Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eltrombopag

Proprietary Product Name: Revolade

Sponsor: GlaxoSmithKline Australia Pty Ltd

December 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Major Variation (Extension of Indications)
Decision:	Approved
Date of Decision:	27 August 2013
Active ingredient(s):	Eltrombopag Olamine
Product Name(s):	Revolade
Sponsor's Name and Address:	GlaxoSmithKline Australia Pty Ltd (GSK) 436 Johnston Street Abbotsford Victoria 3067
Dose form(s):	Tablets
Strength(s):	25 mg, 50 mg and 75 mg
Container(s):	Blister pack
Pack size(s):	14, 28 or 84 tablets.
Approved Therapeutic use:	Revolade is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
Route(s) of administration:	Oral
Dosage:	Revolade dosing regimens must be individualised based on the patient's platelet counts. See Product Information Attachment 1.
ARTG Number (s)	158356, 158419 and 200121

Product background

Revolade (eltrombopag) is a thrombopoietin (TPO) receptor agonist. Since July 2010, Revolade 25 mg and 50 mg tablets have been approved by the TGA for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd to extend the indications of Revolade® to include the treatment of thrombocytopaenia in adult patients with chronic hepatitis C virus (HCV) infection to enable the initiation of interferon-based

therapy and during interferon-based therapy. The sponsor also sought to add two new strengths (75 mg and 100 mg tablets) to the registration.

The proposed additional indication is as follows:

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia:

- *To enable the initiation of interferon-based therapy*
- *During interferon-based therapy.*

A new maximum oral dose of 100 mg/day is proposed for the new indication as compared to 75 mg/day for the existing indication. The proposed starting dose is 25 mg once daily. The dose would need to be adjusted to achieve the minimum target platelet count necessary to maintain full-dose antiviral therapy, up to a maximum dose of 100 mg once daily.

The sponsor also proposed changes for the 25 mg and 50 mg tablets to ensure consistent quality details for all 4 strength tablets (see *Quality findings* below for details).

Regulatory status

The product received its initial the Australian Register of Therapeutic Goods (ARTG) Registration on 16 July 2010.

Eltrombopag, with the trade name of Promacta, is approved by the FDA for the following indications:

Promacta is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Promacta is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy

Product Information

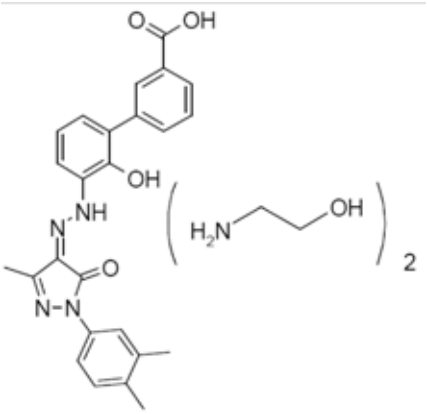
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Introduction

Blister pack of film coated tablets containing Eltrombopag 25 mg and 50 mg were originally (and are currently) marketed in Australia by GlaxoSmithKline Australia Pty Ltd (GSK) under the tradename of Revolade (AUST R 158419 and 158356, respectively). The figure below shows the chemical structure of this compound.

Figure 1. Chemical structure of eltrombopag



GSK has in this application sought to register two new strengths Revolade 75 mg and 100 mg (Eltrombopag) tablets.

GSK also applied for the following changes to the current approved details for the 25 mg and 50 mg tablets and these changes are required to ensure consistent registered details for all four strength tablets.

- Minor change to drug substance specification to tighten the drug related impurities content (by Liquid chromatography–mass spectrometry (LC-MS)).
- Increase drug product shelf life from 36 months to 48 months.

Drug substance (active ingredient)

The active pharmaceutical ingredient (API) manufacturer is no longer manufacturing eltrombopag API for the 75 mg and 100 mg tablet strengths.

GSK is applying for the minor change to the drug substance specifications to tighten the drug related impurities and this will be evaluated below. Otherwise the chemistry, manufacture and stability of the drug substance are the same as previously approved for Revolade Eltrombopag 25 mg and 50 mg film coated tablets, therefore no further assessment of these parts for the drug substance of eltrombopag was required in this report.

Quality control of the drug substance applied by finished product manufacturer

A copy of the amended specification for the drug substance eltrombopag olamine has been provided to include an additional LC-MS test and limit of no more than (NMT) 5 µg/g for the drug-related impurities. This test is a *limit test*.

Validation data including specificity, accuracy, quantitation limits and robustness have been provided and were acceptable for the (LC-MS) limit test.

Certificates of Analysis generated on three commercial scale batches sourced from each API manufacturers were provided. The results of two impurities comply with the proposed acceptance limits of NMT 5 µg/g.

The impurities are controlled to below the "*Threshold of Toxicological Concern*" (TTC) of 1.5 µg/day in the drug substance. Based on the maximum daily dose of eltrombopag as free acid is 100 mg for the treatment of thrombocytopenia in adults with HCV infection, a limit of < 5 µg/g is proposed, which equates to a maximum exposure of 1.5 µg/day for a daily dose of 300 mg eltrombopag free acid. In addition, results of 17 commercial batches showed that the combined level in drug substance is below the TTC. This was considered acceptable.

The company proposed that testing of impurities on a routine basis will be discontinued provided that the results of a total of 30 batches are satisfactory but batches will comply if tested. This was considered acceptable.

The company indicated that solutions of impurity reference standards at the target analyte level (TAL) in diluents have been used in the limit test, however the certificates of analysis for the reference standards have not been provided and this should be sought with the company.

Drug product

The tablets are packaged in blisters composed of polyamide/aluminium foil//polyvinyl chloride (PVC) laminate sealed with a 20 μm aluminium foil lidding with a vinyl acrylic seal coating.

Eltrombopag olamine is the bis-monoethanolamine salt of eltrombopag (free acid). The conversion factor from salt to free acid is 0.784, based on the molecular weights of the free acid (442.5) and the salt (564.6).

GSK indicated that an internal GlaxoSmithKline standard is applied.

Water, Purified, used in the granulation and film coating processes, is removed by drying.

Magnesium stearate is of vegetable origin.

The tablets contain the following excipients; Hypromellose, Titanium Dioxide, Macrogol and Polysorbate 80 (all European Pharmacopiea).

The cores of the four tablet strengths are direct scales while the extra-granular components are different to enable the same weight for these strengths. No cellulose has been used in the 100 mg tablet extra granular formulation and the quantity of sodium starch glycolate (type A) is slightly lower than other strengths. This will be further assessed later.

Biopharmaceutics

No justification has been submitted for not supplying of bioequivalence data for the 75 mg and 100 mg tablets.

It was noted that the summary for the bioequivalence Study TRA102863 was previously assessed to compare the relative bioavailability between multiple Phase 2 tablets of 25 and 50 mg tablets and single strength Phase 3 eltrombopag tablets of 50 mg, 75 mg and 100 mg. No additional bioavailability data were submitted with the present submission.

The following aspects comply with the requirements in Section 2 of ARGPM Appendix 15[1] for the new strengths of an already registered product:

- the biopharmaceutic studies have been performed with the original products of 25 and 50 mg tablets,
- the same granules are used in all four strengths.
- both products are produced by the same manufacturer at the same site.

However, the following aspects do not comply with the requirements in Section 2 of ARGPM Appendix 15[1]:

- it is not clear whether the pharmaceutics of the drug eltrombopag are linear within the therapeutic dose range,

[1] <http://www.tga.gov.au/pdf/pm-argpm-ap15.pdf>

- only *in-vitro* dissolution profiles (pH 6.8) for the eltrombopag tablet batches used in clinical studies have been provided. However no similarity factor f_2 results have been provided, nor have the dissolution profiles in pH 1.2 and pH 4.5 dissolution media utilising the same dissolution conditions to demonstrate the dissolution rate *in vitro* is essentially the same.

Therefore the company should be requested to provide justification for not providing the biopharmaceutic data for the 75 mg and 100 mg tablets. The company should address all of the points in Section 4 of Appendix 15 of the ARGPM.

