



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eltrombopag

Proprietary Product Name: Revolade

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

March 2016

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Contents

Common abbreviations	4
I. Introduction to product submission	6
Submission details	6
Product background	7
Regulatory status	7
Product information	8
II. Quality findings	8
III. Nonclinical findings	8
IV. Clinical findings	8
Introduction	8
Pharmacokinetics	9
Pharmacodynamics	10
Dosage selection for the pivotal studies	10
Efficacy	11
Safety	12
First round benefit-risk assessment	16
First round assessment of benefit-risk balance	17
First round recommendation regarding authorisation	18
Clinical questions	18
Second round evaluation of clinical data submitted in response to questions	18
Second round benefit-risk assessment	19
V. Pharmacovigilance findings	19
Risk management plan	19
VI. Overall conclusion and risk/benefit assessment	31
Quality	31
Nonclinical	32
Clinical	32
Risk management plan	35
Risk-benefit analysis	36
Outcome	39
Attachment 1. Product Information	40
Attachment 2. Extract from the Clinical Evaluation Report	40

Common abbreviations

Abbreviation	Meaning
ABMTRR	Australian blood and marrow transplant recipient registry
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ATG	Anti-thymocyte globulin
BCRP	Breast cancer resistance protein
CBC	Complete blood count
CI	Confidence interval
CR	Complete haematologic response
CsA	Cyclosporin A
EPO	Erythropoietin
FDA	Food and Drug Administration
hATG	Horse anti-thymocyte globulin
Hb	Haemoglobin
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
HRQOL	Health related quality of life
HSP	Haematopoietic stem and progenitor cells
HSCT	Haematopoietic stem cell transplant
IND	Investigational new drug
ISS	Integrated Summary of Safety
IST	Immunosuppressive therapy
ITP	Immune thrombocytopaenic purpura
MDS	Myelodysplastic syndrome

Abbreviation	Meaning
NHLBI	National Heart Lung Blood Institute
NIH	National Institutes of Health
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PR	Partial (haematologic response)
PRA	Primary response assessment
rATG	Rabbit ATG
RBC	Red blood cell
SAA	Severe aplastic anaemia
SAE	Serious adverse event
SD	standard deviation
TPO	Thrombopoietin
TPO-R	TPO receptor
ULN	Upper limit of normal

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	7 December 2015
<i>Date of entry onto ARTG</i>	8 December 2015
<i>Active ingredient(s):</i>	Eltrombopag
<i>Product name(s):</i>	Revolade
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Limited ¹ PO Box 101 North Ryde NSW 1670
<i>Dose form(s):</i>	Tablets, film-coated
<i>Strength(s):</i>	25 mg, 50 mg and 75 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	14, 28 or 84 tablets
<i>Approved therapeutic use:</i>	<i>For the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.</i>
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	<i>Initial Dose Regimen</i> Initiate Revolade at a dose of 50 mg once daily. For patients of East Asian ancestry (e. g Chinese Japanese, Taiwanese, Korean or Thai), Revolade should be initiated at a dose of 25 mg once daily (see Pharmacology and Dosage and Administration – Special populations) <i>Monitoring and dose adjustment</i> Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting Revolade (see Clinical Studies). Adjust the dose of Revolade in 50 mg increments every 2 weeks as necessary to achieve the target platelet count $\geq 50 \times 10^9 / L$.
<i>ARTG number (s):</i>	158419, 158356, 200121

¹ NB: This changed from GlaxoSmithKline Australia Pty Ltd during the TGA evaluation phase.

Product background

This AusPAR describes the application by the sponsors to extend the indications for Revolade (eltrombopag) to include the following indication:

The treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.

The current approved indications in Australia are:

1. *Treatment of chronic idiopathic thrombocytopenic purpura (ITP)*
2. *Adult patients with chronic hepatitis C (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.*

No new dosage forms, strengths or new packs are proposed.

Eltrombopag is agonist of the thrombopoietin receptor (TPO-R) which interacts with the membrane domain of the TPO-R present on megakaryocytes and human bone marrow progenitor cell. Efficacy in SAA may be via stimulation of multi-lineage haematopoiesis by the induction of proliferation and differentiation of early bone marrow progenitor cells.

Severe aplastic anaemia (SAA) is a rare (1 to 2/million in Western countries) life threatening acquired bone marrow failure disorder with, prior to the introduction of current therapies, an almost uniformly fatal outcome. Current effective therapies, immunosuppressive therapy (IST) and allogeneic haematopoietic stem cell transplantation have however led to a substantial improvement in survival rates. However not all patients will respond to such therapy. For instance approximately 40% fail to respond to IST and not all patients are suitable for allogeneic transplantation, either because of age limitations, medical co-morbidity or the lack of a suitable donor.

Regulatory status

Australian Orphan Drug Designation (ODD) for the proposed indication was designated on 15 July 2014 in patients with SAA who have had insufficient response to immunosuppressive therapy.

No medicines are approved for SAA in Australia. Use of for example cyclosporin and anti-thymocyte globulin (ATG) is currently off-label.

FDA (USA) and Health Canada have approved eltrombopag for patients with SAA who have had an insufficient response to immunosuppressive therapy (IST) (see Table 1).

Table 1 summarises the international regulatory status.

Table 1: International regulatory status

Region	Tradename	Approval date	Indication
EU	Revolade	CHMP positive recommendation on 24 July 2014	Approval pending
US	Revolade	24 August 2014	Indicated for the treatment of patients with severe aplastic anaemia who have had an insufficient response

Region	Tradename	Approval date	Indication
			to immunosuppressive therapy.
Canada	Revolade	6 May 2015	Indicated for the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.
Switzerland	Revolade	Estimated 1 May 2016	Approval pending

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The clinical rationale for this application is described under *Product background* on page 7 of this AusPAR.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Pivotal efficacy/safety Study ELT112523.

- Other relevant efficacy/safety studies: ELT116643 and ELT116826 (in combination with Cyclosporin A, CsA). Study PMA112509 provides additional safety data albeit in a different disease indication

Paediatric data

The studies cited in the submission were primarily restricted to adult patients. The pivotal Study ELT112523 (efficacy and safety data) was restricted to patients 12 years or older but only contained 2 patients < 18 years of age (both age 17 at study entry) In supportive Studies ELT116812 and ELT116643 7, 3 (20%) and 7 (15%) of participants respectively were in the 12 to 17 years of age group. Study PMA112509 (additional safety data) was conducted solely in adults.

Good clinical practice

ELT112523, ELT116826 and ELT116643 were undertaken in accordance with the standard operating procedures of the National Institutes of Health, USA, (NIH), which comply with the principles of Good Clinical Practice. According to the sponsor², PMA112509 was undertaken in accordance with standard operating procedures of the GSK Group of Companies, which comply with the principles of Good Clinical Practice. All studies were reported to have been conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

Pharmacokinetics

No additional clinical biopharmaceutic studies were completed for this application.

Results from clinical biopharmaceutic studies have previously been submitted in the original Marketing Authorisation Application (MAA) to support eltrombopag use in adult patients with chronic idiopathic thrombocytopaenic purpura.

The following was however included by the sponsor for reference³.

A preliminary pharmacokinetic (PK) result from Cohort 1 of Study ELT116643 has become available since the ISS and are presented here. In Cohort 1 of Study ELT116643, a PK sample was taken from 23 subjects at the 3 month visit. PK is not being performed in Cohort 2 of the study. In cohort 1, plasma concentrations of eltrombopag were sampled from 23 subjects at the 3 month visit. Thirteen (57%) subjects were female, 2 (9%) were elderly, and 3 (13%) were adolescents. Steady state eltrombopag geometric mean PK parameters for the 150 mg daily dose in these 23 subjects were C_{max} 35.0 µg/mL (50%) and $AUC_{(0-\infty)}$ 693.7 µg.h/mL (43%). The observed eltrombopag exposure in the 23 SAA subjects is 2 to 3 times higher than that observed in healthy subjects or patients with chronic ITP.

The higher eltrombopag exposure may be due to a possible drug-drug interaction between eltrombopag and CsA. Studies have shown CsA inhibits drug transporters such as organic anion transporting polypeptide and breast cancer resistance protein

²GlaxoSmithKline (GSK) group of companies.

³From a supplementary PK report provided during the TGA evaluation phase for clinical Study ELT116643. The report evaluated eltrombopag in combination with standard IST in treatment-naive SAA patients. The study was an open-label, Phase I/II study of eltrombopag in combination with standard regimen of hATG/CsA in 62 treatment-naive subjects ages 2 and above with SAA.

(BCRP), thereby potentially impacting plasma levels of substrates of these transporters [Gupta, 2006⁴]. Eltrombopag is a substrate of BCRP’.

