Avatrombopag is produced as a 20 mg film-coated tablet. To allow for titration of doses the draft PI provides a scale of dosing intervals, between 20 mg weekly and 40 mg daily. However, in Study 302 there were '5, 10, 20, 30, or 40-mg doses', and all patients took a dose of study drug every day. This suggests that several dosage forms may have been provided for the trial additional to the 20 mg form approved for marketing.

6 Table 1, https://apps.who.int/iris/handle/10665/37200. Accessed 21 July, 2022

6.17 The baseline characteristics of patients in the trials used for the indirect comparison were similar (Table 4).

Table 4: Baseline characteristics of patients in the trials

	Study 302		RAISE	
	Avatrombopag N = 32	Placebo N = 17	Eltrombopag N = 135	Placebo N = 62
Age, years				
Mean (SD)	46.6 (14.2)	41.2 (14.7)	NR	NR
Median (range)	45 (20-69)	43.0 (18-65)	47.0 (34-56)	52.2 (43-63)
Female, n (%)	23 (71.9%)	8 (47.1%)	93 (69%)	43 (69%)
BMI, kg/m²			NR	NR
Mean (SD)	29 (7.32)	29 (6.44)		
Median (range)	28 (19-52)	27 (19-46)		
Splenectomy, n (%)	11 (34.4%)	5 (29.4%)	50 (37.0%)	21 (34%)
Use of concomitant ITP treatment at baseline	15 (47%)	7 (41%)	63 (47%)	31 (50%)
Baseline platelet count (x 10^9/L)				
Mean (SD)	14.06 (8.64)	12.71 (7.84)	NR	NR
Median, Range (302) or IQR (RAISE)	12.5 (1.0-31.5)	9.5 (4.0-27.0)	16.0 (9.0-24.0)	16.0 (8.0-22.0)
Baseline Platelet Count ≤ 15 x 10^9/L	18 (56%)	10 (59%)	67 (50%)	30 (49%)
Baseline Platelet Count 15-30 x 10^9/L[a]	13 (41%)	7 (41%)	68 (50%)	32 (51%)

Source: Study 305 CSR Table 14.1.2.1.1; Cheng G, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377:393–402.

[a] One patient in the avatrombopag group had a baseline platelet count > 30 x 10^9/L.

BMI = Body Mass Index; IQR = Inter-quartile range; ITP = immune thrombocytopenia; NR = not reported; SD = standard deviation.

6.18 The durations of treatment with avatrombopag and placebo in Study 302 were markedly different, and although the duration of the double-blind phase was 26 weeks, only a minority of placebo-treated patients had 8 or more weeks on treatment, and only a little more than half the avatrombopag-treated patients completed 26 weeks treatment in the double-blind phase (Table 5). Although the open-label extension phase could extend to 24 months, the median duration of exposure in the combined double-blind and open-label phases was 44 weeks and the maximum duration of exposure was 75 weeks.

6.19 The submission suggested that the shorter duration of placebo treatment 'likely influenced the results by decreasing the chance of events to occur in the placebo group […] such as need for rescue treatment, bleeding events or AEs'.

6.20 The submission also suggested that because 'observed percentages of patients […] may underestimate the true risk of events in the placebo groups,' analysis should be 'based on the comparison of event rates rather than comparison of crude proportions'. However, withdrawal censors exposure and therefore risk of adverse events in every trial, but comparison is based on observed events. For this reason, the evaluation presented data based on observed events. The PSCR disagreed with this assessment, stating that incidence rate ratios (IRR) do account for all observed events,

and that therefore, the submission appropriately included an IRR analysis to account for early and unbalanced discontinuation.

Table 5: Progress of patients through the double-blind phase of Study 302

	Avatrombopag N = 32	Placebo N = 17
Exposure, n (%)		
Any	32 (100%)	17 (100%)
≥ 6 weeks	30 (94%)	10 (59%)
≥ 8 weeks	30 (94%)	7 (42%)
≥ 12 weeks	28 (88%)	3 (18%)
≥ 18 weeks	26 (81%)	3 (18%)
≥ 26 weeks	17 (53%)	1 (6%)
Duration of exposure, weeks		
Mean (SD)	22.8 (7.44)	8.9 (7.36)
Median (range)	26.0 (3.7-31.1)	6.0 (2.1-29.9)

Source: Study 302 CSR, Table 15, p109/2180 and Figure 3, p102/2180.

Additional evidence

6.21 Besides the pivotal RCT for marketing approval (Study 302), the ESC noted other published evidence on the efficacy and safety of avatrombopag was not provided in the submission and considered that given the paucity of evidence in Study 302, any additional evidence may be informative. Other published evidence on the efficacy and safety of avatrombopag includes:

- A meta-analysis versus placebo (that included earlier phase studies with short follow-up that used response rates—platelets > $50/10^9$—as the primary endpoint) (Li et al, 2019[7])
- Network meta-analyses comparing TPO-RAs (Wojciechowski et al, 2021[8]; Deng et al, 2021[9]; and Yang et al 2019[10])
- Real-world data on the efficacy and safety of avatrombopag after switching from romiplostim or eltrombopag (Al-Samkari et al 2022[11]).

[7] Li C, Li X, Huang F, Yang J, Wu A, Wang L, Qin D, Zou W, Wu J. Efficacy and safety of avatrombopag in patients with thrombocytopenia: a systematic review and meta-analysis of randomized controlled trials. Frontiers in Pharmacology. 2019 Jul 26;10:829.

[8] Wojciechowski P, Wilson K, Nazir J, Pustułka I, Tytuła A, Smela B, Pochopien M, Vredenburg M, McCrae KR, Jurczak W. Efficacy and safety of avatrombopag in patients with chronic immune thrombocytopenia: a systematic literature review and network meta-analysis. Advances in therapy. 2021 Jun;38(6):3113-28.

[9] Deng J, Hu H, Huang F, Huang C, Huang Q, Wang L, Wu A, Yang J, Qin D, Zou W, Wu J. Comparative Efficacy and Safety of Thrombopoietin Receptor Agonists in Adults With Thrombocytopenia: A Systematic Review and Network Meta-analysis of Randomized Controlled Trial. Frontiers in pharmacology. 2021:1951.

[10] Yang R, Lin L, Yao H, Ji O, Shen Q. Therapeutic options for adult patients with previously treated immune thrombocytopenia–a systematic review and network meta-analysis. Hematology. 2019 Jan 1;24(1):290-9.