Quality summary and conclusions

Summary of initial evaluation

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Primary assessment

A number of significant deficiencies in the application data were identified during the initial assessment, as follows:

Drug substance

1. Please provide the certificates of analysis for the reference standard used in the limit test.

Drug product

1. Please provide confirmation that the analytical methods for assay, related substances, identification and dissolution for the new strength 75 mg and 100 mg eltrombopag tablets are the same as those methods which have been previously evaluated for the registration of 25 mg and 50 mg eltrombopag tablets apart from preparation procedures.
2. Please provide commitment that one commercial batch of each strength per year will be placed on long term stability trials.
3. Please explain why the dissolution testing was performed using dissolution medium containing polysorbate 20 rather than the proposed polysorbate 80 in some cases in the stability studies.

Pharmacokinetics and biopharmaceutics

1. Please provide justification for not providing the biopharmaceutic data for the 75 mg and 100 mg tablets. The justification should address all points in section 4 of Appendix 15 of the ARGPM.

Conclusion from the initial evaluation

Registration of the product for distribution in Australia was not recommended until each of these issues was satisfactorily resolved.

Response to questions

In a letter dated 20 March 2013 the company responded to the questions raised in the by the TGA.

1. A certificate of analysis has been provided for the reference material of the impurity substance.
2. The analytical methods for assay, related substances, identification and dissolution are the same for the new, 75 mg and 100 mg, tablets as for the already registered 25 mg and 50 mg tablets.
3. During each year that the product is manufactured post approval, one production batch of each tablet strength will be incorporated into the ongoing stability program.
4. Dissolution testing of some stability samples using polysorbate 20 instead of polysorbate 80 was due to laboratory error. However, stability samples at time points either side of the erroneous tests confirmed that there is no trend in dissolution rate during tablet storage.
5. GSK stated that the 25 mg and 50 mg tablets are currently approved for the ITP indication. The current application seeks approval for the use of 25 mg, 50 mg, 75 mg and 100 mg tablets in the HCV indication. The application is based on pivotal clinical studies using all four strength tablets. As the new 75 mg and 100 mg tablets are not proposed for use in the ITP indication, GSK does not consider the 75 mg and 100 mg tablets as new strengths. However, the PI allows doses up to 75 mg in the ITP indication and does not preclude the use of the 75 mg tablet for this purpose. In any case, even for a single indication, bioequivalence across all proposed dosage strengths should be established.
6. The company has now provided comparative dissolution profiles for the four strengths of tablet using the routine quality control dissolution method. While the three lower strength tablets show similar dissolution profiles, the 100 mg tablet dissolves significantly more slowly, although by the 30 minute time point the extent of dissolution is the same as the three lower strengths. Comparative dissolution profiles have not been provided at lower pH (for example, pH 4.5 and 1.0) because of incomplete dissolution under those conditions. Given these dissolution results and the fact that the same drug granules are used in the manufacture of all four tablet strengths, it is considered unlikely that significant differences in bioavailability would arise when the different strength tablets are administered at the same dose.

   Clinical aspects of the company's response to this question should be assessed by the clinical evaluator.

Recommendations

There are no objections in respect of chemistry, manufacturing and controls to registration of 75 mg and 100 mg eltrombopag tablets.

The company's justification for not submitting bioequivalence studies on the 75 mg and 100 mg tablets versus the existing 25 mg and 50 mg tablets (see Point 5, above) should be assessed from a clinical perspective.

III. Nonclinical findings

Introduction

No nonclinical data were provided to support the new indication or additional strengths. The focus of this assessment is in regard to the safety of the higher proposed dose, resulting in higher systemic exposures (area under the concentration time response curve

(AUC) increase from 168 to 354 µg.h/mL and peak plasma concentration (C_{max}) increase from 12.7 to 19.2 µg/mL) in the proposed patient group.

The original nonclinical evaluation report for eltrombopag olamine highlighted several concerns regarding the then submitted dossier. The toxicological profile did not include receptor-mediated toxicities; however, based on data available at the time, the safety profile of eltrombopag appeared to be inferior to the other registered thrombopoietin (TPO) receptor agonist, romiplostim, with the following potentially clinically relevant findings:

- *In vitro* indications of cardiotoxicity at concentrations below the expected clinical C_{max};
- Hepatic toxicity at doses resulting in exposures similar to that expected clinically;
- Increased incidence of cataracts with chronic administration at doses resulting in exposures similar to the clinical exposure; and
- Evidence of renal toxicity in mice at systemic exposures similar to that anticipated clinically.

Due to deficiencies in the nonclinical dossier and the numerous adverse findings, an acceptable safety profile was considered not to have been demonstrated in the submitted nonclinical dossier for the proposed product (Eltrombopag olamine, Revolade®).

As the systemic exposures are higher with the proposed new indication, the above findings remain a concern. Of particular relevance to the proposed patient group is the incidence of hepatotoxicity, which warranted a black box warning on the FDA Product Information. An excerpt from the previous Nonclinical Evaluation Report is shown below with exposure ratios adjusted for the new indication:

"Hepatotoxic effects included centrilobular vacuolation in mice that had received 100 mg/kg/day (ER_{AUC}=2.9[2]), centrilobular degeneration and necrosis in rats at 60 mg/kg/day (ER_{AUC}=2.9) and hepatocellular hypertrophy in both rats and dogs at exposure ratios (based on AUC) 1.9 and 3.8-fold the anticipated clinical exposure, respectively. These microscopic changes in the liver were accompanied by increased serum ALP[3] and ALT[4] levels(up to 16-fold) in rats and/or dogs. These findings were reversible when treatment was ceased. The mechanisms underlying the hepatotoxic effects are not clear from the submitted animal studies. Although increased CYP450 levels (specific enzymes not identified) were reported in the liver of rats treated with ≥100 mg/kg/day eltrombopag for 4 days and dogs treated with 30 mg/kg/day for 14 days, this finding could not fully explain the hepatic changes observed in the toxicity studies (centrilobular degeneration and necrosis as well as elevated ALP and ALT levels). ... the observed hepatic changes are more indicative of hepatotoxicity, rather than adaptive changes in the liver. The NOEL[5] for hepatic toxicity in mice, rats and dogs was below the anticipated clinical exposure (based on AUC). Caution should therefore be exercised when eltrombopag is used in clinical practice."

Nonclinical summary and conclusions

- No nonclinical data were provided to support the new indication.
- The higher daily dose in the new patient group results in higher exposures (2.1 times and 1.5 times the clinical AUC and C_{max}, respectively) compared to the currently-registered dose to ITP patients. This indicates a potential increase in adverse effects compared to the currently-registered indication.

[2] ER_{AUC}, exposure ratio based on animal to human $AUC_{0\text{-}24h}$ values.
[3] ALP=Alkaline phosphatase
[4] ALT=Alanine aminotransferase
[5] NOEL=No observable effect level

- Toxicities observed in animal/*in vitro* studies at clinically relevant doses/concentrations included: cardiotoxicity, hepatotoxicity, cataract formation and renal toxicity.
- Based on nonclinical data, an adequate safety profile is not considered to have been demonstrated for the proposed new indication and new maximum dose.
- The nonclinical evaluator proposed amendments to the proposed Product Information document should the extension of indication and increase in dose be approved on clinical grounds but these are beyond the scope of this AusPAR.

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

Eltrombopag olamine is an orally bioavailable, small molecule thrombopoietin receptor (TPO-R) agonist. TPO-R receptor agonists function in a similar manner to endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag works as a supportive care agent to increase the platelet count prior to and throughout interferon-based treatment of HCV infection, to give patients with advanced fibrosis or cirrhosis an opportunity to initiate and help optimise and maintain the dose and duration of their antiviral therapy, thereby improving the likelihood of achieving sustained virologic response (SVR). The importance of SVR is reflected by a 4 to 10 fold decrease in mortality and a 2 to 4 fold decrease in the incidences of decompensated liver disease and hepatocellular carcinoma in HCV patients compared to patients with persistent HCV infection. Even for patients who have developed hepatic decompensation, achieving SVR prior to liver transplantation can improve outcomes after transplantation by avoiding HCV recurrence.