Evaluator’s conclusions on pharmacokinetics

Note is made of the higher plasma levels seen in Study ELT116643 in which eltrombopag was given with CsA. No additional/new adverse events (AEs) appear to have been reported and the possible explanation, drug-drug interactions, seems reasonable.

Pharmacodynamics

Studies providing pharmacodynamic data

No additional data were provided⁵.

Evaluator’s conclusions on pharmacodynamics

Not applicable as no new data were submitted.

Dosage selection for the pivotal studies

Eltrombopag 50 mg once daily was selected as the starting dose for the pivotal Study ELT112523 because this regimen has been demonstrated to be safe and effective in increasing platelet counts in patients with chronic immune thrombocytopenic purpura (ITP) and Hepatitis C virus (HCV). A starting dose of 25 mg once daily was selected for East Asian patients due to ethno-pharmacologic differences in exposure. The dose of eltrombopag could be increased every 2 weeks in 25 mg increments up to a maximum dose of 150 mg once daily based on the following considerations:

1. The effective dose in SAA subjects was unknown.
2. 300 mg per day was the maximum dose previously studied in the eltrombopag programme.
3. In healthy subjects, a clear dose and exposure response was seen for eltrombopag doses of 10 mg to 200 mg once daily for 5 days with geometric mean area under the curve between time zero and infinity ($AUC_{0-\infty}$) values of 302 $\mu\text{g}\cdot\text{h}/\text{mL}$ for the 200 mg once daily regimen. Eltrombopag was well tolerated in healthy subjects at all dose levels.
4. There is evidence that higher doses of growth factors are required in bone marrow failure syndromes. For instance, the effective erythropoietin (EPO) dose in MDS is several times higher than the EPO dose used in anaemia of renal failure.
5. To ensure subject safety, a dose escalation scheme in which subjects were exposed to the lowest dose required to achieve desired platelet counts was used.
6. The dose of eltrombopag 150 mg/day in the two supportive studies (ELT116826 and ELT116643) was based upon the results of ELT112523. In ELT112523 nearly all subjects escalated to 150 mg once daily prior to observation of responses.

⁴Gupta, V., Dai Y., Vethanayagam R.R., et.al. Cyclosporin A, tacrolimus and sirolimus are potent inhibitors of the human breast cancer resistance protein (ABCG2) and reverse resistance to mitoxantrone and topotecan. *Cancer Chemother Pharmacol.* 2006, 58, 374383.

⁵in severe aplastic anaemia population.

Efficacy

Studies providing efficacy data

- Pivotal efficacy/safety Study ELT112523 of SAA in patients with an insufficient response to immunosuppressive therapy (IST) (Anti-thymocyte globulin, ATG and Cyclosporin A (CsA)).

Evaluator's conclusions on efficacy

The pivotal Study EELT112523 and supporting Study ELT116826, whilst non-randomised, provide evidence for the efficacy of eltrombopag in a significant minority of patients who meet the study criteria.

The evaluator does however have some comments that relate to inclusion criteria in these studies. The evaluator's impression is that already available, albeit not totally effective, alternative therapy options may have not been considered in some patients included in these studies. In particular;

1. Patients could be entered into these studies after having failed only one prior IST. It is well recognised from the literature, and it is accepted practice, that a proportion of patient who fails a first course of IST will respond to a second course.
2. It is also curious that little mention is made of the use of allogeneic haematopoietic stem cell transplantation in suitable patients with SAA. It is to be noted that not all patients with SAA are suitable recipients of such a transplant with availability of a suitable donor, patient age and co-morbidities being key inclusion/exclusion criteria. However, in the context of this rare condition this therapy is 'widely' practiced Australia (and the rest of the world). For instance, the Australian Bone Marrow Transplant Recipient Registry (ABMTRR, Annual Data Summary 2013) reports that in 2013, 4 children and 15 adults in Australia were the recipients of allogeneic stem cell transplants for the management of aplastic anaemia. The ABMTRR contains data on more than 160 recipients of such transplants with long term follow up >9 years. Survival in adult the adult cohorts (16+ years) was 72% (Human leukocyte antigen (HLA) matched sibling donor) and 56% (HLA-identical unrelated donor). In paediatric patients (n=43) survival for aplastic anaemia (AA), SAA and very SAA was 95%. The evaluator's belief is that the majority of adult patients in this data base would have come to transplant after failure of at least 1 course of IST. In paediatric practice by contrast the evaluator believes that a transplant is therapy of choice provided that a suitable donor is available.

Given the caveats noted above the submitted data does support efficacy (with acceptable toxicity) in this group of patients. The efficacy endpoints reported (for instance reduction in red blood cell and platelet transfusion requirements) can be clinically meaningful to those patients who achieve them.

Particular note is made of the following that reflect on long-term efficacy and the ability for drug withdrawal. Note is also made of bi-lineage and tri-lineage responses, the ability to titrate down to the lowest effective dose and the ability for eventual drug withdrawal in a (limited) number of patients).

1. The gradual improvement of haematologic responses across multiple lineages over time and the maintenance of response for 1 year provide evidence of the long-term efficacy of eltrombopag in heavily pre-treated SAA patients.
2. Responses were maintained throughout the treatment period, with subjects receiving 150 mg eltrombopag for up to 39 months.

3. Relapses were few and occurred early in treatment course. No relapses occurred after 6 months of treatment and no relapses occurred in subjects with multilineage responses.
4. Based upon these data, there is no evidence for development of tolerance to eltrombopag or loss of efficacy following continued treatment with eltrombopag.
5. In addition, all subjects meeting 'trilineage haematopoiesis' criteria who had eltrombopag tapered off, have maintained their response with a median follow-up of 20.6 months as of data cut-off. This provides evidence supporting the persistence of efficacy following treatment with eltrombopag in patients with SAA.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- The primary safety data is from the pivotal Phase II Study ELT112523 (National Institute of Health [NIH] 09-H-0154); the safety and efficacy proposed for the labelling is based on this study.
- Available supportive safety data in SAA subjects is provided from the ongoing Phase II Study ELT116826 (NIH 13-H-0133) in subjects with an insufficient response to IST, as well as the ongoing Phase I/II Study ELT116643 (NIH 12-H-0150) in treatment naïve subjects.
- Additional supportive safety data are provided from a completed, placebo-controlled Phase I/II Study PMA112509 in subjects with advanced MDS or acute myeloid leukemia (AML)

Data from ITP and Hepatitis C Studies

Eltrombopag is an approved product with an established safety profile in chronic ITP and HCV indications based upon review of placebo-controlled databases:

1. Chronic ITP: randomised controlled safety database: n=427 (eltrombopag n=299, placebo n=128). Total eltrombopag chronic ITP safety database: n=446
2. HCV: randomised controlled safety database: n=1439 (eltrombopag n=955, placebo n=484). Total eltrombopag HCV safety database: n=1576.

The sponsor reports that an estimated 3,900 subjects have been exposed to eltrombopag in sponsored ongoing and completed interventional studies; this includes subjects with ITP, liver diseases, haematology-oncology related thrombocytopenia, as well as healthy volunteers. The eltrombopag SAA clinical development programme includes a safety database of 88 Eltrombopag-treated subjects with SAA from 3 open label trials included in this submission (Table 2).

Table 2: SAA and MDS/AML patients treated with Eltrombopag. Safety database

Study	Eltrombopag (SAA population)	Double-Blind Study Treatment (advanced MDS/AML patient population)	
		Placebo	Eltrombopag
ELT112523	43 ^a	NA	NA
ELT116826	15	NA	NA
ELT116643	44 ^b	NA	NA
PMA112509	NA	34	64

a. One additional subject was enrolled, but did not receive eltrombopag treatment.

b. Three additional subjects were enrolled, 1 did not receive eltrombopag treatment, 2 had not received eltrombopag treatment as of the clinical cut off date.

The sponsor also provided additional safety data from a placebo controlled study in subjects with advanced MDS or AML receiving up to twice the maximum dose of eltrombopag in SAA. Both SAA and the MDS/AML population are characterised by severe pancytopenia and its complications.

Summary: The safety profiles observed in both SAA and MDS/AML populations (PMA112509) seem to be consistent with what has been reported for eltrombopag in chronic ITP and HCV. No new safety signals have been identified in the SAA population with doses up to eltrombopag 150 mg.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) in SAA patients were assessed in the pivotal study (ELT112523) and the 2 supporting studies (ELT116826 and ELT116643)
 - Of the 43 subjects who received eltrombopag in Study ELT112523, 93% were escalated to the maximum dose of eltrombopag 150 mg. Three subjects received a maximum dose of eltrombopag 125 mg. Given the design of the study, in which subjects who did not meet response criteria were discontinued from treatment after 3 months, the median (range) time on treatment was 3.6 months (2 to 39). Eltrombopag treatment was received for at least 3 months in 77% of subjects. As of the clinical cut-off date, 28% and 21% of subjects received eltrombopag for >6 and 12 months, respectively, with a maximum duration of 39 months
- AEs of particular interest in the SAA patient group including hepatobiliary, thromboembolic, haematological malignancies and clonal cytogenetic changes were monitored (relevant clinical and laboratory assessments) and are reported for all studies
- Laboratory tests, including standard haematology, biochemistry were performed according to study protocol. Specialised investigations included bone marrow aspiration and biopsy and cytogenetic analysis.