[11] Al-Samkari H, Jiang D, Gernsheimer T, Liebman H, Lee S, Wojdyla M, Vredenburg M, Cuker A. Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: A multicentre US study. British Journal of Haematology. 2022 May;197(3):359-66.

The ESC and the PBAC noted that although these meta-analyses and real-world data did not provide definitive evidence that avatrombopag was non-inferior to eltrombopag, it also considered there was no definitive signal of any difference in efficacy between the two oral TPO-RAs.

Comparative effectiveness

Indirect comparison of avatrombopag with eltrombopag

6.22 The results of the indirect comparison for the efficacy of avatrombopag and eltrombopag, as presented in the submission, are shown in Table 6.

Table 6: Efficacy outcomes vs placebo and indirect comparison of avatrombopag vs eltrombopag

	Patients with platelet count > 50 x10^9/L for 6 of the last 8 weeks treatment, n/N (%)	Reduction in concomitant ITP treatments in use at baseline, n/N (%)	Any bleeding event n/N (%)	Bleeding events WHO Grade 2-4 n/N (%)	Need for rescue therapy n/N (%)
Avatrombopag vs placebo (Study 302); RR or RD (95% CI)					
Ava.	11/32 (34.38%)	5/15 (33.33%)	14/32 (43.75%)	3/32 (9.38%)	7/32 (21.88%)
Plac.	0/17 (0.00%)	0/7 (0.00%)	9/17 (52.94%)	0/17 (0.00%)	2/17 (11.76%)
RR	12.6 (0.78, 200.72)	5.50 (0.35, 87.59)	0.83 (0.46, 1.50)	3.82 (0.21, 69.9)	1.86 (0.43, 7.98)
RD	**0.34 (0.16, 0.52)**	**0.33 (0.05, 0.62)**	-0.09 (-0.38, 0.20)	0.09 (-0.04, 0.22)	0.10 (-0.1, 0.31)
Eltrombopag vs placebo (RAISE); RR or RD (95% CI)					
Eltro.	57/95 (60.00%)	37/63 (54.41%)	106/135 (78.52%)	44/135 (32.59%)	24/135 (17.78%)
Plac.	4/39 (10.26%)	10/31 (32.26%)	56/61 (91.80%)	32/61 (52.46%)	25/62 (40.32%)
RR	**5.85 (2.28, 15.02)[a]**	**1.82 (1.05, 3.16)**	**0.86 (0.76, 0.96)**	**0.62 (0.44, 0.87)**	**0.44 (0.27, 0.71)**
RD	**0.50 (0.36, 0.63)[a]**	**0.26 (0.06, 0.47)**	**-0.13 (-0.23, -0.04)**	**-0.20 (-0.35, -0.05)**	**-0.23 (-0.36, -0.09)**
Indirect treatment comparison: avatrombopag vs eltrombopag; RR or RD (95% CI)					
RR	2.145 (0.114, 40.212)[a]	3.022 (0.181, 50.48)	0.965 (0.528, 1.763)	6.161 (0.331, 114.655)	4.227 (0.908, 19.687)
RD	-0.16 (-0.385, 0.065)[a]	0.07 (-0.281, 0.421)	0.04 (-0.265, 0.345)	**0.29 (0.092, 0.488)**	**0.33 (0.08, 0.58)**

Source: Tables 2-14 to 2-29, pp60-66, and Tables 2-42 to 2-46, pp74-81 of the submission.
Ava. = avatrombopag; Eltro. = eltrombopag; CI = confidence interval; n = number of participants with event; N = total participants in group; Plac. = placebo; RD = risk difference; RR = relative risk. **Bold = statistically significant.**
[a] Corrected in the PSCR.

6.23 During the evaluation it was noted that there appeared to be some typographical errors in the estimates of relative risk and risk differences calculated by the submission, and in the indirect treatment comparisons. Without access to the raw data, it was not possible to correct these during the evaluation. However, given the width of the confidence intervals, the overall conclusions from the analysis would unlikely be altered. The PSCR provided corrected values.

6.24 The submission did not nominate a minimum clinically important difference in (outcome) as the basis for assessing comparative effectiveness. The submission stated:

> 'the minimal clinically important difference (MCID) is difficult to define as there is no generally accepted level of clinically important difference for any of the efficacy outcome measures for ITP patients. Thus, this submission does not

nominate an MCID. Notably, the PBAC has previously accepted durable platelet count as the key outcome in the assessment of the effectiveness of TPO-RAs in treating ITP without a defined MCID which resulted in a successful listing for both romiplostim (Romiplostim PSD, March 2010) and eltrombopag (Eltrombopag PSD, March 2011).'

6.25 The evaluation considered that this statement is not correct. In considering romiplostim, the PBAC stated that the clinically relevant endpoint was bleeding, and that platelet counts were a surrogate outcome with, as the submission notes, an uncertain relationship to bleeding. It would be inappropriate to nominate a MCID for a surrogate marker with no clear relationship to a clinically relevant outcome. Although the PBAC acknowledged that the totality of the evidence suggests it is reasonable to conclude that romiplostim reduces severe bleeding events, in patients at high risk for bleeding" based on the increase in platelet counts, it did not define the term "durable platelet response" (section 12, romiplostim, PSD, March 2010 PBAC meeting). 'Durable platelet response' is a term used in the submission as 'the key outcome'. The PSCR quoted a number of studies to support claims that low platelet counts are associated with worse outcomes; this has been accepted by the PBAC.

6.26 The statistical comparisons presented by the avatrombopag submission showed no significant difference between treatments on any metric but the confidence intervals were wide because of the very small sample sizes of the trials.

6.27 Overall, interpretation of the comparison with eltrombopag is limited by:

- The inadequate justification of exclusion of potentially relevant studies;
- The small number of patients included in the selected trials;
- The likely introduction of bias due to early switching of placebo-treated patients to open label active treatment;
- The uncertainty about the dosing regimen of avatrombopag used in the trial compared to the proposed dosing regimen in the PI.

6.28 The Pre-PBAC Response acknowledged the limitations associated with Study 302, however made a number of additional statements regarding the study, including:

- Early withdrawal in the placebo arm decreases the chance of events (bleeding events or adverse events) being observed in the placebo arm;
- Low event rates in the placebo arm of Study 302 biases the estimates towards equivalence and overestimates variances between study arms;
- Study 302 had more stringent inclusion criteria in terms of ITP definition than RAISE (eltrombopag) (≥12 months duration for Study 302 and ≥6 months duration for RAISE), which likely contributed to the Study 302 population having a lower response rate; and
- The availability of eltrombopag likely lowered the incentive for responding patients to enrol in Study 302.