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies.
- 1 other efficacy/safety studies.
- Supporting information including pooled analyses and Periodic Safety Update Reports (PSURs).

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Information provided by the sponsor indicated that all studies were undertaken in accordance with standard operating procedures of the sponsor, which comply with the principles of Good Clinical Practice. All studies were 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 authorities.

Pharmacokinetics

Studies providing pharmacokinetic data

Results from clinical biopharmaceutics studies were provided in the original marketing authorisation application (MAA) to support eltrombopag use in adult patients with chronic idiopathic thrombocytopenic purpura. No additional clinical biopharmaceutics studies were completed for this application. Pharmacokinetic data provided was limited to some information on drug-drug interactions (concurrent administration of peginterferon alfa-2a + ribavirin or peginterferon alfa-2b + ribavirin) and some information on pharmacokinetics in the target patient population. For the latter, plasma eltrombopag concentration-time data collected in 635 subjects with chronic HCV infection in the Phase II study TPL102357 and the Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from 28 healthy adult subjects (from the Phase I study SB-497115/002, previously submitted) in a population PK analysis.

Evaluator's overall conclusions on pharmacokinetics

Eltrombopag was approved for use in Australia in July 2010. As such, the pharmacokinetics for this medication have been extensively characterised and considered previously. In this application, additional information was provided on pharmacokinetics in the target population only. This information was obtained from the clinical efficacy studies and also encompassed the pharmacokinetics of the proposed new strengths, 75 mg and 100 mg.

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%. Eltrombopag is highly bound to human plasma proteins (> 99.9 %). Eltrombopag is a substrate for BCRP[6] but is not a substrate for P-glycoprotein or OATP1B1[7]. Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione or cysteine. Minor metabolites, each accounting for < 10% of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabelled eltrombopag, it is estimated that approximately 20% of a dose is metabolised by oxidation. Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26-35 hours in ITP patients.

Plasma eltrombopag concentration-time data collected in 635 subjects with chronic HCV infection in the Phase II study TPL102357 and the Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from 28 healthy adult subjects (from the Phase I study SB-497115/002) in a population PK analysis. Plasma eltrombopag

[6]BCPR=ATP-binding cassette sub-family G member 2 is a protein that in humans is encoded by the ABCG2 gene.

[7]OATP1B1=Solute carrier organic anion transporter family member 1B1 is a protein that in humans is encoded by the SLCO1B1 gene

concentration over time was accurately predicted for all dosages, including the proposed 75 mg and 100 mg tablets.

Pharmacokinetic data on special populations including renal impairment, hepatic impairment, race, gender and elderly population were provided. These appears to be consistent with previous experience with this medication.

Eltrombopag has the potential to affect the pharmacokinetics of co-administered drugs that are substrates of CYP2C8, CYP2C9, UGTs, OATP1B1 or BCRP. A clinical drug-drug interaction study between eltrombopag and boceprevir or telaprevir had not been conducted at the time of this evaluation. From the efficacy studies provided, plasma eltrombopag exposure was not altered by concurrent administration of peginterferon alfa-2a + ribavirin or peginterferon alfa-2b + ribavirin and plasma peginterferon alfa-2a and alfa-2b exposures were not altered by concurrent administration of eltrombopag.

Pharmacodynamics

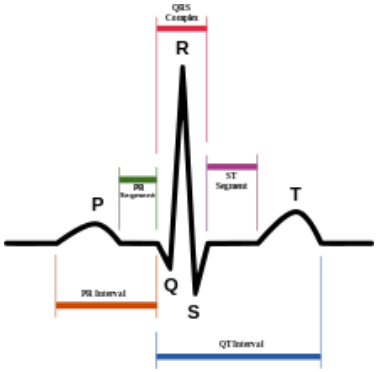
Studies providing pharmacodynamic data

No specific pharmacodynamics studies were provided. Information on the pharmacodynamics of eltrombopag was available from the previous submission. In addition, specific analyses were conducted to characterise the relationship between plasma eltrombopag exposure and platelet response in subjects with chronic HCV infection and the relationship between plasma eltrombopag exposure and QTc[8] in patients with chronic HCV infection.

Evaluator's overall conclusions on pharmacodynamics

The mechanism of action of eltrombopag has been well characterised from previous submissions. Thrombopoietin (TPO) is the main cytokine involved in regulation of megakaryopoiesis and platelet production and is the endogenous ligand for the thrombopoietin receptor (TPO-R). Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag differs from TPO with respect to the effects on platelet aggregation. Unlike TPO, eltrombopag treatment of normal human platelets does not enhance adenosine diphosphate (ADP) induced

[8] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval).To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated. A graphic tracing of the variations in electrical potential caused by the excitation of the heart muscle and detected at the body surface is shown here.



aggregation or induce P-selectin expression. Eltrombopag does not antagonise platelet aggregation induced by ADP or collagen.

To assess the pharmacodynamics of eltrombopag, a population pharmacokinetic (PK)/pharmacodynamic (PD) model was constructed in a step-wise fashion. Initially, a PK/PD model was developed based on data from eltrombopag mono-therapy to characterise the stimulatory effect of eltrombopag on platelet counts. The model was then extended to incorporate the inhibitory effects of IFN (alfa-2a and alfa-2b) by including data from antiviral therapy in the modelling. Due to a lack of serum concentrations of IFN alfa-2a and IFN alfa-2b in the majority of patients, a kinetic-pharmacodynamic (KPD) modelling approach was used to characterise the inhibitory effect of IFN on platelet counts during antiviral therapy. The plasma eltrombopag concentration was related to the increase in production ate of platelet precursors (KIN) through an maximum effect (E_{max}) relationship, with 50% of maximum stimulation achieved at the eltrombopag concentration (EC_{50}) of 29 μg/mL. The estimated maximum effect was a 15.4 to fold increase in platelet production. The inhibitory effect of peginterferon on platelet production was linearly associated with peginterferon concentrations. This modelling allowed for a prediction of required starting dose for eltrombopag and requirement for dose adjustment during treatment. This modelling was then assessed in the pivotal efficacy studies.

Pharmacodynamic interactions were noted with rosuvastatin, lopinavir/ritonavir, polyvalent cations and food interactions. Eltrombopag demonstrated no clinically significant effect on cardiac repolarisation in patients with HCV infection.

Efficacy

Dosage selection for the pivotal studies

The 25 mg starting dose of eltrombopag administered in ENABLE 1 and ENABLE 2 was based on evidence from the Phase II program (Study TPL102357), in which 75% of HCV-infected subjects receiving the lowest dose of eltrombopag (30 mg) achieved platelet counts >100 Gi/L after the initial 4 week pre-antiviral dosing period. Study TPL102357 used eltrombopag doses of 30, 50 and 75 mg and not the 100 mg dose.

As noted above, PK and PD data showed that repeat, once daily dosing led to platelet count increases after 8 days of dosing and a maximal platelet count response was achieved approximately 2 weeks after the start of dosing. A PK/PD model estimated that 54% of subjects would require an eltrombopag dose of 100 mg to maintain a platelet count >80 Gi/L during peginterferon therapy. Therefore, the 100 mg dose was introduced in the ENABLE 1 and ENABLE 2 studies.

Evaluator's conclusions on clinical efficacy

Information on clinical efficacy for the proposed indication was provided by 2 pivotal studies, ENABLE 1 and ENABLE 2, as well as one supporting study, TPL102357. The pivotal studies had identical study designs and differed only in the pegylated interferon (peginterferon) used. They were global, multicenter, two-part studies that used a randomised withdrawal design. They consisted of an open-label (OL), Pre-Antiviral Treatment Phase (Part 1) and a randomised, double-blind (DB), placebo-controlled, Antiviral Treatment Phase (Part 2). Subjects entered the studies with a platelet count of <75 Gi/L and were stratified at baseline by platelet count, level of HCV RNA at screening and HCV genotype.