Pivotal studies that assessed safety as a primary outcome

In addition to the pivotal Study ELT112523, Studies ELT116826, ELT116643 and PMA112509 assessed safety as a primary outcome. The safety population consisted of all patients who had received at least one dose of eltrombopag.

Dose-response and non-pivotal efficacy studies

Dose rationale and dosing strategy have been described above.

The ongoing non-randomised Phase II Study ELT116826 dose modification study evaluated patients who commenced treatment at the maximum dose used in ELT112523 (150 mg/day, with modifications for East Asians and children) and then evaluated, in responding patients, the lowest dose that maintained stable platelet counts.

Study ELT116643 provides data on dosing of eltrombopag in combination with CsA/horse anti-thymocyte globulin (hATG).

Patient exposure

Study ELT112523

1. Forty three subjects initiated treatment with eltrombopag 50 mg and were dose escalated in 25 mg increments every 2 weeks to a maximum of eltrombopag 150 mg.
2. Of the 43 subjects who received eltrombopag, 40 (93%) were escalated to the maximum dose of eltrombopag 150 mg. Three subjects did not receive the maximum dose of 150 mg. The maximum dose received for these 3 subjects was 125 mg.
3. The median subject daily dose was calculated by dividing the cumulative dose received by the days of treatment. Due to the protocol specified dose escalation, the average daily dose is < 150 mg for all subjects (Table 3).

Table 3: Summary of Exposure to Eltrombopag in pivotal study ELT112523

	Eltrombopag (N=43)
Subject Daily Dose (mg)^a	
Mean (SD)	113.2 (19.65)
Median (min-max) ^b	110.2 (47-147)
Time on Study Treatment (Months)^c	
Mean (SD)	8.4 (10.44)
Median (min-max)	3.6 (2-39)
<3 months, n (%)	10 (23)
≥3 months, n (%)	33 (77)
>6 months, n (%)	12 (28)
>12 months, n (%)	9 (21)
Cumulative Actual Dose (mg)	
Mean (SD)	32508.1 (45466.65)
Median (min-max)	11300.0 (4025-175075)

Data Source: m5.3.5.2 ELT112523 CSR Section 7.1

Abbreviations: SD=standard deviation

- a. The subject daily dose (the cumulative actual dose divided by the duration of exposure) is calculated for each subject first and the summary statistics are calculated based on the subject average daily dose.
- b. Median subject daily dose was calculated by dividing the cumulative dose received by the days of treatment. Due to the protocol-specified dose escalation and the study design, the average daily dose is <150 mg for all subjects.
- c. Time on study drug does not exclude dose interruptions.

4. Given the design of the study, in which subjects who did not meet response criteria were discontinued from treatment after 3 months, the median time on treatment was 3.6 months. The majority of subjects received treatment for at least 3 months. Nine subjects received eltrombopag for more than 12 months, with a maximum duration of 39 months.

Study ELT116826 exposure

Of the 15 subjects who received eltrombopag up to 150 mg in Study ELT116826, 5 subjects completed 6 months of treatment with eltrombopag and 4 of the 5 subjects had entered the extension phase of the study. As of the clinical cut-off date (31 March 2014), the 4 subjects received between 57 to 85 days of treatment in the extension phase. No further exposure data are available for this ongoing study.

Study ELT116643 exposure

Of the 44 subjects who received eltrombopag up to 150 mg in Study ELT116643, 19 subjects completed the planned 6-month eltrombopag treatment period in Cohort 1. Five Cohort 1 subjects tapered off eltrombopag due to increased platelet count: 1 subject received 5 months of eltrombopag treatment, 1 subject received 4 months, 1 subject

received 2 months and 2 subjects received 1 month. Three subjects from Cohort 2 completed the planned 3-month eltrombopag treatment period. No further exposure data is provided.

Study PMA112509 exposure

Subjects received a starting daily dose of 50 mg eltrombopag or matching placebo. The dose could be increased, depending on platelet and bone marrow blast response, every 2 weeks up to a maximum dose of 300 mg/day (150 mg for East Asian subjects). The goal of this dosing schema was to maintain a stable platelet count in the safe range without exceeding platelet counts $> 400 \times 10^9/L$.

Most subjects in the eltrombopag group (56%) and in the placebo group (65%) received the maximum dose of IP (300 mg, or 150 mg for East Asian subjects) (Table 4). Nine subjects (14%) receiving eltrombopag and 1 subject (3%) receiving placebo continued treatment for > 6 months in the extension treatment periods.

Table 4: Exposure to study drug

	Placebo (N=34)	Eltrombopag (N=64)
Total Days on Study Drug^a		
Mean (sd)	76.6 (55.19)	111.1 (124.07)
Median (Min-Max)	69.5 (2-253)	71.5 (3-676)
Maximum Dose – East Asians, n (%)		
50 mg	0	1 (2)
100 mg	0	3 (5)
150 mg	7 (21)	14 (22)
Maximum Dose – Non-East Asians, n (%)		
50 mg	5 (15)	9 (14)
100 mg	4 (12)	7 (11)
150 mg	0	2 (3)
200 mg	3 (9)	6 (9)
300 mg	15 (44)	22 (34)

Data Source: Table 8.0000

a. Total days on study drug = total number of days on study drug, including interruptions; therefore, it was based on the first exposure date and the last exposure date.

Safety issues with the potential for major regulatory impact

Note is made of the specific safety issues (thromboembolic events, development of new cytogenetic abnormalities and haematological malignancies) evaluated in the submitted studies and discussed in the supplied material. Within the limitations of available follow-up data there does not seem to be a new safety signal, and that the occurrence of these 'events', in particular cytogenetic evolution and the development of a haematological malignancy, would seem to be consistent with the known clinical behaviour of patients with aplastic anaemia.

However note should be made of the relatively short follow-up time and ongoing monitoring for these events would be appropriate and prudent.

In addition, safety data in the paediatric population is clearly limited.

Post-marketing data

This is noted above in relation to the use of eltrombopag in the currently approved indications ITP and Hepatitis C associated thrombocytopenia.

Evaluator's conclusions on safety

In the context of the particular patient group being evaluated, it appears that the safety data reported are consistent with the known safety signals reported for eltrombopag in the currently approved indications (ITP and Hepatitis C associated thrombocytopenia).

Note is made of the three particular safety issues; thromboembolic events, the development of cytogenetic abnormalities and haematological malignancies.

1. No safety signal was detected for thromboembolic events.
2. New cytogenetic abnormalities and haematological malignancies were reported in a limited number of patients. It is well recognised that both occurrences are seen in long term follow-up of patients with SAA treated along conventional lines. In addition such events do not seem to have been identified in the patients treated ITP and Hepatitis C associated thrombocytopenia.

Thus the evaluator agrees with the sponsor's assessment that there does not appear to be an unexpected increase in the incidence of these events. However the evaluator would strongly recommend that long-term follow-up for these complications is undertaken in the SAA patients treated with eltrombopag.

First round benefit-risk assessment

First round assessment of benefits

SAA is a rare condition frequently treated with immunosuppressive therapy and or haematopoietic stem cell transplantation. Patients who fail 1 to 2 courses of IST and who are unsuitable for matched sibling transplantation, have very limited therapeutic options apart from supportive care (antimicrobials and transfusion support for platelets and red cells), an unrelated or mismatched allogeneic transplant or a novel clinical trial. Such patients have a very limited long-term survival and would be the potential beneficiaries.

The benefit of eltrombopag, reported in the pivotal clinical Study ELT112523 and supporting studies, is the availability of a new therapeutic option for patients who fail or are unsuitable for conventional therapies. The action of this agent (stimulation of haematopoietic stem cells) is mechanistically distinct from conventional therapies (IST and transplantation) thus implying the potential for activity in patients resistant or relapsing from such therapy.

A significant minority of patient entered into the studies in reported for the target population achieved meaningful haematopoietic responses in at least one lineage. Bi and tri-lineage responses and improvements in bone marrow cellularity are reported as is the ability for dose reduction and eventual cessation. Responses can be long-term. Limited quality of life data and improvements are also reported.