6.29 Further, the Pre-PBAC Response also noted the meta-analyses and real-world evidence (outlined in paragraph 6.21) demonstrated a high proportion of patients switching to avatrombopag (from eltrombopag) achieved both a platelet response and complete platelet response (10/11 patients from Al-Samkari et al 2022).

Comparative harms

Indirect comparison of avatrombopag with eltrombopag

6.30 An overview of adverse events reported in the trials is shown in Table 7. The submission also provided safety data from the open label follow-up study, but these were not included in the indirect comparison. The most commonly reported adverse events in the double-blind phase were headache: avatrombopag 8/32 (25%) vs placebo 0/17; and nausea and vomiting: avatrombopag 7/32 (22%) vs placebo 1/17 (6%). There were two episodes of venous thrombosis associated with avatrombopag treatment, one deep vein thrombosis during the double-blind phase and one jugular vein thrombosis during the open-label extension.

Table 7: Safety outcomes vs placebo and indirect comparison of avatrombopag vs eltrombopag

	Treatment-related AEs n/N (%)	AEs leading to study discontinuation n/N (%)	Treatment-related adverse events ≥ Grade 3
Avatrombopag vs placebo (Study 302)			
Avatrombopag	31/32 (96.9%)	3/32 (9.4%)	6/32 (18.75%)
Placebo	10/17 (58.8%)	0/17 (0%)	0/17 (0.00%)
RR (95% CI)	**1.65 (1.10, 2.46)**	3.82 (0.21, 69.88)	7.09 (0.42, 118.79)
RD (95% CI)	**0.38 (0.14, 0.62)**	0.09 (-0.04, 0.22)	**0.19 (0.03, 0.34)**
Eltrombopag vs placebo (RAISE)			
Eltrombopag	118/135 (87.4%)	13/135 (9.6%)	20/135 (14.81%)
Placebo	56/61 (91.8%)	4/61 (6.6%)	7/61 (11.48%)
RR (95%CI)	0.95 (0.86, 1.05)	1.47 (0.50, 4.32)	1.29 (0.58, 2.89))
RD (95% CI)	-0.04 (-0.13, 0.04)	0.03 (-0.05, 0.11)	0.03 (-0.07, 0.13)
Indirect treatment comparison: avatrombopag vs eltrombopag			
RR (95% CI)	**1.737 (1.147, 2.629)**	NR	5.5 (0.29, 103.39)
RD (95% CI)	**0.42 (0.165, 0.675)**	NR	0.16 (-0.02, 0.34)

Source: Tables 2-32 to 2-40, pp68-72, and Tables 2-48 to 2-49, pp84-85 of the submission.
Statistically significant comparisons are in **bold**. CI = confidence interval; n = number of participants with event; N = total participants in group, NR = not reported; RD = risk difference; RR = relative risk.

6.31 The evaluation noted that the limitations of the studies as described above make it difficult to make a reliable assessment of the comparative safety of avatrombopag and eltrombopag. The ESC noted that the available safety data was limited, and that thromboembolic events are an apparent potential clinical concern with avatrombopag but were not adjudicated in the submission.

6.32 The ESC considered that having data from more patients with a longer follow-up would be informative. The Pre-PBAC Response provided an updated Periodic Safety Update Report (PSUR) to May 20, 2022 and noted that (i) identified risks in the proposed TGA Risk Management Plan included thrombotic/thromboembolic events and bone marrow fibrosis related to long-term and repeat use; and (ii) 7.0% of patients

experienced a thromboembolic event, with events typically occurring in patients with a platelet count below the upper limit of normal, with no established relationship to drug dose. Further, the Pre-PBAC Response noted that less than 1% of subjects in the ITP avatrombopag treatment groups experienced the treatment emergent adverse event of bone marrow reticulin fibrosis.

Indirect comparison of avatrombopag and romiplostim

6.33 Table 8 presents the key features of the included trials for the avatrombopag versus romiplostim comparison.

Table 8: Key features of the included evidence – indirect comparison avatrombopag vs romiplostim

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Study 302	49	R, DB 6 months, 2:1 randomisation avatrombopag: placebo; OL extension up to 24 months	High	Adults with ITP >12 months, average of two platelet counts <30 x 10^9/L and no count >35 x 10^9/L, at least one successful previous treatment normal prothrombin time and APTT and no history of thrombo-embolic disease, no history of atrophic gastritis or elevated gastrin.	Titration of dose to achieve platelet count >50 x 10^9/L and primary outcome the proportion of subjects who have at least 6 out of 8 weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of treatment in the absence of rescue therapy; mean cumulative number of weeks with platelet count ≥50 x 10^9/L during the 6-month treatment period; reduction in concomitant medication for ITP, rescue therapy, bleeding events.
Kuter 2008; NCT00102323 and NCT00102336[a]	125	R, DB 6 months; 2;1 randomisation romiplostim: placebo	Low	Adults with ITP, no duration specified, mean of 3 platelet counts <30 x 10^9/L and no count >35 x 10^9/L, no active malignancy or history of stem cell disorder; creatinine concentration 176.8 µmol/L or less, bilirubin no more than 1.5 times upper limit of normal, and haemoglobin 90 g/L or higher. Patients older than 60 years were required to have a bone-marrow examination consistent with the diagnosis of ITP.	Titration of dose to achieve platelet count >50 x 10^9/L and primary outcome the proportion of subjects who have at least 6 out of 8 weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of treatment with no rescue medication at any time during the study; a transient platelet response was four or more weekly platelet responses without a durable platelet response from week 2 to 25; the frequency of overall platelet response (durable plus transient rates of platelet response), the number of weekly platelet responses, the proportion of patients needing rescue drugs, and the frequency of durable platelet response with a stable dose (dose maintained within 1 µg/kg during the last 8 weeks of treatment); changes in concurrent ITP therapies.

Source: Table 2-13, pp56-7 of the submission; Kuter D, Bussel J, Lyons R, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; 371: 395–403

DB = double blind; R = randomised; OL = open label.

[a]The trials were analysed together and were identical except that 00101323 enrolled splenectomised patients and 00101336 enrolled non-splenectomised patients.

6.34 Efficacy and safety outcomes for avatrombopag vs placebo (Study 302), romiplostim vs placebo (Kuter 2008) and the indirect comparison of avatrombopag and romiplostim are shown in Table 9.