During Part 1, all subjects in ENABLE 1 and ENABLE 2 received eltrombopag dosed once daily with the objective of increasing platelet counts to the required threshold to initiate

antiviral therapy (≥90 Gi/L to initiate peginterferon alfa-2a plus ribavirin in ENABLE 1 and ≥100 Gi/L to initiate peginterferon alfa-2b plus ribavirin in ENABLE 2). The starting dose of eltrombopag was 25 mg once daily for 2 weeks. Dose escalations could occur every 2 weeks up to a maximum of 100 mg eltrombopag. The maximal time subjects could receive open-label eltrombopag was 9 weeks. Subjects not randomised to Part 2 were withdrawn from OL eltrombopag and asked to attend the post-treatment follow-up visits. Once eligible for Part 2, subjects in ENABLE 1 and ENABLE 2 were randomised 2:1 to either continue on the same dose of eltrombopag from OL treatment or receive a matched placebo. These DB treatments were given in combination with antiviral therapy for up to 48 weeks (dependent on HCV genotype). All subjects in ENABLE 1 and ENABLE 2 were to attend post-treatment follow-up visits up to 24 weeks. At the 24 week follow-up visit, SVR was assessed to determine the benefit of the completed treatment regimen.

Guidance on assessment of treatment regimes for chronic hepatitis C is provided in the European Union *Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C*.[9] While there is no specific guidance on supportive agents such as eltrombopag , the overall principles in terms of response of HCV to treatment are applicable. The design of the pivotal studies was consistent with these guidelines. As such, sustained virologic response (SVR) was chosen as the primary endpoint for the pivotal studies. A subject was classified as having achieved SVR only if the subject was a responder at the end of treatment and all subsequent planned visits through to 24 weeks follow-up after completing treatment (for HCV genotype subgroups, 24 weeks after completing treatment corresponds to Week 48 for genotype 2/3, and Week 72 for genotype non 2/3 or genotype 2/3 who received 48 weeks of treatment) and if a subject had a positive HCV RNA ("blip") between two visits with undetectable HCV RNA, the subject was considered a sustained virologic responder provided that the detectable HCV RNA was of the same order of magnitude as the limit of detection. Both pivotal studies were adequately powered to provide statistically meaningful results.

Both studies demonstrated that a greater proportion of eltrombopag subjects achieved SVR than did placebo subjects and this result was statistically significant. In the pooled results, a clinically meaningful and statistically significantly greater proportion of patients treated with eltrombopag achieved SVR compared to the placebo arm (placebo: 13%; eltrombopag: 21%; p=0.0004). The response to eltrombopag during OL treatment (Part 1) was similar in both studies with 97% and 96% of subjects in ENABLE 1 and ENABLE 2, respectively, achieving a platelet count that would allow the initiation of antiviral therapy. Platelet counts began to rise within the first week of treatment with eltrombopag and the median time to achieve the target platelet count (≥90 Gi/L for ENABLE 1 or ≥100 Gi/L for ENABLE 2) was about 2 weeks, with over 75% of subjects achieving these target platelet counts within the first 4 weeks of treatment. At the end of treatment, 48% (ENABLE 1) and 38% (ENABLE 2) of subjects randomised to the eltrombopag arm were HCV RNA negative, significantly more than in the respective placebo arms (37% for ENABLE 1and 23% for ENABLE 2).

TPL102357 was a double-blind, randomised, placebo-controlled, multi-centre, dose-ranging, parallel group, Phase II study to assess efficacy, safety/tolerability and pharmacokinetics of a thrombopoietin receptor agonist, SB-497115-GR (eltrombopag), when administered as 30, 50, and 75 mg once daily for 16 weeks in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with pegylated interferon and ribavirin. A total of 74 subjects were enrolled, despite the statistical plan allowing for 160 subjects. No rationale for this was stated and only limited information on this study was provided. Eltrombopag increased platelet counts to

[9]EMEA/CHMP/51240/2011.
<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102109.pdf>

≥100Gi/L at Week 4 in a dose-dependent manner; 0/18 (0%, placebo), 9/12 (75%, 30 mg), 15/19 (79%, 50 mg) and 20/21 (95%, 75 mg) evaluable subjects achieved the primary endpoint (p<0.0001 for treatment effect). Given the above statistical limitations, this should be interpreted with caution.

Safety

Studies providing evaluable safety data

Pivotal studies that assessed safety as a primary outcome were not provided.

The following studies provided evaluable safety data:

- Pivotal efficacy studies. The following safety data were collected

  Assessment of safety and tolerability of eltrombopag in comparison with placebo, as measured by the nature and frequency of adverse events (AEs), laboratory abnormalities, ocular examinations, 12-lead electrocardiograms (ECG).

- Dose-response and non-pivotal efficacy studies provided safety data, as follows;

  Study TPL 102357 provided data on monitoring of adverse events and laboratory analyses performed throughout the course of the study, including complete blood counts with differentials, blood chemistries, urinalysis, ECGs, vital signs, spleen examinations and qualitative and quantitative toxicities associated with this treatment regimen. Ocular examinations were completed throughout the study. Subjects completed a follow-up visit 4 weeks after the last eltrombopag dose. Subjects were also followed up 6 months post last dose of study medication for assessment of any ocular changes. In addition, blood samples were collected for pharmacokinetic analysis.

No other studies evaluable for safety only were submitted.

Patient exposure

The following tables describe the patient exposure to eltrombopag.

Table 1. Tabulation of subjects contributing to the Safety Analysis of eltrombopag.

GSK Study Number	Open-label Study Treatment	Double-Blind Study Treatment	
		Placebo	Eltrombopag
TPL103922 (ENABLE 1)	715	232	449
TPL108390 (ENABLE 2)	805	252	506
TPL102357 Part1	NA	18	56
TPL102357 Part2	NA	2	45

Table 2. Description and dosing of studies evaluating eltrombopag therapy in HCV.

GSK Study Number	Study Design / Primary Objective	Dosing and Administration	Randomized
Pivotal Phase III Studies			
TPL103922 (ENABLE 1)	Part 1: OL pre-antiviral treatment phase Part 2: DB, randomized, placebo controlled antiviral treatment phase, Improvement in SVR for eltrombopag compared to placebo, measured 6 months post last dose of all investigational products.	Part 1: Eltrombopag 25 mg, 50 mg, 75 mg and 100 mg; daily oral dosing until platelets ≥90Gi/L, with dose escalation every 2 weeks up to a maximum 9 weeks of treatment Part 2: Eltrombopag dose from Part 1 or matching placebo; daily oral dosing in conjunction with pegIFN (alfa-2a)+ribavirin antiviral therapy for up to 48 weeks	OL phase: Eltrombopag 716[a] DB phase: Placebo:232 Eltrombopag: 450[b]
TPL108390 (ENABLE 2)	Part 1: OL pre-antiviral treatment phase Part 2: DB, randomized, placebo controlled antiviral treatment phase, Improvement in SVR for eltrombopag compared to placebo, measured 6 months post last dose of all investigational products.	Part 1: Eltrombopag 25 mg, 50 mg, 75 mg and 100 mg; daily oral dosing until platelets ≥100Gi/L, with dose escalation every 2 weeks up to a maximum 9 weeks of treatment Part 2: Eltrombopag dose from Part 1 or matching placebo; daily oral dosing in conjunction with pegIFN (alfa-2b)+ribavirin antiviral therapy for up to 48 weeks.	OL phase: Eltrombopag:805 DB phase: Placebo:253[b] Eltrombopag: 506
Supportive Phase II Study			
TPL102357	Part 1: DB, randomized, placebo controlled parallel group study, Increase in platelets to ≥70Gi/L or ≥ 100Gi/L by Week 4.	Part 1: Eltrombopag 30 mg, 50 mg, 75 mg or matching placebo; daily oral dosing for 4 weeks Part 2: Eltrombopag 30 mg, 50 mg, 75 mg or matching placebo; daily oral dosing in conjunction with pegIFN (alfa 2a or alfa 2b) +ribavirin antiviral therapy for 12 weeks	Part 1: Placebo: 18 Eltrombopag: 56 Part 2: Placebo: 4[c] Eltrombopag: 45

a. One subject in ENABLE 1 randomized to Part 1 did not receive OL treatment. This subject is not included in the Safety OL Population.
b. One subject in each of the ENABLE 1 and ENABLE 2 studies randomized to Part 2 did not receive DB treatment. These 2 subjects are not included in the Safety DB Population but are included in the ITT Population.
c. Two placebo subjects in TPL102357 were enrolled in Part 2 in error and were withdrawn.