Eltrombopag is orally administered with a convenient dosing schedule. It is reported to be well tolerated with, in the context, an acceptable safety profile and no new safety signals have to date been identified in the SAA population. The safety profile in the SAA patient population is consistent with that observed in approved indications of eltrombopag. Transaminase and indirect bilirubin elevations observed were consistent with information described in the approved labelling for eltrombopag. Thromboembolic events were not observed in the SAA studies and no new identified safety risks were noted. The incidence of cytogenetic abnormalities in the SAA studies of eltrombopag observed were in line with the rates reported in the published literature in SAA patients.

In summary the benefits of eltrombopag in the proposed usage are:

- A novel therapeutic option, with a novel mode of action, for patients who have failed conventional therapy.
- Meaningful responses in a significant minority of patients.
- Orally administered with the potential for drug cessation in
 - responders
 - patients who fail to respond to the initial trial of therapy.

First round assessment of risks

The risks of eltrombopag in the proposed usage are:

- Use in patients for whom a 'suitable/conventional' alternative therapeutic option is available.
 - This issue has been addressed above, but in brief, if the proposed indication included patients who had failed only one prior IST, then the use of this agent has the potential to replace current 'accepted' second line therapy.
 - It should be noted that the accepted second line therapies (a second IST or an allogeneic transplant) are far from ideal and are associated with significant costs and toxicities. There is however no available data comparing eltrombopag with these options to assess the relative efficacy and costs and thus which would be the preferred second line option.
 - It could be well argued that the community would benefit from the availability of a range of options for these patients.
- Prolonged inappropriate use. Care should be taken to ensure that
 - A defined trial period is identified and that ongoing use is restricted to appropriately defined 'responders'. The criteria used in the reported trials seem appropriate.
 - Appropriate dose tapering and cessation criteria are considered. The criteria used in the reported trials seem appropriate.
- Limited paediatric data.
- Possible safety signals; in particular new cytogenetic abnormalities or an increase incidence of haematological malignancies.
 - Note is made of the supplied safety data both in the accepted indications (ITP and hepatitis C) and in SAA population. However, given the action of eltrombopag in the haematopoietic stem cell and the well-recognised potential for patients with SAA to develop additional new cytogenetic abnormalities or progress to a haematological malignancy, ongoing monitoring of this issue would seem appropriate.

First round assessment of benefit-risk balance

The benefit-risk balance of eltrombopag, given the proposed usage, has the potential to be favourable. However the evaluator would recommend particular attention is paid to the exact wording of the indication.

The evaluator certainly thinks that the use of eltrombopag would be appropriate and the risks acceptable for SAA patients who

1. Have failed 2 courses of conventional IST and for whom an allogeneic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities.

A significant issue in this context is to define 'acceptability of available donor'; fully matched sibling versus fully (molecularly)-matched unrelated donor versus mismatched related or unrelated donor. 'Acceptability' will clearly vary depending on the age comorbidities of the patient.

2. Have failed 1 course of conventional IST and for whom a second course of IST would be inappropriate and, in whom, an allogeneic stem cell transplant is not feasible or inappropriate due to lack of an available donor (see above) or patient co-morbidities.

First round recommendation regarding authorisation

The evaluator would not recommend a blanket approval for patients with SAA who have failed (one round) IST as proposed by the sponsors. Rather the evaluator would recommend initial approval as suggested above. The sponsors could be asked to address the issues of the number of rounds of IST required and the place of allogeneic transplantation before in a subsequent submission.

Clinical questions

One clinical question was posed by the Delegate:

1. *The sponsor is invited to comment on any issues raised in this report, particularly those issues raised or summarised within the report regarding benefit, risk, wording of indication and the sponsor's proposed approach to long-term monitoring of safety in SAA.*

Second round evaluation of clinical data submitted in response to questions

The evaluator has read the sponsor's response to the comments relating to the wording of the indication and note their interpretation and arguments. The evaluator certainly agrees that there is sufficient evidence to support activity in the particular patient groups evaluated, including patient who had failed only one round of IST.

The evaluator made the following points:

1. The therapy for SAA patients who have failed initial therapy is suboptimal. There are however a number of well-established paradigms involving consideration of an allogeneic transplant for suitable patients or a second round of IST.
2. Australian and international registry data demonstrate significant use, in the context of a rare disease, of allogeneic transplantation in this area.
3. Given the small numbers of patients evaluated and the high likelihood for differences in patient selection criteria it is inappropriate to compare non-randomised studies. Whilst potential efficacy of all three approaches is demonstrated any attempt to imply that one therapy is better than any of the others is inappropriate.

Thus the evaluator's recommendations can be considered in the context of a global paradigm for the management of SAA patients who have failed previous IST. The following is, according to the evaluator, appropriate;

1. Have failed 2 courses of conventional IST and for whom an allogeneic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities
2. Have failed 1 course of conventional IST and for whom a second course of IST would be inappropriate and , in whom, an allogeneic stem cell transplant is not feasible or inappropriate due to lack of an available donor (see above) or patient co-morbidities.

Second round benefit-risk assessment

Second round assessment of benefits

- Availability of a therapy for patients for whom no other appropriate therapy is possible or appropriate.

Second round assessment of risks

From the reports available to date there does not seem to be an increase in haematopoietic cytogenetic abnormalities in SAA patients. However

- a. Experience with Eltrombopag in SAA is relatively short compared to the other indications
- b. It should be reinforced that SAA is (almost universally) accepted to be a disorder of the haematopoietic stem cell and is thus distinguished from the other indications. The TPO receptor (target of Eltrombopag) is present on haematopoietic stem can progenitor cells.

Thus the evaluator still has the opinion that this issue deserves further monitoring. See Attachment 2 for further details.

For patients who have failed only 1 course of IST and for whom neither a second course of IST nor an allogeneic transplant is contraindicated there is the potential for replacement, without proof of superiority, of currently accepted second line approaches. A cost benefit analysis should be considered.

Second round assessment of benefit-risk balance

There is clearly a benefit for patients with no appropriate alternative.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 27 (dated 29 October 2014, Data Lock Point (DLP) 6 August 2014) and Australian-specific annex (ASA) Version 2.0 (dated 3 February 2015)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Summary of Ongoing safety concerns

Important identified risks	<p>ITP</p> <p>Hepatotoxicity</p> <p>Thromboembolic events</p> <p>Post therapy reoccurrence of thrombocytopaenia</p> <p>Cataract</p> <p>HCV associated thrombocytopaenia</p> <p>Hepatotoxicity</p> <p>Hepatic decompensation</p> <p>Thromboembolic events</p> <p>Portal vein thrombosis</p> <p>Cataract</p> <p>Retinal haemorrhage</p> <p>Post therapy reoccurrence of thrombocytopaenia</p> <p>Severe aplastic anaemia</p> <p>Hepatotoxicity</p> <p>Thromboembolic events</p> <p>Post therapy reoccurrence of Thrombocytopaenia</p> <p>Cataract</p>
Important potential risks	<p>ITP and HCV-associated thrombocytopaenia and Severe aplastic anaemia</p> <p>Potential for increased bone marrow reticulin formation</p> <p>Haematological malignancies</p> <p>Renal tubular toxicity</p> <p>Photo toxicity</p> <p>Potential for haematological changes</p> <p>Potential for endosteal hyperostosis</p> <p>HCV associated thrombocytopaenia</p> <p>QT/QTc interval prolongation</p> <p>Severe aplastic anaemia</p> <p>Cytogenic abnormalities</p>
	<p>ITP and HCV-associated thrombocytopaenia and Severe aplastic anaemia</p> <p>Paediatrics</p> <p>Pregnant or lactating females</p> <p>Asian population</p> <p>Black race population</p>

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information. Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 6.