Table 9: Efficacy and safety outcomes vs placebo and indirect comparison of avatrombopag vs romiplostim

	Patients with platelet count > 50 x 10^9/L for 6 of the last 8 weeks treatment, n/N (%)	Reduction in concomitant ITP treatments in use at baseline, n/N (%)	Bleeding events WHO Grade 2-4[a] n/N (%)	Need for rescue therapy n/N (%)	Treatment-related SAEs n/N (%)	AEs leading to discontinuation n/N (%)
Avatrombopag vs placebo (Study 302): RR or RD (95% CI)						
Ava.	11/32 (34.38%)	5/15 (33.33%)	3/32 (9.38%)	7/32 (21.9%)	9/32 (28.125%)	3/32 (9.4%)
Plac.	0/17 (0.0%)	0/7 (0.00%)	0/17 (0.00%)	2/17 (11.8%)	1/17 (5.88%)	0/17 (0%)
RR	12.6 (0.78, 200.72)	5.6 (0.35, 87.59)	3.82 (0.21, 69.88)	1.86 (0.43, 7.98)	7.1 (0.42, 118.8)	3.82 (0.21, 69.88)
RD	**0.34 (0.16, 0.52)**	**0.33 (0.05, 0.62)**	0.09 (-0.04, 0.22)	0.10 (-0.1, 0.31)	**0.19 (0.03, 0.34)**	0.09 (-0.04, 0.22)
Romiplostim vs placebo (Kuter 2008): RR or RD (95% CI)						
Romi.	41/83 (49.40%)	20/23 (86.96%)	6/84 (7.14%)	18/83 (21.7%)	2/83 (2.4%)	3/83 (3.6%)
Plac.	1/42 (2.38%)	6/16 (37.50%)	5/41 (12.20%)	25/42 (59.5%)	0/41 (0%)	1/42 (2.4%)
RR	**20.75 (2.96, 145.63)**	**2.32 (1.21, 4.45)**	0.59 (0.19, 1.81)	**0.36 (0.23, 0.59)**	2.50 (0.12, 50.91)	1.52 (0.16,14.15)
RD	**0.47 (0.35, 0.59)**	**0.49 (0.22, 0.77)**	-0.05 (-0.16, 0.06)	**-0.38 (-0.55, -0.21)[b]**	0.02 (-0.02, 0.07)	0.01 (-0.05,0.07)
Indirect treatment comparison: avatrombopag vs romiplostim: RR or RD (95% CI)						
RR	**0.605 (0.02, 17.953)**	2.371 (0.139, 40.454)	6.475 (0.287,145.859)	**5.167 (1.114, 24.0)**	**1.912 (0.051, 71.086)**	NR
RD	-0.13 (-0.35, 0.086)	-0.16 (-0.556, 0.236)	0.14 (-0.03, 0.31)	**0.48 (0.21, 0.75)[b]**	**0.2 (0.005, 0.395)**	NR

Source: Tables A-14 to A-19, Attachment A2, pp18-21. Statistically significant comparisons are in **bold**.
AE = adverse event; Ava. = avatrombopag; ITP = immune thrombocytopenia; n = number of participants with event; N = total participants in group; Plac. = placebo; RD = risk difference; Romi = romiplostim; RR = relative risk; SAE = serious adverse event.
Treatment related SAEs are based on figures in Table 14.3.2.1.1 p372 /218, CSR, study 302 rather than Table A18, p 21 Attachment 2A, where the figures are reversed. The ITC for treatment related SAEs appears to have been done correctly.
[a] Attachment 2A, Table A.17, refers only to 'clinically significant bleeding events', but the data for avatrombopag are the data for WHO Grades 2-4 so it is assumed that the same is true for romiplostim.
[b] Corrected in the PSCR.

Benefits/harms

6.35 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.36 The submission described avatrombopag as non-inferior in terms of effectiveness and safety compared to eltrombopag. The evaluation considered the point estimates for some important efficacy outcomes are meaningfully different for eltrombopag and avatrombopag, and although these differences were not statistically significant, the very small sample sizes of the clinical trials used resulted in such wide confidence intervals around the point estimates that clinically significant differences cannot be excluded. The statistically significant differences in some safety outcomes may or may not be reliable due to the sample size.

6.37 The ESC and the PBAC agreed with the evaluation that there was high uncertainty associated with the clinical claim for avatrombopag against eltrombopag and that it was not well supported, noting the very wide confidence intervals. However, the ESC and the PBAC acknowledged that:

- Romiplostim, eltrombopag and avatrombopag are all are effective versus placebo in ITP, but their relative efficacy has not been evaluated in head-to-head RCTs.
- While meta-analyses and real-world data did not provide definitive evidence that avatrombopag was non-inferior to eltrombopag, there was also no definitive signal of any difference in efficacy between the two oral TPO-RAs.
- Unlike eltrombopag, avatrombopag can be taken with food and without dietary restrictions, and unlike romiplostim, it is an oral treatment.

6.38 The submission also claimed that avatrombopag is non-inferior in efficacy and safety to romiplostim. The evaluation considered that this claim was not adequately supported. As with eltrombopag, the point estimates for some important outcomes were meaningfully different, and the small sample sizes mean that clinically significant differences could not be excluded.

6.39 In their consideration of eltrombopag for chronic ITP, the PBAC defined certain differences between results in the RAISE trial (eltrombopag vs placebo) and the Kuter 2008 trial (romiplostim vs placebo) as meaningful, notably the difference in the proportion of patients receiving rescue treatment: in RAISE, 38% eltrombopag vs 63% placebo, and in Kuter 2008, 22% romiplostim vs 60% placebo (section 7, eltrombopag PSD, November 2010 PBAC meeting). These differences are smaller than those between some important point estimates in Study 302 and RAISE.

6.40 In March 2011, the PBAC did not accept that the data demonstrated non-inferiority of eltrombopag to romiplostim for chronic ITP, and recommended listing of eltrombopag 'on the basis of acceptable cost effectiveness at the revised price (less effective and less expensive compared with romiplostim)' (section 12, eltrombopag PSD, March 2011 PBAC meeting).

6.41 The PBAC considered the claim of non-inferior comparative effectiveness was uncertain based on the indirect comparison presented in the submission; however, when considering the totality of the available evidence (including meta-analyses and real-world evidence raised by the ESC), considered the claim was, on balance, likely to be reasonable.