Table 3. Safety populations

	TPL103922 (ENABLE 1)		TPL108390 (ENABLE 2)		TPL102357		
Study Population	Part 1	Part 2	Part 1	Part 2	Part 1	Part 2	Total
Safety OL Population	715	--	805	--	--	--	1520
Safety DB Population	--	681	--	758	--	--	1439
Safety Phase II/III Population	--	681	--	758	--	47	1486
Overall Safety Population	715	--	805	--	56[a]	--	1576
Intent-to-Treat Population	--	682	--	759	--	--	1441

a. 74 subjects were enrolled in Part 1 of study TPL102357 but only the 56 subjects who received eltrombopag are included in the Overall Safety Population

Postmarketing experience

Eltrombopag was first approved for marketing in the US on 20 November 2008 for the treatment of thrombocytopenia in patients with chronic ITP. Based on latest data available from IMS (Intercontinental Medical Statistics) Health data, it is estimated that approximately 6,664 patient years of eltrombopag treatment have been prescribed worldwide as of December 2011. This calculation is based on available sales information volume and assumes a once-daily dose of 12.5 mg, 25 mg, 50 mg or 75 mg tablets.

As of 31 March 2012, there were 2261 spontaneous and post marketing cases received from marketed use of eltrombopag. A total of 5215 spontaneous and post marketing AEs (serious and non serious) have been received from the marketed use of eltrombopag (2261 cases). A summary of adverse events appears below.

Table 4. Ten most frequent reported adverse events from spontaneous and postmarketing surveillance cases.

MedDRA Preferred Term	Adverse Events n(%)
All Preferred Terms	5215 (100)
Drug ineffective	865 (16.6)
Death	162 (3.1)
Platelet count decreased	152 (2.9)
Thrombocytopenia	73 (1.4)
Fatigue	65 (1.2)
Platelet count increased	64 (1.2)
Nausea[a]	63 (1.2)
Deep vein thrombosis[a]	61 (1.2)
Headache	56 (1.1)
Liver function test abnormal[a]	51 (1.0)
Idiopathic thrombocytopenic purpura	50 (1.0)

a. Adverse events included in the eltrombopag Core Safety Information.

MedDRA = Medical Dictionary for Regulatory activities

As of 31 March 2012, there were 489 cases with a fatal outcome out of the 2261 cases reported from marketed usage of eltrombopag. A review of these cases of death reveals no significant new safety findings associated with the use of eltrombopag. In terms of hepatotoxicity, there were 206 cases identified in this search of the worldwide clinical safety database from 20 November 2008 through 31 March 2012. In general, most cases describe mild and transient elevations in liver function parameters, which resolved or improved following eltrombopag discontinuation or dose reduction. Some cases were of severe liver injury or liver failure in the setting of other co-morbid conditions such as sepsis leading to multi-organ failure or worsening liver function in patients with pre-existing liver disease (hepatitis, cirrhosis).

There were 210 cases reviewed that pertained to thromboembolic events from first approval of eltrombopag for chronic ITP in 20 November 2008 through 31 March 2012. The most frequently reported events in these 210 cases were deep vein thrombosis (58), pulmonary embolism (48), myocardial infarction (22), thrombosis (20), cerebrovascular accident (15), acute myocardial infarction (9) and portal vein thrombosis (9). The outcomes of the 210 cases were improved/resolved (81), resolved with sequelae (3), unresolved (24), worse (1), fatal (34) and unknown (67). The patients with a fatal thromboembolic event had multiple co morbidities including congestive heart failure, leukemia, diabetes, hypertension, coronary artery disease, carotid arterial stenosis and hyperlipidemia. In conclusion, an overall review of cases of thromboembolic events (TEEs) does not suggest any new trends or changes in incidence or severity of TEEs.

Safety issues with the potential for major regulatory impact

Liver toxicity

During the double-blind (DB) Phase on-treatment plus 30 day follow-up period, a higher proportion of eltrombopag subjects reported hepatobiliary events compared with placebo subjects. However, the proportion of AEs that led to withdrawal or were considered serious were similar for eltrombopag treated and placebo treated subjects. In addition, the majority of AEs resolved in both treatment groups.

In this patient population, 2 types of hepatobiliary events were noted to be of particular relevance: drug induced liver injury (DILI) and events suggestive of hepatic decompensation. The data do not indicate eltrombopag as a cause for DILI in this study. DILI requires evidence of hepatocellular injury (that is, greater incidence of alanine aminotransferase (ALT) >3 times the upper limit of normal (xULN) in the treatment group than in the control group. A greater incidence of ALT >3x ULN was observed in the placebo group than in the eltrombopag group.

The safety results from this section show that hepatobiliary adverse events, events suggestive of hepatic decompensation and hepatobiliary laboratory abnormalities are common in the patient population studied, as expected for patients with HCV-induced liver cirrhosis. Safety findings reported more frequently on the eltrombopag-treatment group included events suggestive of hepatic decompensation, such as ascites and hepatic encephalopathy. The incidence of other events suggestive of hepatic decompensation (HCC and death), was similar between the treatment groups. It should be noted, however, that hepatic decompensation is a known risk in cirrhotic HCV patients receiving pegylated interferon and that subjects in the eltrombopag group received ≥60% more peginterferon and the median observation time for the eltrombopag group is longer than for subjects in the placebo-treatment group. In addition, events showing a higher frequency in the eltrombopag-treatment group can be observed as a complication of antiviral treatment with peginterferon and ribavirin and represent known complications of chronic HCV-infections occurring over time in patients with HCV-induced liver cirrhosis.

Overall, eltrombopag treated subjects were similar to placebo treated subjects with respect to several measures of hepatic function and prognosis, including Child-Pugh (CP) score, serum albumin values, INR (prothrombin time ratio) values, total bilirubin values and model for end-stage liver disease (MELD[10]) score.

Haematological toxicity

No significant haematological toxicity was noted for eltrombopag.

Serious skin reactions

No significant trend of skin reactions was noted.

Cardiovascular safety

Most subjects who had an ECG recorded at antiviral baseline had normal or abnormal, not clinically significant results. The pattern of ECG results during the DB Phase was similar between the treatment groups, with most subjects having a worst post baseline ECG reading of 'normal' or 'abnormal – not clinically significant' (82% for both placebo and eltrombopag subjects). A greater proportion of eltrombopag subjects were considered to have a clinically significant change from baseline compared with placebo subjects.

Assessment of the potential impact of eltrombopag on the QTc interval in subjects with HCV was incorporated into the Phase III clinical trials (TPL103922 and TPL108390). As a result, eltrombopag is predicted to have no clinically significant effect on QTc intervals at either therapeutic or supratherapeutic dose in HCV subjects.

Unwanted immunological events

No significant trend of unwanted immunological events was noted.

[10]A score that is used to rank the urgency for liver transplant. The worse your liver works, the higher your MELD score and the higher your position on the transplant list.

Evaluator's overall conclusions on clinical safety

Information on clinical safety was available from the pivotal efficacy studies, supporting efficacy study, information previously submitted to TGA and postmarketing surveillance data submitted by the sponsor. There was no specific safety studies submitted.

Interpretation of the safety profile was complicated by the overall health status of the target population, especially those subjects with more severe baseline liver impairment and requiring more intensive therapy (and hence with more side-effects of treatment). In addition, the results from the efficacy studies indicated a proportion of patients who would have been unable to be treated previously because of low platelet counts, who could now be treated more aggressively. Given the role of eltrombopag, as a supportive care agent, patients would tend to receive more intensive anti-viral treatment and hence be more prone to side-effects.