Table 6: Additional pharmacovigilance activities planned by the sponsor

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
TRA105325/ EXTEND Clinical Category 3 Ongoing	Bone Marrow Reticulin Formation	Extension study in adults with ITP long term safety including collection of bone marrow reticulin	Final study report September 2015
TRA112940/ Bone Marrow Study Clinical Category 3 Ongoing	Bone Marrow Reticulin Formation	Safety in adults with ITP long term safety including collection of bone marrow reticulin	Final study report September 2015
WWE116951: Prospective observational study of ENABLE clinical trial patients to understand later outcome patterns among patients with and without a Thromboembolic event. Pharmacoepidemiology Category 3 Ongoing	Thromboembolic event (TEE)	TEE in patients with HCV associated thrombocytopenia	Final study report December 2017
Drug utilisation study Pharmacoepidemiology Category 3 Ongoing	Off label use	Collect data of 'real-world' use of Eltrombopag post approval	Final report December 2016
GSK PASS Study: Post Authorization Safety Study of HCV patients treated with	TEE and Hepatic decompensation	Assess occurrence of safety events among HCV patients who	6 months interim analysis, December

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
<p>Eltrombopag: Multicentre, Prospective Observational Cohort Study of Thrombocytopenic HCV Patients Receiving Eltrombopag Pharmacoepidemiology Category 3 Ongoing</p>		<p>receive Eltrombopag in the post approval, real world setting</p>	<p>2016 12 months interim analysis, June 2017 18 months interim analysis, October 2018 Final report, November 2019</p>
<p>HCV-TARGET: Proposed Post Authorization Safety Study of HCV patients treated with Eltrombopag: Hepatitis C Therapeutic Registry and Research Network Pharmacoepidemiology Category 3 Ongoing</p>	<p>TEE and Hepatic decompensation</p>	<p>Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting</p>	<p>First interim, October 2016 Final report, October 2019</p>
<p>HCV Research UK: Proposed Post Authorization Safety Study of HCV patients treated with Eltrombopag Pharmacoepidemiology Category 3 Ongoing</p>	<p>TEE and Hepatic decompensation</p>	<p>Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting</p>	<p>First interim, October 2016 Final report, October 2019</p>
<p>Effectiveness of Eltrombopag Educational Materials for Hepatitis C associated thrombocytopenia Category 3 Ongoing</p>	<p>Key elements within the educational materials including Hepatic decompensation, TEEs and fatal adverse events</p>	<p>Measurement of the effectiveness of the Eltrombopag Risk Minimisation education materials</p>	<p>Interim report, April 2015 Final report, September 2015</p>

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
ELT116826 Clinical Category 3	Safety in SAA patients unresponsive to IST	Safety of eltrombopag in SAA patients unresponsive to IST	April 2016
ELT116643 Clinical Category 3 Ongoing	Safety in front-line SAA patients receiving treatment with IST	Safety in front-line SAA patients receiving treatment with IST	May 2016
RAD201583 Clinical Category 3 Planned	Drug-drug interaction (DDI) –cyclosporin and eltrombopag	Determine effect of cyclosporin on PK of eltrombopag	September 2015
RAD200936 Clinical Category 3 Planned	Paediatrics	Safety of eltrombopag in paediatric SAA	December 2020

Risk minimisation activities

The sponsor is proposing routine risk minimisation activities. In the EU-RMP, the sponsor is proposing health care professional and patient education as additional risk minimisation activities.

However, in the ASA, the sponsor states the following:

No additional risk minimisation measures are planned following the extension of indication to SAA patients. The risk communication in the product labelling associated with cytogenetic abnormalities is considered to be the primary risk minimisation tool and is sufficient to inform prescriber and patient.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and an evaluation of the sponsor's responses.

Table 7: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may	<i>Pharmacodynamic,</i>	The sponsor's

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>be raised by the nonclinical and clinical evaluators through the consolidated request for further information and/or the Clinical Evaluation Report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>pharmacokinetic, and toxicological evaluations with eltrombopag were completed as part of the nonclinical program in support of the initial registration for Revolade and the subsequent application to register the HCV Indication. There are no new nonclinical pharmacology, pharmacokinetic, or toxicology studies to report, and the planned line extension submission did not include a nonclinical module.</i></p> <p><i>The sponsor responded to the safety considerations raised by the clinical evaluator (see Clinical findings, Second round evaluation above).</i></p>	<p>response has been noted.</p>
<p>2. The ASA does not include a justification for the differences between the SmPC and proposed PI wording. The sponsor should provide this justification.</p>	<p><i>Information has been included in the Australian Specific Annex v2.1 [Module 1.8.2] to justify the differences in wording between the EU SmPC and the proposed Australian PI.</i></p>	<p>The sponsor's response has been noted.</p>
<p>3. Any ASA updates should be provided in the current ASA format.</p>	<p><i>The Australian Specific Annex v2.1 [Module 1.8.2] has been updated to include all information outlined in the TGA's RMP Q & As (dated 4 May 2015).</i></p>	<p>The sponsor's response has been noted.</p>
<p>4. It is noted that the sponsor has listed some of the safety concerns as only applying to HCV-associated thrombocytopaenia, but not the other indications. Given that the proposed new indication of severe aplastic anaemia (SAA) could be due to any cause of aplastic anaemia, including hepatitis C infection, this appears to be rather questionable and the sponsor should provide a compelling justification for this or assign all safety concerns to all indications.</p>	<p><i>Although SAA has numerous potential underlying etiologies, once SAA has been diagnosed, the risks associated with its treatment are as outlined in the submission. Likewise the risks associated with HCV infection are specific to the underlying advanced liver disease observed in this population. Hepatitis associated aplastic anaemia (HAAA) occurs several weeks after an episode of acute hepatitis, and in most cases the hepatitis does not become chronic. Treatment of severe HAAA must be undertaken</i></p>	<p>This is considered acceptable in the context of this application.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>with urgency, as it is fatal without treatment. In contrast, the long term complications of chronic liver disease develop over decades.</i></p> <p><i>The RMP has been organized to reflect the varied indications and populations studied. If a patient were to have both SAA and HCV, the associated risks of treatment with eltrombopag would be inclusive of the risks noted for each. Assigning all safety concerns to all indications would be inconsistent with the available evidence, as risks observed in the currently studied populations have been different, with some overlap of constitutional-type symptoms. The risks assigned to different indications have only been observed in those specific populations, and are believed to be a function of the underlying disease. For example, portal vein thrombosis, the most frequently occurring thromboembolic event in patients with advanced chronic liver disease, was observed only in patients with chronic liver disease. Hepatic decompensation, a well described complication of advanced chronic liver disease, was observed only in patients with advanced HCV. Cytogenetic abnormalities, which have not been observed above background rate in patients with SAA, are not typically associated with ITP or HCV.</i></p>	
<p>5. It is not clear whether no additional risk minimisation activities are planned for the Australian market or whether the existing additional risk minimisation activities for the existing indications are</p>	<p><i>Educational materials for cITP and HCV will be used in Australia as a risk-minimization tool to communicate known risks and their management to physicians and patients. These</i></p>	<p>This is considered acceptable in the context of this application.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
proposed. The sponsor should clarify this.	<i>materials will be updated to include an indication statement for SAA, following possible approval of this application. Additionally please refer to our responses to 6 and 7.</i>	
6. It is recommended the existing additional risk minimisation activities be updated to include the proposed indication and specific risks associated with that indication (for example, cytogenetic abnormalities).	<p><i>No additional educational materials are proposed for the indication of SAA, but the existing educational materials will be updated to include an indication statement for SAA, following possible approval of the SAA application.</i></p> <p><i>A known complication of SAA is the appearance of cytogenetic abnormalities in bone marrow cells. Cytogenetic abnormalities have been reported in 15 to 20 % of patients with SAA.⁶ The clinical consequences are variable, depending upon the specific abnormality and the presence or absence of clinical sequelae such as dysplasia or worsening cytopenias.⁶ Novartis does not propose to include any specific information about cytogenetic abnormalities in the educational materials. Information communicated to physicians through the Australian PI document is considered the primary tool to educate physicians about this risk.</i></p> <p><i>No other regulatory body including the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) have requested</i></p>	<p>The updating of the existing materials is considered acceptable. However, information on cytogenetic abnormalities is considered essential for the treatment of SAA patients and should be included. This can be brief.</p> <p>It is recommended the existing additional risk minimisation activities be updated to include specific risks associated with the SAA indication (in particular cytogenetic abnormalities and the need for long-term follow-up). The sponsor should provide the updated materials to the TGA.</p>

⁶Maciejewski JP, Risitano A, Sloand EM, Nunez O, Young NS. Distinct clinical outcomes for cytogenetic abnormalities evolving from aplastic anemia. *Blood*. 2002; 99: 3129-3135.

Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. *New Engl J Med*. 2011;365:430-438.

Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Wu CO, Young NS. Activity of alemtuzumab monotherapy in treatment-naïve, relapsed, and refractory severe acquired aplastic anemia. *Blood* 2012a; 119(2):345-354.⁷

Maciejewski JP et al. Distinct clinical outcomes for cytogenetic abnormalities evolving from aplastic anaemia. *Blood* 2002; 99 (9): 3129-3135

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<i>the addition of such information in the currently implemented educational materials.</i>	
<p>7. The sponsor should provide the TGA with the following details for agreement:</p> <ul style="list-style-type: none"> -All draft education materials; -A clear distribution plan; and -A clear plan to measure the effectiveness of the education programme as an additional risk minimisation activity. 	<p><i>The educational materials for cITP have been finalised by Novartis and are provided in the attachment of Australian Specific Annex v2.1 [Module 1.8.2]. The educational materials for HCV are currently being amended by Novartis, and it is estimated that these will be available by 18 September 2015. For further details regarding the different educational materials and their availability please refer to [Table 7b].</i></p> <p><i>Both sets of educational materials will be amended to align with the Australian PI and mailed out to the prescribers of Revolade for all indications, within 90 days following availability of the educational materials (see table above). The amended materials can be provided to the TGA for review prior to distribution if requested by the TGA.</i></p> <p><i>The prescribing physicians for Revolade for all indications are specialised haematologists. There are about 380 registered specialised haematologists in Australia. The educational materials for the cITP indication and the HCV indication will be mailed out to all registered haematologist with 'return to sender marked', within a maximum of 90 days, following the release of the educational materials for the HCV indication (18 September 2015). These materials will be available for distribution on an ongoing</i></p>	<p>Given the new information provided, this is considered acceptable in the context of this application.</p> <p>The amended materials are herewith requested.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>basis.</i></p> <p><i>Following possible approval of the SAA application the educational materials will be updated to include an indication statement for SAA, and will be made available for distribution in Australia within 90 days.</i></p> <p><i>The final report titled: The measurement of the effectiveness of educational materials in the risk minimisation programme for eltrombopag for the treatment of chronic hepatitis C associated thrombocytopenia report was provided with this response. This survey was concluded in June 2015, and was carried out in Europe and Canada. It is considered that the results of this study are also applicable to the Australian market and therefore, Novartis Australia does not consider that a measurement of effectiveness in Australia would yield further information.</i></p> <p><i>The measurement of the effectiveness of risk minimization activities will be carried out by reviews of adverse event reports at the time of data analysis for Periodic Safety Update Report (PSUR) generation. The results of these analyses will be communicated to the TGA through PSURs, which will be provided to the TGA as per regulatory requirement.</i></p>	
<p>8. The sponsor should provide the interim report for the additional pharmacovigilance activity 'Effectiveness of Eltrombopag Educational Materials for Hepatitis C associated thrombocytopenia'.</p>	<p><i>The final report titled: The measurement of the effectiveness of educational materials in the risk minimisation programme for eltrombopag for the treatment of chronic hepatitis C associated thrombocytopenia report was provided. The</i></p>	<p>The sponsor's response has been noted.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>survey sample contained 232 physicians in Europe and Canada. Seventy-three percent acknowledged receipt of educational materials relating to correct eltrombopag use, and twenty-seven percent had not received eltrombopag educational materials. The surveyed sample of physicians did not establish a correlation between exposure to educational materials and improved understanding of correct eltrombopag usage. Therefore, it could not be concluded that educational materials/activities relating to the appropriate use of eltrombopag have been effective in increasing physician knowledge of the appropriate use of eltrombopag.</i></p>	
<p>9. Haemoglobin and albumin values should be reported in the Standard International (SI) unit g/L which is more commonly used in Australia.</p>	<p><i>This has been addressed in the revised PI.</i></p>	<p>This is considered acceptable in the context of this application pending approval by the Delegate.</p>
<p>10. Platelet values should be reported in the unit $\times 10^9/L$ which is more commonly used in Australia.</p>	<p><i>This has been addressed in the revised PI.</i></p>	<p>This is considered acceptable in the context of this application pending approval by the Delegate.</p>
<p>11. In the 'Precautions' section, the PI should contain similar information on hepatic decompensation, as found in the SmPC.</p>	<p><i>This has been addressed in the revised PI.</i></p>	<p>This is considered acceptable in the context of this application pending approval by the Delegate.</p>
<p>12. In the 'Adverse Events' Section, the PI should align with the proposed EU SmPC that contains many additional adverse events not proposed to be included in the Australian PI. This applies to all indications. Uncommon events may be grouped</p>	<p><i>This has been addressed in the revised PI.</i></p>	<p>This is considered acceptable in the context of this application pending approval by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
separately.		
13. In the 'Overdosage' section, the PI should include the poison information telephone number.	<p><i>The sponsor confirms that the current Revolade CMI contains the Poisons Information Centre contact number, and that the proposed PI has been revised to also include this data in the OVERDOSAGE section.</i></p> <p><i>The revised, draft Product Information and Consumer Medicine Information are provided. In addition, please see the responses to 9, 10, 11, 12, 13 and 14.</i></p> <p><i>Furthermore, the sponsor provides an update on the international regulatory status of similar applications overseas and the currently approved Product Information in the USA, Canada, and Europe.</i></p>	This is considered acceptable in the context of this application pending approval by the Delegate.
14. It is recommended to the Delegate that the draft consumer medicines information document be revised to accommodate the changes made to the product information document.	<p><i>The sponsor have revised the current CMI document to include Severe Aplastic Anemia (What Revolade is used for), How much to take it, and possible side effects. The revised document is included with this response.</i></p>	This is considered acceptable in the context of this application pending approval by the Delegate.

Table 7b: Availability of Novartis Revolade educational materials

Indication	Required RMP Educational Materials	Optional Educational Materials	Global Delivery Date
Chronic cITP	<ul style="list-style-type: none"> • Revolade cITP RMP Safety Guide G-REV-1121903 • Revolade cITP RMP HCP Guide G-REV 1121902 • Revolade cITP RMP Patient Support Booklet G-REV-1121415 	<ul style="list-style-type: none"> • Revolade cITP RMP Patient Quick Ref Guide G-REV-1121906 • Revolade cITP RMP Patient Meal Planner G-REV-1121904 • Revolade cITP RMP Patient Treatment Tracker G-REV-1121907 • Revolade cITP RMP Patient Pack Stickers G-REV-1121905 • Revolade cITP RMP Patient Pack Folder G-REV-1121908 	Available
Chronic HCVaT	<ul style="list-style-type: none"> • Revolade cHCVaT RMP Doctor Booklet • Revolade cHCVaT RMP Patient Support Booklet 		Estimated: 09/18
Severe Aplastic Anemia (SAA)	Existing educational materials will be updated with SAA indication statement		

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

RMP issues

It is recommended the existing additional risk minimisation activities be updated to include specific risks associated with the SAA indication (in particular cytogenetic abnormalities and the need for long-term follow-up). The sponsor should provide the updated materials to the TGA.

Key changes to the updated RMP

- EU-RMP Version 27 (dated 29 October 2014, DLP 6 August 2014) and Australian-specific annex (ASA) Version 2.0 (dated 3 February 2015) has been superseded by:
- EU-RMP Version 33 (dated 27 July 2015, DLP 12 February 2015) and Australian-specific annex (ASA) Version 2.1 (dated 10 September 2015).

A summary of the key changes are shown in the table below.

Table 8: Summary of key changes between RMP version 27 and 33

Document	Key change
EU RMP	As agreed with EMA, consolidation of 3 versions of EU RMP.
ASA changes	Changes to reflect transfer to Novartis. Updated pharmacovigilance section. Updated risk minimisation activity section (including educational materials for SAA indication).

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- Implement EU-RMP Version 33 (dated 27 July 2015, DLP 12 February 2015) and Australian-specific annex (ASA) Version 2.1 (dated 10 September 2015), and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator is broadly supportive of the use of eltrombopag in SAA but suggests a modified indication. To paraphrase the evaluator's suggestion:

Eltrombopag is indicated in patients with severe aplastic anaemia who:

- 1. Have failed two courses of conventional immunosuppressive therapy and for whom an allogenic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities.*
- 2. Have failed one course of conventional immunosuppressive therapy and for whom a second course of immunosuppressive therapy would be inappropriate and in whom an allogenic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities.*

Overview of data

There was a single pivotal study, ELT112523. This was an open label, single arm and single centre (National Institutes of Health (NIH)) study of 43 patients with SAA.

The following studies in SAA patients were supportive:

- ELT116826 (open label, single arm, single centre study; starting dose of 150 mg; interim results, with only 15 patients enrolled as of 31 March 2014)
- ELT116643 (open label, single arm, single centre study; eltrombopag used in combination with hATG/CsA).

Study PMA112509 provided safety data, from a different patient population (advanced myelodysplastic syndrome or AML); it was a placebo controlled study.

Most data were from adults and the proposed indication is in adults.

Pharmacokinetics (PK)

In a cohort of 23 subjects from Study ELT116643, a snapshot of exposure at the 3 month visit revealed mean peak plasma concentration (C_{max}) of 35 $\mu\text{g/mL}$ and mean $\text{AUC}_{0-\infty}$ 694 $\mu\text{g.h/mL}$, said to be 2 to 3 times higher than exposures observed in healthy subjects or patients with chronic ITP. It is further stated by the sponsor:

The higher eltrombopag exposure may be due to a possible drug-drug interaction between eltrombopag and CsA. Studies have shown CsA inhibits drug transporters such as organic anion transporting polypeptide and breast cancer resistance protein (BCRP), thereby potentially impacting plasma levels of substrates of these transporters [2006]. Eltrombopag is a substrate of BCRP.