6.42 The PBAC considered that the claim of non-inferior comparative safety was also uncertain due to the limited amount of available data, however considered the meta-analyses and real-world evidence did not raise any additional safety signals.

Economic analysis

6.43 The submission presented a CMA for the economic analysis. The approach and assumptions are shown in Table 10. The prices were based on the published AEMP

price for eltrombopag with the submission noting the SPA for that product. The analysis based on the effective price is shown in the Committee-In-Confidence (CIC) section.

Table 10: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be non-inferior
Evidence base	Indirect comparison of proposed medicine and main comparator
Equi-effective doses	Avatrombopag 22.34 mg /day = eltrombopag 55.2 mg dose/day
Direct medicine costs	Annual costs, based on published prices for eltrombopag: Avatrombopag: $37,542 per patient Eltrombopag: $37,235 per patient
Other costs or cost offsets	Annual costs of monitoring liver function tests during administration of eltrombopag included as cost offset, based on PI requirement for eltrombopag.

Source: Table 3.1, p94 of the submission.

6.44 The proposed equi-effective doses were estimated as 22.34 mg avatrombopag daily and 55.2 mg eltrombopag daily, until the platelet count increases, or unacceptable toxicity occurs. This estimate was based on the indirect comparison of the trials in the submission.

6.45 The evaluation considered that this estimate may not be reasonable if the trial-based comparison of avatrombopag with eltrombopag does not adequately support non-inferiority. If avatrombopag is inferior to eltrombopag in clinical practice, higher doses of avatrombopag are likely to be used. However, the PBAC considered the real-world evidence presented in Al-Samkari et al 2022 (described in paragraph 6.21) was informative for triangulating the likely dose in practice and noted the mean weekly avatrombopag dose observed was 154.1 mg (22.01 mg daily), and also noted this was similar to the proposed trial-based equi-effective dose for avatrombopag.

6.46 The evaluation also considered that taking the equi-effective dose as the mean dose used in the trial is unreasonable because only the 20 mg dose of avatrombopag will be PBS listed and used in practice, with dose adjustment achieved by varying the dosing interval. Therefore, the doses in practice will not be identical to those used in the trial. For example, in the trial, patients requiring a dose increase from 20 mg daily took 30 mg daily. In clinical practice, those patients will be asked to take 20 mg four times a week and 40 mg three times a week. Because this complex schedule is likely to cause errors in dosing, clinicians may elect to use 40 mg daily. The ESC considered calculation of the equi-effective dose to be challenging, given that clinicians are likely to round the dose up or down to make it simpler for the patient, and micro-adjustments that were possible in Study 302 would not be possible in clinical practice. While the PBAC acknowledged this issue, it considered that the proposed trial-based avatrombopag equi-effective daily dose (22.34 mg) could be reconciled with real-world published dosages (see paragraph 7.2 below).

6.47 The evaluation noted the complexity of the dosing regimen for avatrombopag in the proposed PI means that any substitution of avatrombopag for eltrombopag may not

be straightforward. The two dosage strengths for eltrombopag mean that dose titration is relatively simple; similarly, for romiplostim, it is straightforward to titrate.

6.48 The submission included the annual costs of liver function tests (LFTs) performed as a requirement for use of eltrombopag as a cost offset. The frequency of LFTs was justified on the basis of the recommendation in the TGA Public Assessment Report dated 2013, which suggested monitoring LFTs every 2-4 weeks. The submission therefore included the cost of LFT monitoring every 3 weeks in its estimation of the annual cost of eltrombopag, a total of 17.38 tests per year. No justification based on current guidelines or practice was presented to confirm whether this requirement is still reasonable. The PSCR stated the Sponsor is willing to accept uncertainty around frequency of LFTs and has removed it as a cost-offset in the CMA. This update reduced the proposed published EMP for avatrombopag to $2,737.96 per pack.

6.49 The results of the analysis as presented in the submission, based on the published AEMP for eltrombopag, are shown in Table 11 .

Table 11: Calculation of the proposed price for avatrombopag over one year

		Avatrombopag	Eltrombopag	Source
A	AEMP (published)	$2,760.58	$2,585.52	Eltrombopag = ex-man price 5826P 50 mg Avatrombopag = C*B
B	Pack size	30	28	Eltrombopag = pack size Avatrombopag = pack size
C	Drug cost per tablet	$92.02	$92.34	Eltrombopag = A/B Avatrombopag = (F/E)*D
D	Tablet strength (mg)	20	50	Eltrombopag = tablet strength Avatrombopag = tablet strength
E	Mean daily dose (mg)	22.34	55.2	Eltrombopag = mean daily dose RAISE Avatrombopag = mean daily dose Study 302
F	Drug cost per day	$102.79	$101.94	Eltrombopag = (C/D)*E Avatrombopag = G/365.25
G	Drug cost per year	$37,542.44	$37,234.81	Eltrombopag = F*365.25 Avatrombopag = K-J
H	Liver function monitoring	$17.70	$17.70	Eltrombopag = MBS item 66512 Avatrombopag = MBS item 66512
I	Frequency/year	0	17.38	Eltrombopag = every 3 weeks (TGA PAR) Avatrombopag = 0
J	Monitoring cost/year	$0	$307.63	Eltrombopag = H*I Avatrombopag = H*I
K	Total cost/year	$ 37,542.44	$37,542.44	Eltrombopag = G+J Avatrombopag = equal to eltrombopag

Source: Table 3.5, page 97 of the submission.
PAR = public assessment report.

6.50 Given the non-inferiority claims have been accepted by the PBAC, the cost per patient for treatment with avatrombopag should be no more than the cost per patient of eltrombopag. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

6.51 When considering the totality of the available evidence, the PBAC considered the dose equivalence estimated in the submission was likely reflective of clinical practice, and also considered the introduction of avatrombopag would be acceptably cost effective if listed on a cost minimisation basis to eltrombopag, including removal of LFT costs as it was uncertain if and how often such tests are undertaken in patients treated with eltrombopag.

Cost per patient per year

6.52 The cost per patient per year, based on the drug cost per year shown in Table 11 and the proposed dispensed price for maximum quantity (DPMQ) for 1 pack, is $39,736 ($37,542.44 / $2,760.58 * $2,921.86).

Estimated PBS usage & financial implications

6.53 This submission was not considered by DUSC. The submission presented a market share approach to estimating PBS usage and financial implications based on PBS data for eltrombopag and romiplostim. Key inputs used in the estimates are summarised in Table 12.