The incidence of AEs in the on-treatment plus 30 days follow-up period was similar between the treatment groups. The most common AEs included anaemia, neutropaenia, pyrexia, fatigue, headache, nausea, diarrhoea, decreased appetite and influenza like illness. In terms of serious AEs (SAEs), there was a 5% higher incidence of SAEs in the eltrombopag group (20%) compared with the placebo group (15%) in the on-treatment plus 30 days follow-up period, for both of the ENABLE studies and also for the pooled data set. The most common SAE in both treatment groups was hepatic neoplasms. SAEs related to the Gastrointestinal (GI) and Hepatobiliary disorders system organ classes (SOC) occurred ≥2% more frequently in the eltrombopag group compared with the placebo group.

With regard to deaths, for the pooled data from the 2 Phase III studies, 39 subjects (3%) with 57 fatal AEs died during the on-treatment plus 6 months follow-up period: 10 (2%) in the placebo group and 29 (3%) in the eltrombopag group. Of these, 8 of the subjects in the placebo group (80%) and 22 of the subjects in the eltrombopag group (76%) had a baseline MELD score ≥10. The most common causes of death in both treatment groups for both studies were events suggestive of hepatic decompensation, such as hepatic failure, variceal bleeding, ascites, GI bleeding and infections.

Thromboembolic/thrombotic complications were observed more frequently in the eltrombopag treatment group than in the placebo treatment group. Reported TEEs included both arterial and venous events, including portal vein thrombosis. The majority of TEEs in eltrombopag subjects resolved and most on-treatment events did not lead to discontinuation from antiviral treatment.

Events suggestive of hepatic decompensation were observed in the ENABLE study population, and more commonly in eltrombopag-treated subjects. Subjects with poor liver function at baseline had a greater risk of hepatic decompensation. Given that hepatic decompensation is a known risk in cirrhotic HCV patients receiving peginterferon therapy, this result was not unexpected.

The incidence and progression of cataracts occurred more frequently in the eltrombopag treatment group compared to the placebo treatment group. This has previously been recognised in the original application.

In terms of postmarketing surveillance, approximately 6,664 patient years of eltrombopag treatment have been prescribed worldwide as of December 2011. A total of 5215 spontaneous and post marketing AEs (serious and non serious) have been received from the marketed use of eltrombopag (2261 cases). No significant trends were identified that would impact on the safety profile of eltrombopag.

First round benefit-risk assessment

First round assessment of benefits

The benefits of eltrombopag in the proposed usage are:

Eltrombopag enabled the introduction of antiviral therapy in 95% of study subjects who would otherwise have been ineligible or poor candidates for peginterferon-based therapy. Both ENABLE studies met the primary endpoint: the pooled ENABLE data showed that the addition of eltrombopag to standard antiviral therapy resulted in a statistically significant and clinically meaningful improvement in SVR (21%) compared with standard antiviral therapy + placebo (13%) (p=0.0004). The benefit offered by eltrombopag treatment is that 1 out of 5 patients who were previously ineligible or poor candidates for antiviral therapy achieved SVR and now have the opportunity to experience the long-term benefits of SVR.

The results were robust and similar across all 3 stratification factors (baseline platelet count, HCV genotype, viral load). There was no meaningful difference in the SVR rates for subjects with <50 Gi/L compared to subjects ≥50 Gi/L. As expected, the SVR rates were higher for HCV genotype 2/3 compared to HCV genotype non-2/3. However, eltrombopag-supported antiviral therapy nearly doubled the SVR rate from 8% to 15% for HCV genotype non-2/3 subjects.

First round assessment of risks

The risks of eltrombopag in the proposed usage are:

The safety profile observed in the ENABLE studies is consistent with the peginterferon/ribavirin safety profile and the established safety profile of eltrombopag. Thrombotic/thromboembolic events, including portal vein thrombosis and occurrence of cataracts are already described in the eltrombopag label. Thrombotic events were reported 2% more frequently in the eltrombopag group compared to the placebo group. There was no clear correlation between platelet counts, duration of treatment with eltrombopag or other direct eltrombopag-specific risk factors and reports of thrombotic events.

Hepatic decompensation is a known side effect of interferon therapy in patients with cirrhosis and was observed in the pivotal studies.

The safety profile was largely influenced by the degree of liver impairment prior to initiating treatment. Subjects with more severe baseline liver impairment had a higher incidence of hepatic decompensation and thromboembolic events.

First round assessment of benefit-risk balance

The benefit-risk balance of eltrombopag, given the proposed usage, was considered to be favourable.

First round recommendation regarding authorisation

Eltrombopag was approved for use in Australia in July 2010 for treatment of adult patients with chronic immune (idiopathic) thrombocytopaenic purpura (ITP) who have had an inadequate response or are intolerant, to corticosteroids and immunoglobulins. This application sought to extend the application to the treatment of thrombocytopenia adult patients with chronic hepatitis C virus (HCV) infection to enable the initiation of interferon-based therapy and also during interferon-based therapy. As such, eltrombopag treatment would raise platelet counts to allow thrombocytopenic HCV subjects to become eligible for the initiation of interferon-based antiviral therapy; and would allow

continuation of antiviral therapy at higher doses with less need for thrombocytopenia-induced dose reductions of interferon, thereby increasing the likelihood of achieving SVR .

The pharmacokinetics and pharmacodynamics of eltrombopag have previously been well characterised. Additional information was provided on pharmacokinetics in the target population, including the proposed new dosage strengths of 75 mg and 100 mg as well as pharmacodynamic modelling in HCV. There were no unexpected trends or adverse findings.

There is no specific European Medicines Agency (EMA) guidance on thrombopoietin agonists, although the need for this has been recognised. EMA guidance does exist on the clinical evaluation of medicinal products for the treatment of chronic hepatitis C. The pivotal efficacy studies reflected this guidance and were appropriately designed and powered to be clinically meaningful. Both studies demonstrated that a greater proportion of eltrombopag subjects achieved SVR than did placebo subjects and this result was statistically significant. The response to eltrombopag during OL treatment was similar in both studies with 97% and 96% of subjects in ENABLE 1 and ENABLE 2, respectively, achieving a platelet count that would allow the initiation of antiviral therapy. Platelet counts began to rise within the first week of treatment with eltrombopag, and the median time to achieve the target platelet count was about 2 weeks, with over 75% of subjects achieving these target platelet counts within the first 4 weeks of treatment. At the end of treatment, 48% (ENABLE 1) and 38% (ENABLE 2) of subjects randomised to the eltrombopag arm were HCV RNA negative, significantly more than in the respective placebo arms (37% for ENABLE 1and 23% for ENABLE 2).

Interpretation of safety results was complicated by the nature of the target population and the impact of a supportive agent (eltrombopag), allowing for more intensive anti-viral treatment than would otherwise be possible. Nonetheless, the safety profile was comparable between treatment and placebo groups. Thromboembolic/thrombotic complications were observed more frequently in the eltrombopag treatment group than in the placebo treatment group. Events suggestive of hepatic decompensation were observed more commonly in eltrombopag treated subjects. Subjects with poor liver function at baseline had a greater risk of hepatic decompensation. The incidence and progression of cataracts occurred more frequently in the eltrombopag treatment group compared to the placebo treatment group. None of these issues were unexpected and surveillance for these conditions is recommended during treatment. Given the nature of the target population, all patients undergoing this treatment for this condition will require close surveillance to reduce morbidity and mortality from both the condition itself and any medication-related effects.

Overall, it was considered that this medication has an acceptable benefit-risk profile and registration was recommended for the proposed indication.

List of questions

No questions were raised by the evaluator.

Second round evaluation of clinical data submitted in response to questions

No second round evaluation was conducted.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

An Australian Specific Annex (ASA) to the European Union (EU) RMP version 15 was created to support the application for the extension of indication. This document supplements the EU RMP which has been included in the application and provides specific information regarding the implementation of pharmacovigilance and risk management activities in Australia. Furthermore, it identifies and explains the reasons for any differences with activities planned overseas, where this is applicable.