A drug interaction study is planned (in healthy subjects) to investigate this potential influence.

The evaluator notes in this regard that no new AEs were reported (despite higher exposure) and that the proposed explanation (interaction with CsA) seems reasonable.

Separately, the sponsor has proposed additional text in the PI about influence of hepatic impairment on PK of eltrombopag based on population PK analysis.

Question for sponsor

1. *It is acknowledged this proposed new text is in response to the RMP Evaluation report. Has the population PK analysis referred to in the PI text been submitted to the TGA? If not, please submit the report of this population PK analysis, for information.*

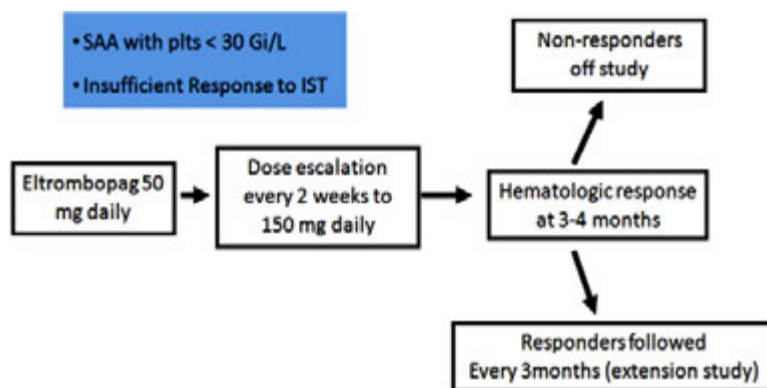
Efficacy**Study ELT112523**

This study was a Phase II, open label, single arm and single (US) centre study. It is ongoing; the data cut-off date for results here was 9 May 2014.

A key inclusion criterion was a diagnosis of severe aplastic anaemia with refractory thrombocytopenia following ≥ 1 course of (horse or rabbit) ATG + cyclosporin. Concurrent stable treatment with CsA or G-CSF was permitted. Grounds for withdrawal of treatment include no treatment [response] at the Primary Response Assessment (this was at 12-16 weeks) and various safety related grounds.

Eltrombopag was given as 50 mg once daily (25 mg in East Asian patients), increasing by 25 mg daily each 2 weeks based on platelet response count, to a maximum of 150 mg per day (75 mg in East Asians).

The study scheme is depicted below.

Figure 1: Study scheme

Forty-four subjects were enrolled and 43 were treated. The clinical evaluator states that *'as this is a rare clinical scenario the number of enrolled and treated patients is appropriate'*. It is notable that many patients were on iron chelation (for example deferasirox) and antiviral therapy which is reflective of ongoing red blood cell (RBC) transfusions causing an increase in body iron and consequent susceptibility to infection. Based on the company study report (CSR Table 1.0410), 4/43 patients were on concomitant cyclosporin.

Questions for sponsor

2. *Did these four patients receiving CsA have any outlying or atypical efficacy or safety outcomes in the study that might plausibly be related to altered eltrombopag exposure? Is there information about whether CsA levels (and attendant risks, for example nephrotoxicity) might be influenced by co-administration with eltrombopag?*

The primary efficacy outcome was investigator-assessed haematological response at 12 to 16 weeks after drug commencement. This response required meeting *one or more* of the following criteria:

- Platelet count increase to $20 \times 10^9/L$ above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks.

- Haemoglobin (Hb) increase by > 1.5g/dL (15 g/L) for patients with pre-treatment Hb levels of < 9 g/dL, or a reduction in the units of RBC transfused by at least 4 for 8 consecutive weeks, compared with the 8 weeks pre-treatment.
- An absolute neutrophil count (ANC) increase of 100% (for pre-treatment levels < 0.5 x 10⁹/L) or an ANC increase > 0.5 x 10⁹/L.

Other efficacy endpoints are described in the Extract from the CER, Attachment 2.

At the primary response assessment (Weeks 12 to 16), a haematological response was seen in 17/43 (40%) patients.

The breakdown of response in these 17 patients is summarised in Table 9 below. For example, only one patient had a tri-lineage response (at the Primary response assessment (PRA)). However, others had a tri-lineage response as 'best observed response' (that is, at other time-points), and 5/43 had tri-lineage response at last assessment. Three of 17 responders relapsed by the last assessment (these patients were uni-lineage responders and relapsed within 6 months of starting therapy). 6 responders have been followed for ≥ 2 years without relapse and without new therapy for SAA.

Table 9: Breakdown of the haematological response in 17 patients

	Primary Response Assessment	Best Response Observed	Response at Last Assessment
	Eltrombopag (N=17)	Eltrombopag (N=17)	Eltrombopag (N=17)
Response Criteria: Response Due To, n (%)			
Uni-lineage	13 (76)	8 (47)	5 (29)
Multi-lineage	4 (24)	9 (53)	9 (53)
Bi-lineage	3 (18) ^a	4 (24)	4 (24)
Tri-lineage	1 (6)	5 (29)	5 (29)
Relapsed by Last Assessment			3 (18)
Response By Lineages^b, n (%)			
Platelet	11 (65)	12 (71)	12 (71)
Hemoglobin	3 (18)	8 (47)	6 (35)
Neutrophils	8 (47)	11 (65)	10 (59)

Data Source: Table 2.0010, Table 2.0020 and Table 2.0030

- a. Subject [redacted] responded according to ANC criteria at Week 12, and then had a Week 16 visit at which he responded according to ANC and platelet criteria.
- b. Subjects could be counted as a response according to more than 1 criteria

Transfusion independence and changes in bone marrow cellularity are described in the Extract from the CER, Attachment 2.

Study ELT116826

This open label, single arm study is not influential, since it uses a different dosing regimen (150 mg starting dose, modified by age and ethnicity) and only interim data were supplied in only 15 SAA subjects.

Its efficacy outcomes do not undermine those reported in the pivotal study.

Study ELT116643

This open label, single arm study is not influential. It tests use of eltrombopag (starting dose 150 mg, modified by age and ethnicity) in combination with immunosuppressive therapy (hATG/CsA), as a first-line regimen. Patients not eligible for allogeneic stem cell transplant (SCT) were considered for enrolment. Interim data (using a cut-off of 31 March 2014) refer to 47 enrolled patients.

Safety

The evaluator notes that the safety profile of eltrombopag is well characterised in patients with chronic ITP, thrombocytopenia in HCV and other groups. However, the SAA safety dataset is not extensive: only 88 subjects from the three trials discussed under 'Efficacy'

above. There were no controlled data in SAA; the placebo controlled Study PMA112509 was in MDS/AML and it used a different (higher) eltrombopag dose regimen.

In the pivotal Study ELT112523, 40/43 (93%) were escalated to 150 mg; 3/43 to 125 mg. Median time on treatment was 3.6 months; 21% of subjects received eltrombopag for > 12 months (maximum duration 39 months). In this study, 12% of subjects (5/43) discontinued due to AEs (cataract; abdominal discomfort; acute Hepatitis B (HBV); viral infection; and sepsis). The evaluator considered the profile of AEs consistent with the established safety profile of eltrombopag.

Interestingly, infectious serious AEs (SAEs) were reported in a smaller proportion of responders than non-responders, despite longer duration of follow-up in responders.

Two deaths due to infection occurred within 30 days of the last dose of eltrombopag; 4 other occurred > 110 days after the last dose. No death was considered drug related.

Three subjects in ELT112523 were diagnosed with MDS following eltrombopag therapy. The clinical evaluator concluded that no increased risk of progression was conferred by eltrombopag use. A caveat was placed given the short follow-up time in these SAA studies. The evaluator strongly recommended long-term follow-up for (1) new cytogenetic abnormalities; and (2) haematological malignancy.

In the placebo-controlled Study PMA112509, the step-up in toxicity in the eltrombopag arm (relative to the placebo arm) as measured by SAEs was not great, despite higher doses in this study. Some 62 to 63% of subjects had died across arms, in the large majority of cases due to disease under study.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's RMP evaluation section although a second round RMP evaluation report is pending.

The clinical evaluator suggested long term follow-up for new cytogenetic abnormalities and haematological malignancy.

The RMP notes Study ELT116826 and Study ELT116643 may provide more data about new cytogenetic abnormalities.

It is further stated that *'the proposal for a [targeted follow-up questionnaire] to collect information for cytogenetic abnormalities is currently being reviewed by the European Medicines Agency'*. There is also a questionnaire for use in SAA (and other) patients with haematological malignancies. Data from questionnaires would contribute to post-market pharmacovigilance.

Risk minimisation is via provision of information in the PI; Novartis does not propose to include specific information about cytogenetic abnormalities in educational materials.