6.54 The submission noted the outcome of the PBAC May 2022 Intracycle meeting concerning the recommended change in restrictions for eltrombopag and romiplostim and included the potential impact of these changes in their estimates. The submission did not include any adjustment for patients switching between treatments.

Table 12: Key inputs for financial estimates

Data	Value	Source	Comment
Treatment utilisation			
Utilisation of eltrombopag 2021	6,494	Medicare Statistics PBS Item reports for 5825N, 5826P, 5827Q, 5828R	
Utilisation of romiplostim – Year 2021	4,073	Medicare Statistics PBS Item reports for 9696H, 9697J, 9698K, 9699L	
Market share avatrombopag in eltrombopag market	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Sponsor assumption	No justification provided. Assumes that both the 25 mg and 50 mg strengths of eltrombopag will be substituted at the same rate. The PBAC considered uptake rates to be uncertain but from a clinical perspective the estimates appeared reasonable.
Market share avatrombopag in romiplostim market	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Sponsor assumption	No justification provided. Assumes that both the 250 microgram and 500 microgram strengths of romiplostim will be substituted at the same rate.
Rate of yearly growth of TPO-RAs	16%	Assumed to follow the average annual growth rate between 2016 and 2021 based on Medicare Statistics PBS Item reports for 5825N, 5826P, 5827Q, 5828R, 9696H, 9697J, 9698K, 9699L	Reasonable

Data	Value	Source	Comment
Percentage increase in patients eligible for TPO-RA treatment due to removal of splenectomy restriction	7%	Estimated based on the NHS data (Secondary Care Medicines Data, NICE, Prescribing costs in hospital and community 2017/18) prior to and following the removal of the splenectomy restriction	May be reasonable although access to splenectomy in the UK may not be the same as in Australia.
Grandfathered	-	Submission did not include grandfathered patients in its estimates.	The submission did not provide an estimate of the number of grandfathered patients, although it described the access program to be established. The Pre-PBAC Response noted < 500 patients are currently receiving compassionate supply in Australia.
Scripts dispensed	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][2] Yr 6: [redacted][3]	Based on assumed market share across different strengths of eltrombopag and romiplostim.	Given caveats concerning dose equivalence and assumed rate of substitution for different strengths, may or may not be reasonable.
Costs			
Avatrombopag 20 mg	$2,761	Requested price	
Eltrombopag* 25 mg 50 mg	$1,293 $2,586	5825N, 5827Q 5826P, 5828R	Appropriate
Romiplostim 250 microgram 500 microgram	$494 $988	9696H, 9697J 9698K, 9699L	Appropriate
Patient copayment	$18.92 PBS; $4.83 RPBS	Based on eltrombopag use in 2022	Appropriate
MBS costs liver function test infusion administration costs	$17.70 $114.20	66512 13950	Suggested frequency of testing – every 3 weeks – is likely to be an overestimate. Given uncertainty about dose equivalence vs romiplostim, cost offset may or may not be reasonable.

Source: Table 4.1, p98; Table 4.12, pp106-107; Table 4.16 p109: Table 4.23. p114; Table 4.24, p 112 of the submission. * published prices.

The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] 5,000 to < 10,000
[3] 10,000 to < 20,000

6.55 The submission used a single pack (30 tablets) in its calculation of financial estimates, while the requested listing is for a maximum quantity of 2 packs. The Pre-PBAC Response noted that in clinical practice, patients would either receive one or two tablets of avatrombopag per day, so the requested maximum quantity of 2 packs was reasonable for patients who require a 40 mg daily dose. The PBAC considered that it would be appropriate to limit the maximum quantity to 1 pack.

6.56 Minor corrections to update the dispensing fees, patient copayments, and the cost for MBS item 13950 were made during the evaluation. The corrected estimated use and

financial implications as presented in the submission are shown in Table 13, based on the published prices.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
Estimated financial implications for avatrombopag[b]						
Cost to PBS/RPBS less copayments, based on DPMQ ($)	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][6]
Estimated financial implications for eltrombopag and romiplostim[b]						
Cost to PBS/RPBS less copayments ($)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net financial implications						
Net cost to PBS/RPBS ($)	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to MBS[b] ($)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to PBS/RPBS/MBS ($)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Table 4.19, p 111-112; Table 4.20, p 112; Table 4.26, p 115 of the submission.
DPMQ = dispensed price for maximum quantity.
[a] Assuming 13.6 scripts per year as estimated by the submission.
[b] Dispensing fee has been updated to $7.82; patient copayment has been calculated using updated copayment fees of $42.50 for PBS and $6.80 for RPBS; and MBS cost for item 13950 has been updated to $114.20 from the $112.40 used in the submission.

The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] 5,000 to < 10,000
[3] 10,000 to < 20,000
[4] $0 to < $10 million
[5] $10 million to < $20 million
[6] $20 million to < $30 million
[7] net cost saving

6.57 The net cost to the PBS/RPBS of listing avatrombopag, based on the published price of eltrombopag, was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing.

6.58 The ESC advised that the methods used to derive the utilisation and financial estimates and the structure of the estimates model are likely to be reasonable, however it considered there was substantial uncertainty regarding the likely uptake of avatrombopag in practice, given its uncertain comparative effectiveness to alternative TPO-RAs and the likely additional convenience the administration of avatrombopag provides over the alternative therapies. The PBAC considered the potential convenience advantages offered by avatrombopag, such as less restrictive administration around mealtimes, may increase uptake.

6.59 The submission provided the following sensitivity analyses:

- Uptake rate of avatrombopag. Uptake in eltrombopag population was [redacted]% in year 1 increasing to a maximum of [redacted]% by Year 6 of listing in the base case. Uptake in romiplostim population was [redacted]% of the eltrombopag uptake rate. Uptake rate in eltrombopag was increased and decreased by 10% in the sensitivity analysis.

- Rate of TPO-RA natural market growth. Rate of natural yearly growth of eltrombopag and romiplostim was assumed to following the average annual growth rate between 2016 and 2021 based on Medicare Statistics PBS Item reports. Natural market growth was increased and decreased by 5% in the sensitivity analysis.
- Increase in eligible patients following the removal of the splenectomy restriction. An additional 7% applied to the natural market growth of TPO-RAs in year 1 in the base case. Increase in eligible patients following the removal of the splenectomy restriction was increased and decreased by 5% in the sensitivity analysis.