The proposed EU indication and that proposed for Australia in this application for Revolade were the same.

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA's Office of Scientific Evaluations (OSE) and the clinical aspects of the SS by the TGA's Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 5 below.

Table 5. Ongoing Safety Concerns

Important identified risks	ITP Hepatotoxicity Thromboembolic Events Post Therapy Reoccurrence of Thrombocytopenia HCV Hepatotoxicity Hepatic Decompensation Thromboembolic Events Portal Vein Thrombosis
Important potential risks	ITP Potential for Increased Bone Marrow Reticulin Formation Haematological Malignancies Cataracts Renal Tubular Toxicity Phototoxicity Potential for Haematological changes Potential for Endosteal Hyperostosis HCV Haematological Malignancies Cataracts

	Renal Tubular Toxicity Phototoxicity Potential for Haematological changes Potential for Endosteal Hyperostosis
Important missing information	ITP and HCV Paediatrics Pregnant or lactating females
Discharged Risks	ITP and HCV Cardiac - Prolongation of QT interval

OPR reviewer comment:

Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, it was recommended that the above summary of ongoing safety concerns was acceptable.

Pharmacovigilance plan

A list of planned and ongoing studies outlined in the EU RMP was provided. All studies were considered to be relevant to Australian patients and additional information about the clinical program was provided in the EU RMP.

In addition, safety data arising from ongoing GSK sponsored studies and SAE data from collaborative research trials will be reviewed as part of routine pharmacovigilance activities.

Targeted follow-up questionnaires (TFupQ) will be used to collect consistent information on the following adverse events of interest that are reported in the postmarketing setting globally:

- Hepatotoxicity
- Hepatic Decompensation
- Post therapy reoccurrence of thrombocytopenia
- Thromboembolic Events
  - Portal Vein Thrombosis
- Potential for increased bone marrow reticulin formation
- Haematological Malignancies

Following receipt of a completed targeted follow up questionnaire GSK will add any additional information to the case in the global database. This would then be reported to the TGA in the form of a follow-up Council for International Organizations of Medical Sciences (CIOMS) report in line with Australian Guideline for Pharmacovigilance

Responsibilities of Sponsors of Registered Medicines Regulated by the Drug Safety and Evaluation Branch.[11]

Risk minimisation activities

All of the concerns identified in the EU RMP are relevant for patients in Australia. The risk minimisation activities proposed in the EU RMP will be implemented in Australia with the exception of some labelling differences.

As a routine risk minimisation activity for each of the safety concerns, appropriate wording has been proposed for inclusion in the Australian PI and Consumer Medicine Information (CMI) which is aligned with that described in the EU RMP and included in the EU Summary of product Characteristics (SmPC).

For all safety concerns, the text included in the Australian PI is aligned with the GSK global core label for eltrombopag. Consequently, GSK consider that the text included in the Australian PI adequately addresses these safety concerns.

Differences from the EU SmPC are the result of local EU variations resulting in deviations from the GSK global core label.

As an additional risk minimisation activity, education materials will be provided to prescribers in Australia, addressing the key messages discussed in the EU RMP.

The education materials provide prescribers with information regarding the monitoring and management of patients with hepatotoxicity, thromboembolic events, post therapy reoccurrence of thrombocytopenia, potential for increase in bone marrow Reticulin formation and haematological malignancies. Included in Appendix 8 of the EU RMP are educational materials representative of those provided in the EU. Educational materials for Australian prescribers may differ in format. With exception of the following differences, all key messages in section 5.1 of the EU RMP are relevant to Australian prescribers treating ITP and HCV patients.

Hepatotoxicity

To be consistent with the proposed Revolade PI, Australian education materials will inform prescribers to discontinue Revolade if ALT levels increase ≥ 5x the upper limit of normal [ULN] or to ≥ 3x ULN in patients with normal liver function or ≥ 3x baseline in patients with elevations in transaminases before treatment and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

[11] <http://www.tga.gov.au/safety/australian-pharmacovigilance-sponsors-00.htm>. This document replaces advice contained in previous documents relating to pharmacovigilance reporting requirements for either listed or registered medicines, including;

- the Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch; and
- the Australian Regulatory Guidelines for Complementary Medicines.

Dose adjustments

The dose reduction and dose interruption thresholds differ between the Australian PI and EU SmPC. Consequently, Australian educational materials will be consistent with the Australian PI. Table 6 from the current approved Revolade PI is reproduced below. This information is located in Table 5 and Table 6 of the proposed Revolade PI.

Table 6. Dose reduction and dose interruption (from Australian PI)

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 200,000/µl to ≤ 400,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400,000/µl	Stop REVOLADE; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150,000/µl, reinitiate therapy at a lower daily dose*.

* - For patients taking 25 mg once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

Haematological malignancies

Proposed text in educational materials will be consistent with the Australia PI.

Hepatic decompensation

Proposed text in educational materials will be consistent with the Australia PI.

Portal vein thrombosis

Proposed text in educational materials will be consistent with the Australia PI.

The following table (Table 7) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the second round OPR evaluation of the sponsor's responses.

Table 7. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Question 6: It was recommended to the Delegate that the sponsor implement EU RMP Version 15 dated 2 May 2012 Data lock point 31 March 2012, with Australian Specific Annex Version 2 dated July 2012, and any future updates as a condition of registration.	GSK agreed to implement EU RMP Version 15 dated 02 May 2012 Data lock point 31 March 2012, with Australian Specific Annex Version 2 dated July 2012, and any future updates as a condition of registration.	This was considered acceptable.
Question 7: Educational Program (i) It was recommended to the Delegate that the sponsor update the draft educational program materials to include relevant information for the use of Revolade in patients with HCV infection, including relevant study data and safety information in the Safety Guide for Revolade (eltrombopag) for prescribers and relevant information on HCV infection and dosage and administration information on Revolade in all materials. These updated draft materials should be submitted to the TGA within 3 months of approval (if achieved) of this submission.	GSK agreed to provide an updated draft *Safety Guide for Revolade (eltrombopag)* to TGA within 3 months of approval. GSK proposes to update other educational materials within the 3 months prior to Pharmaceutical Benefits Scheme (PBS) listing for the HCV indication, if achieved. GSK commits to providing these draft materials to TGA during the 3 months prior to PBS listing. GSK does not anticipate that patients will access Revolade for the treatment of HCV via the private market or current PBS listing for the treatment of patients with Idiopathic Thrombocytopenic Purpura (ITP). The PBS authority approval for ITP requires that a strict criterion be met and that prescribers apply on a case by case basis. In addition, patients with ITP are managed by haematologists, whilst patients with HCV are managed by gastroenterologists, hepatologists or infectious disease specialists. Due to high costs access to Revolade in Australia via the private market is not anticipated. GSK believes that it is appropriate to delay updating educational materials, other than the *Safety Guide for Revolade (eltrombopag)*, with HCV relevant information until the 3 month period prior to PBS listing.	This was considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
(ii). It was recommended to the Delegate that the sponsor provide further details of the educational program planned for Australia. That is, the intended duration of the proposed educational program and how the sponsor plans to assess the effectiveness of the educational program in Australia and how this will be demonstrated to the TGA.	GSK anticipated implementing an educational program that would commence at the time of PBS listing. The proposed duration is of 12 months and the educational activities currently under consideration include: · An educational launch meeting series · Sales representative education · Medical Science Liason interactions with physicians GSK proposed to distribute feedback forms during educational launch meetings to assess the effectiveness of the educational program.	The sponsor's proposed assessment of effectiveness through feedback forms was not considered to be sufficient. An evaluation of the education should be conducted. Furthermore, it was recommended that the sponsor commit to providing a summary on the effectiveness of the educational program to the TGA as part of the PSURs.
Question 8 **Risk Management Plan. Recommendation to the Delegate about Haematological malignancies.** It was recommended to the Delegate consider adding the additional information that the SmPC contains in regards to the clinical trial data and considerations that prescribers should give to ongoing monitoring and testing.	GSK acknowledged that there is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematopoietic malignancies. However, GSK considers that eltrombopag is a different medicine to romiplostim, based on its mechanism of action as well as preclinical and clinical data. Placebo-controlled data from a trial of eltrombopag in patients with advanced MDS and AML (Study PMA112509) is now available and shows no evidence of harm in patients treated with eltrombopag; in fact, the data suggests a potential favourable outcome following treatment with eltrombopag compared to placebo. In light of the lack of evidence that eltrombopag stimulates progression of myeloid malignancies, GSK considers that the wording in the current Australian Product Information (PI) appropriately reflects the risk regarding haematological malignancies. Due to the length of the sponsor's response, the full response to this concern has not been included here.	The sponsor provided an extensive response to this question. Of note is Item 6 in the sponsors' conclusion. It was recommended that the Delegate consider the addition of sentence 1-2 from Item 6 to the Australian PI: *'GSK has received post-marketing cases describing appearance or progression of MDS in patients receiving eltrombopag. However, the information included in the post-marketing reports does not provide sufficient evidence to establish a causal relationship between treatment with eltrombopag and the appearance or worsening of MDS.'*