Question for sponsor

3. *Can the sponsor confirm that a targeted questionnaire will be used for new cytogenetic abnormalities in Australia and provide an update about dialogue with the EMA in this regard?*

Risk-benefit analysis

Delegate's considerations

Pharmacology

The proposed PI recommends increasing dose in increments of 50 mg every 2 weeks to find the effective dose; in the pivotal study, the increments were 25 mg.

In the pivotal study, the maximum dose in East Asians was 75 mg; this is not reflected in the proposed PI (perhaps because the pivotal study did not enrol a sufficient number of East Asian patients to allow characterisation of this approach; a single Asian patient was enrolled).

There is a signal that eltrombopag exposure may be higher with concomitant use of CsA.

Efficacy

The clinical evaluator notes that in relation to Study ELT112523 and Study 116826:

- a. Patients could be entered onto study after having failed only one prior course of IST (yet 'a proportion of patients who fail a first course of IST will response to a second course')
- b. There is evidence of the long-term success of allogeneic stem cell transplantation in aplastic anaemia, generally in adults after failure of at least 1 course of IST but in children as first-line therapy.

Despite these caveats, the evaluator is generally supportive of efficacy, in SAA. See also the benefit / risk discussion, below.

Safety/RMP New cytogenetic abnormalities

A study of 30 patients with AA (28/30 with SAA; 25/30 adult) and normal karyotype at presentation noted that clonal karyotypic evolution occurred at a constant rate, 50% of new abnormalities developing within 30 months.⁷ By extrapolation, this might suggest an approximately 12% frequency of changes purely in chromosome 7 and within 3 to 4 months of starting eltrombopag is rather high.

Question for sponsor

4. *If all 5 patients with new chromosome 7 abnormalities had these detected by weeks 12-16 (PRA), would this be considered a major departure from the natural history of treated SAA, in terms of the tempo of development of such cytogenetic abnormalities?*

Long-term follow-up for new cytogenetic abnormalities appears to rely on reporting of any detected cytogenetic abnormalities to the sponsor as an 'AE', and the subsequent completion of a targeted questionnaire on the subject, which will eventually be factored into post-market pharmacovigilance. Given the uncontrolled nature of eltrombopag studies in SAA does not allow assessment of the role of eltrombopag, if any, in acceleration of new cytogenetic abnormalities, is this apparently passive approach acceptable? The use of a registry, for example, would be a stringent but potentially effective way to check that new cytogenetic abnormalities/clonal evolution/haematological malignancy are not occurring at unacceptable rates in patients on eltrombopag. Such approaches might be more reasonable if a broader indication is adopted (since efficacy and safety are less well characterised in patients who have only failed one line of IST and it is very difficult to compare efficacy and safety in this setting with outcomes of current best practice).

⁷ Maciejewski JP et al. Distinct clinical outcomes for cytogenetic abnormalities evolving from aplastic anaemia. *Blood* 2002; 99 (9): 3129-3135

Question for ACPM

- *Are any other approaches required to strengthen long-term follow-up for new cytogenetic abnormalities/haematological malignancies?*

Benefit/risk

There is a thoughtful discussion of benefit/risk in the clinical evaluation (Attachment 2). As noted earlier, the evaluator argues for the following indication:

Eltrombopag is indicated in patients with severe aplastic anaemia who:

- *Have failed two courses of conventional immunosuppressive therapy and for whom an allogenic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities.*
- *Have failed one course of conventional immunosuppressive therapy and for whom a second course of immunosuppressive therapy would be inappropriate and in whom an allogenic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities.*

The sponsor has responded to this view (in response to *Question posed by clinical evaluator* see Extract from the CER, Attachment 2).

The sponsor states '*patients who failed one round of IST were included in the pivotal trial*'. Study ELT112523 shows that (a) all patients received ≥ 1 prior IST; (b) 84% received ≥ 2 prior ISTs; (c) 33% received ≥ 3 prior ISTs. So, most data are from subjects who received ≥ 2 prior ISTs. It is not clear how many subjects have received > 1 line of therapy (that is, if a line of therapy is considered to be, for example, CsA + ATG).

Questions to sponsor

5. *Given CsA and ATG may be used together, initially or as a second course, can prior ISTs be re-analysed according to 'line of therapy' ('line' implying use of one or more agents)?*

That is, how many patients in the pivotal study had only one prior line of therapy (for example, combined CsA and ATG)? How many had two prior lines (for example, initial CsA and ATG, then a repeat course; or initial CsA and ATG, then alemtuzumab)? How many had 3+ prior lines of therapy?

This is not immediately clear from inspection of the ELT112523 study report.

6. *Could the primary efficacy outcome be presented for subjects who had only 1 prior line of IST, 2 prior lines, or 3+ prior lines?*

It seems likely most patients in the pivotal study had tried ≥ 2 lines of IST (the sponsor has been asked to confirm this). Even given the rarity of SAA and the acceptance that sample size in pivotal studies cannot be large, there are too few patients treated with 1 prior line of IST to characterise efficacy and safety of eltrombopag clearly in that group.

The sponsor argues that only a minority of subjects respond to a second line of IST but earlier the sponsor suggested that a second course of IST (ATG/CsA or alemtuzumab) allows haematologic response in 21 to 37% of patients. Cross-study comparison is difficult, as noted by the evaluator.

It is very likely patients eligible for allogeneic SCT would not have enrolled in this study. It seems reasonable to exclude such patients from the indicated population on the basis that efficacy and safety of eltrombopag has not been characterised in that patient group. The EU indication, but not the US indication, has adopted that approach.

Questions for ACPM

1. *Does eltrombopag have a positive benefit/risk balance in SAA patients, and if so, what is the most appropriate wording for the indication?*

Summary of issues

Severe aplastic anaemia is very rare. The dataset in support of this extension of indication was limited, for example very few patients were studied and the studies were at a single centre and uncontrolled.

One key issue is whether the SAA indication should be broad (as proposed by the sponsor) or narrow (as argued by the clinical evaluator). Informing this issue, the pivotal study enrolled n = 43 patients, but most of these patients, it appears, had failed more than one prior line of immunosuppressive therapy. This is being confirmed with the sponsor.

New cytogenetic abnormalities were detected in a number of patients in the pivotal study. For example, 5/43 patients were found to have new (post-baseline) chromosome 7 changes, all within 12 to 16 weeks of starting eltrombopag. One of these five patients went on to be diagnosed with hypocellular MDS which was fatal. The role of eltrombopag is unclear.

Proposed action

The proposed new use may be approvable with a modified indication, subject to ACPM advice.

Request for ACPM advice

1. *Does eltrombopag have a positive benefit/risk balance in SAA patients, and if so, what is the most appropriate wording for the indication?*
2. *Are any other approaches required to strengthen long-term follow-up for new cytogenetic abnormalities/haematological malignancies?*

Product information

Novartis accepts all of the recommended changes proposed by the Delegate and have revised the proposed product information accordingly.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Revolade tablets containing 25 mg, 50 mg and 75 mg of eltrombopag to have an overall positive benefit-risk profile for the proposed indication;

Revolade is indicated for the treatment of:

- *adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.*

In making this recommendation the ACPM was of the view that a broader indication similar to that proposed for the USA and Canada was more appropriate to allow more flexibility for the prescribing physician.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does eltrombopag have a positive benefit/risk balance in SAA patients, and if so, what is the most appropriate wording for the indication?*

The ACPM advised that there is sufficient evidence that eltrombopag has a positive benefit/risk balance. The ACPM noted that the indication proposed by the evaluator was possibly too prescriptive and would not allow for flexibility when evidence from ongoing studies is provided. The ACPM noted that eltrombopag might be useful as a relatively non-toxic bridge to transplant while a donor is being worked up or planning is underway. Therefore, the ACPM advised that the indication should not include reference to 'patients in whom an allogeneic stem cell transplant is not feasible or inappropriate' as proposed by the evaluator as this may limit eltrombopag's use. The ACPM considered as eltrombopag will be prescribed only by specialists, that the broader indication as proposed by the sponsor is more appropriate and allowed more flexibility for prescribers.

2. *Are any other approaches required to strengthen long-term follow-up for new cytogenetic abnormalities / haematological malignancies?*

The ACPM advised that ongoing studies will provide further information on the cytogenetic abnormality issue. The ACPM noted that the Australasian Leukaemia and Lymphoma Group (ALLG) already have a registry for aplastic anaemia so there is no need for another registry. The ACPM advised that the RMP proposed by the sponsor is acceptable.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Revolade containing eltrombopag for the new indication

For the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.

Specific conditions of registration applying to these goods

The Revolade EU-RMP Version 33 (dated 27 July 2015, DLP 12 February 2015) and Australian Specific Annex (ASA) Version 2.1 (dated 10 September 2015), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Revolade at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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