6.60 The PBAC considered that initial uptake could be up to 50%, based on Al-Samkari et al 2022. Given the fundamental problems with the estimation of dose equivalence as well as the unknown degree of substitution of avatrombopag for eltrombopag and romiplostim, the PBAC considered that it is not possible to determine the true likely financial impact of PBS listing. The PBAC noted however, the results of the sensitivity analyses presented, and that these indicated that avatrombopag would remain cost-neutral/cost-saving for each of the analyses presented.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program – Public and Private Hospital), Authority Required listing of avatrombopag for the treatment of severe thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of avatrombopag would be acceptable if it were cost minimised to eltrombopag. The PBAC considered, based on the evidence presented (including observational evidence and meta-analyses identified following the submission), that avatrombopag is likely to be of non-inferior comparative effectiveness and safety to eltrombopag.

7.2 The PBAC noted there was some uncertainty with determining the equi-effective doses of avatrombopag and eltrombopag, as the trial-based equi-effective doses were of uncertain applicability to likely clinical practice (multiple dose forms were available in the clinical trials, however only the 20 mg tablet will be TGA registered and PBS listed for use in Australia). However, the PBAC considered the real-world evidence presented in Al-Samkari et al 2022 (described in paragraph 6.21) was informative for triangulating the likely dose in practice and noted the mean weekly avatrombopag dose observed was 154.1 mg (22.01 mg daily). The PBAC therefore considered the trial-based doses adequately applicable and the equi-effective doses were avatrombopag 22.34 mg daily = 55.2 mg eltrombopag daily (as proposed in the submission).

7.3 The PBAC considered there was a moderate need for additional clinical options for the

management of severe thrombocytopenia in patients with ITP in the later line setting (after failure or intolerance to corticosteroid and immunoglobulin therapy). The PBAC noted the comments from patients and consumers highlighted the challenges of treatment with romiplostim and eltrombopag and agreed there was a clinical place for avatrombopag as an alternative treatment option. The PBAC noted issues with the current PBS listed thrombopoietin-receptor agonist (TPO-RAs) highlighted in the consumer comments, with romiplostim being difficult to self-administer and eltrombopag causing hepatotoxicity in some cases and also having a significant cationic chelation effect, which places significant dietary and mealtime restrictions on patients.

7.4 The PBAC considered it was appropriate to align the listing of avatrombopag with eltrombopag, and for the recommendations from review of PBS restrictions for thrombopoietin receptor agonists (TPO-RA) at the May 2022 Intracycle meeting to be incorporated into the listing. The PBAC agreed with the Secretariat-proposed change (accepted in the Pre-PBAC Response) to include criteria in the restriction relating to switching due to intolerance to other TPO-RAs. The PBAC noted a grandfather listing was requested for patients transitioning from a planned patient access program and considered this was reasonable.

7.5 The PBAC considered the nominated primary comparator of eltrombopag, as an alternative TPO-RA with a similar mechanism of action and mode of administration, was reasonable and considered the nominated secondary comparators of romiplostim and splenectomy were also reasonable.

7.6 The PBAC noted the pivotal trial evidence presented in the submission, which informed the indirect comparison and cost minimisation approach, was based on one RCT of avatrombopag (Study 302) and one RCT of eltrombopag (RAISE). The Committee noted the sample sizes of the trials were small, especially for Study 302 (with only 32 patients treated with avatrombopag), and considered the limited evidence made assessing the clinical claim based on the ICT challenging and highly uncertain. This was evidenced by the wide 95% confidence intervals across the five outcomes for which an ITC of avatrombopag and eltrombopag was undertaken. The PBAC considered interpretation of the evidence presented in the submission was further complicated by the early withdrawal of patients in the placebo arm of Study 302 (16/17 withdrew early), of whom 15 proceeded to the open label phase and were subsequently treated with avatrombopag.

7.7 In addition to the RCT evidence, the PBAC considered the additional evidence raised by the ESC, including meta-analyses and real-world evidence (described in paragraph 6.21), was informative supportive evidence to assess the comparative effectiveness of avatrombopag and eltrombopag. The PBAC considered it was reasonable to consider the totality of the available evidence and noted that while the evidence may not be definitive in establishing non-inferiority, there was no clear signal of a difference in effectiveness between avatrombopag and eltrombopag. Overall, while there were residual uncertainties with the evidence, the PBAC considered a claim of non-inferior

comparative effectiveness between avatrombopag and eltrombopag was likely to be reasonable.

7.8 Similarly, the PBAC considered the comparative harms of avatrombopag were uncertain and difficult to assess due to the limited available data provided in the submission. The Committee noted however, there was no signal for increased harms with avatrombopag in the available data and considered that overall a claim of non-inferior comparative safety to eltrombopag may be reasonable.

7.9 The PBAC considered the CMA was overall likely to be reasonable, based on the recommended equi-effective doses (paragraph 7.2) and drug costs alone. The PBAC noted the PSCR agreement to exclude liver function test (LFT) costs from the CMA.

7.10 The PBAC considered the uptake of avatrombopag was highly uncertain and was of the view a substantial proportion of patients currently treated with romiplostim and eltrombopag could switch. The PBAC noted the utilisation and financial estimates indicated the listing of avatrombopag would be marginally cost saving to the PBS, however given the uncertain uptake, the Committee was of the view the listing of avatrombopag was more likely to be cost neutral.

7.11 The PBAC advised that avatrombopag is not suitable for prescribing by nurse practitioners, consistent with other TPO-RA listings.

7.12 The PBAC recommended that the Early Supply Rule should not apply.

7.13 The PBAC considered the flow-on changes would be required to restrictions for eltrombopag (5825N, 5826P, 5827Q and 5828R) and romiplostim (9696H, 9697J, 9698H, and 9699L).

7.14 The PBAC considered avatrombopag should not be considered interchangeable with any other drugs, including romiplostim and eltrombopag as there are clinically relevant differences between these therapies.

7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because avatrombopag is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over eltrombopag, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.16 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 item, as described below. Flow on changes to romiplostim 500 microgram (9698K, 9699L), romiplostim 250 microgram (9696H, 9697J), eltrombopag 50 mg (5826P, 5828R) and eltrombopag 25 mg (5825N, 5827Q) will be required to allow for switching to avatrombopag, and to remove the treatment dose and duration for prior corticosteroid therapy.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
AVATROMBOPAG					
avatrombopag 20 mg tablets, 30	NEW	1	30	5	Doptelet

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required – (in writing-legacy) - Postal/HPOS upload
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Severe thrombocytopenia
	Treatment Phase: Initial treatment – New patient
	Clinical criteria:
	The condition must be severe chronic immune (idiopathic) thrombocytopenic purpura (ITP)
	AND
	Clinical criteria:
	Patient must have failed to achieve an adequate response to, or be intolerant to, corticosteroid therapy
	AND
	Clinical criteria:
	Patient must have failed to achieve an adequate response to, or be intolerant to, immunoglobulin therapy
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist (TRA) for this condition
	Prescribing Instructions: The following criteria indicate failure to achieve an adequate response to corticosteroid and/or immunoglobulin therapy and must be demonstrated at the time of initial application; (a) a platelet count of less than or equal to 20,000 million per L; OR (b) a platelet count of 20,000 million to 30,000 million per L, where the patient is experiencing significant bleeding or has a history of significant bleeding in this platelet range.
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form, (2) a completed Idiopathic Thrombocytopenic Purpura Initial PBS Authority Application - Supporting Information Form, and (3) details of a platelet count supporting the diagnosis of ITP. All reports must be documented in the patient's medical records.
	Prescribing Instructions: The platelet count must be no more than 4 weeks old at the time of application and must be documented in the patient's medical records.
	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 can 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

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required – (Telephone /electronic)
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Severe thrombocytopenia
	Treatment Phase: First Continuing treatment or Re-initiation of interrupted continuing treatment
	Clinical criteria:
	The condition must be severe chronic immune (idiopathic) thrombocytopenic purpura (ITP)
	AND
	Clinical criteria:
	Patient must have demonstrated a sustained platelet response to PBS-subsidised treatment with this drug for this condition under the Initial treatment or Grandfather treatment restriction if the patient has not had a treatment break, confirmed through a pathology report from an Approved Pathology Authority; or
	Patient must have swapped treatment from romiplostim or eltrombopag under the Balance of Supply/Change of Therapy and demonstrated a sustained response, confirmed through a pathology report from and Approved Pathology Authority; or
	Patient must have demonstrated a sustained platelet response to the most recent PBS-subsidised treatment with this drug for this condition prior to interrupted treatment, confirmed through a pathology report from an Approved Pathology Authority
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist (TRA) for this condition.
	Prescribing Instructions: For the purposes of this restriction, a sustained response is defined as the patient having the ability to maintain a platelet count sufficient to prevent clinically significant bleeding based on clinical assessment.
	Prescribing Instructions: The platelet count must be conducted no later than 4 weeks from the date of completion of the most recent PBS-subsidised course of treatment with this drug and must be documented in the patient's medical records.
	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).

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID	**Category / Program:** Section 100 – Highly Specialised Drugs Program

(for internal Dept. use)		**Prescriber type:** ☒Medical Practitioners
		Restriction type: ☒Authority Required – (Telephone /electronic)
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Indication: Severe thrombocytopenia
		Treatment Phase: Second or Subsequent Continuing treatment
		Clinical criteria:
		The condition must be severe chronic immune (idiopathic) thrombocytopenic purpura (ITP)
		AND
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition under first continuing or re-initiation of interrupted continuing treatment restriction
		AND
		Clinical criteria:
		Patient must have demonstrated a continuing response to PBS-subsidised treatment with this drug
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist (TRA) for this condition
		Prescribing Instructions: The platelet count must be no more than 4 weeks old at the time of application and must be documented in the patient's medical records
		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).
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Highly Specialised Drugs Program
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – (Telephone /electronic)
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Indication: Severe thrombocytopenia
		Treatment Phase: Balance of supply or change of therapy
		Clinical criteria:
		The condition must be severe chronic immune (idiopathic) thrombocytopenic purpura (ITP)
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist (TRA) for this condition
		AND
		Clinical criteria:
		Patient must have received insufficient therapy with this drug for this condition under the Initial treatment restriction OR
		Patient must have received insufficient therapy with this drug for this condition under the First Continuing treatment or Re-initiation of interrupted continuing treatment restriction OR
		Patient must have received insufficient therapy with this drug for this condition under the Second and Subsequent Continuing treatment restriction OR

	Patient must have received insufficient therapy with this drug for this condition under the Grandfather treatment restriction OR
	Patient must be swapping therapy from romiplostim or eltrombopag to this drug for this condition
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 24 weeks of treatment under this restriction.
	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).

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required – (in writing - legacy) - Postal/HPOS upload
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Severe thrombocytopenia
	Treatment Phase: Grandfather treatment
	Clinical criteria:
	The condition must be severe chronic immune (idiopathic) thrombocytopenic purpura (ITP)
	AND
	Clinical criteria:
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date of avatrombopag]
	AND
	Clinical criteria:
	Patient must have failed to achieve an adequate response to, or intolerance to, corticosteroid therapy prior to initiating non-PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have failed to achieve an adequate response to, or intolerance to, immunoglobulin therapy prior to initiating non-PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated a sustained platelet response to the non-PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised thrombopoietin receptor agonist (TRA) for this condition
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form, (2) a completed Idiopathic Thrombocytopenic Purpura Initial PBS Authority Application - Supporting Information Form, and (3) details of a platelet count supporting the diagnosis of ITP. All reports must be documented in the patient's medical records.
	Prescribing Instructions: The following criteria indicate failure to achieve an adequate response to corticosteroid and/or immunoglobulin therapy and must be demonstrated at the time of initial application; (a) a platelet count of less than or equal to 20,000 million per L; OR

	(b) a platelet count of 20,000 million to 30,000 million per L, where the patient is experiencing significant bleeding or has a history of significant bleeding in this platelet range.
	Prescribing Instructions: The platelet count must have been no more than 4 weeks old at the time ~~of~~ that non-PBS-subsidised treatment with this drug was initiated and must be documented in the patient's medical records.
	Prescribing Instructions: For the purposes of this restriction, a sustained response is defined as the patient having the ability to maintain a platelet count sufficient to prevent clinically significant bleeding based on clinical assessment.
	Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the First Continuing treatment or Re-initiation of interrupted continuing treatment criteria.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	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 can 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,

These restrictions 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

Swedish Orphan Biovitrum Pty Ltd. welcomes the PBAC's positive recommendation to list avatrombopag on the PBS for patients with ITP. Swedish Orphan Biovitrum Pty Ltd. looks forward to working with the Department of Health and Aged Care to provide timely access to patients in need.