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Question 9. Risk Management Plan. Recommendation to the Delegate about Hepatotoxicity. It was recommended to the Delegate consider requesting the sponsor to include alternative wording in the proposed Australian PI for the recommendations to prescribers on when to discontinue Revolade based on increases in ALT levels (see suggested changes to the Australian PI statement below).	GSK proposes the following wording for the recommendations to prescribers on when to discontinue Revolade based on increases in ALT levels: *Discontinue Revolade if ALT levels increase to >3x upper limit of normal [ULN] in patients with normal liver function or >3x baseline in patients with elevation in transaminases before treatment and are:* • *progressive, or* • *persistent for >4 weeks, or* • *accompanied by increased direct bilirubin, or* • *accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation*	This was considered acceptable.
Proposed wording in Australian PI *Discontinue Revolade if ALT levels increase > 5x the upper limit of normal [ULN] or to >3x ULN in patients with normal liver function or >3X baseline in patients with elevations in transaminases before treatment and are:* • *progressive, or* • *persistent for >4 weeks, or* • *accompanied by increased direct bilirubin, or* • *accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation* **Suggested changes to the Australian PI statement** *Discontinue Revolade if ALT levels increase to >3x upper limit of normal [ULN] in patients with normal liver function or >3x baseline in patients with elevation in*	The proposed wording by GSK harmonises the different requirements of patients with chronic immune thrombocytopenia (ITP) and patients with chronic hepatitis C virus (HCV) associated thrombocytopenia. The removal of the *5x ULN* limit does not materially affect patients with chronic ITP because the limitation is essentially encompassed in the criteria that patients be discontinued if elevations in ALT are progressive. However, the specification of '*max to 5x ULN*' in the suggested changes to the Australian PI statement means that some patients with HCV associated thrombocytopenia would be required to stop treatment unnecessarily. In fact, the suggested changes to the Australian PI statement mean that some patients with HCV associated thrombocytopenia would be required to discontinue treatment immediately after they begin treatment because patients with HCV are known to have increases in ALT > 5x ULN at	This was considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
transaminases (max to 5x ULN) before treatment and are: • *progressive, or* • *persistent for >4 weeks, or* • *accompanied by increased direct bilirubin, or* • *accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation*	baseline (that is, before treatment). The ENABLE studies demonstrated that increases in ALT during treatment were less common in the group treated with Revolade compared to the group treated with placebo. This finding, in conjunction with a comprehensive analysis of hepatobiliary laboratory parameters, indicates that Revolade is not a cause of drug-induced liver injury in the HCV associated thrombocytopenia population.	
	The ENABLE studies required that patients discontinue Revolade if ALT increased to 5x baseline (maximum to 20x ULN) in patients with elevation in transaminases before treatment. During the ENABLE studies no patients achieved the 20x ULN threshold. Nevertheless, GSK recommended a more conservative approach than was used in the clinical trials in order to harmonise the different requirements of patients with chronic immune thrombocytopenia (ITP) and patients with chronic hepatitis C virus (HCV) associated thrombocytopenia. GSK proposes removing the specification of '*max to 5x ULN*' in the suggested changes to the Australian PI statement so that all patients with HCV associated thrombocytopenia treated with eltrombopag and interferon-based antiviral therapy have the best opportunity to achieve SVR.	

Question 8 Risk Management Plan – Recommendation to the Delegate about Haematological malignancies.	
EU SmPC (EU-RMP v15)	**Australian PI**
"TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS. *In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.* *The diagnosis of ITP or thrombocytopenia in patients with HCV in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.* *The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used outside of clinical trials for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than the registered indication."*	*"There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS (see Carcinogenicity). Across the clinical trials in ITP (n = 493) and HCV (n = 1439) no difference in the incidence of malignancies or haematological malignancies was demonstrated between placebo- and Revolade treated patients."*

Summary of recommendations

It was 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 (see Outstanding issues below).

Outstanding issues

Issues in relation to the RMP

Question 7: Part 2:

Evaluators comment: It was recommended to the Delegate that the sponsor provide further details of the educational program planned for Australia. That is, the intended duration of the proposed educational program and how the sponsor plans to assess the effectiveness of the educational program in Australia and how this will be demonstrated to the TGA.

Outstanding issue: The sponsor's proposed assessment of effectiveness through feedback forms was not considered to be sufficient. An evaluation of the education should be conducted. Furthermore, it was recommended that the sponsor commit to providing a summary on the effectiveness of the educational program to the TGA as part of the PSURs.

Question 8. Risk Management Plan. Recommendation to the Delegate about Haematological malignancies.

Evaluators comment: It was recommended the Delegate consider adding the additional information that the SmPC contains in regards to the clinical trial data and considerations that prescribers should give to ongoing monitoring and testing.

Outstanding issue: The sponsor provided an extensive response to this question. Of concern is Item 6 in the sponsors' conclusion. It was recommended that the Delegate consider the addition of sentence 1 and 2 from Item 6 to the Australian PI:

GSK has received post-marketing cases describing appearance or progression of MDS in patients receiving eltrombopag. However, the information included in the post-marketing reports does not provide sufficient evidence to establish a causal relationship between treatment with eltrombopag and the appearance or worsening of MDS.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Implement EU-RMP Version 15 dated 02 May 2012, Data lock point 31 March 2012 with Australian Specific Annex (version 2, July 2012) and any future updates as a condition of registration.

PSUR

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were no objections in respect of Chemistry, Manufacturing and Controls to the registration of 75 mg eltrombopag tablets. The quality evaluator pointed out that the company's justification for not submitting bioequivalence studies on the 75 mg and 100 mg tablets versus the existing 25 mg and 50 mg tablets should be assessed from a clinical perspective.

The evaluator noted that the Product Information allows doses up to 75 mg for the ITP indication which means that the use of the 75 mg tablet for ITP is not precluded. The evaluator is of the view that even for a single indication; bioequivalence across all proposed dosage strengths should be established.

The comparative dissolution profiles of the four strengths were later provided by the sponsor. While the three lower strength tablets show similar dissolution profiles, the 100 mg tablet dissolves significantly more slowly, although by the 30 minute time point the extent of dissolution is the same as the three lower strengths. Comparative dissolution profiles have not been provided at lower pH because of incomplete dissolution under those conditions. Given these dissolution results and the fact that the same drug granules are used in the manufacture of all four tablet strengths, the evaluator was of the opinion that significant differences in bioavailability are unlikely to arise when the different strength tablets are administered at the same dose.

On 16 May 2013, TGA was informed by GSK that there was an issue with Revolade 100 mg tablet. There were problems with the tablet appearance and dissolution behaviour during the validation work for the commercial product of the 100 mg tablet. GSK was at this time trying to fully understand these issues but the timing means that GSK would not be in a position to launch the 100 mg presentation without further adjustments to the manufacturing process. All other tablet strengths are unaffected, including the proposed 75 mg presentation. In the absence of the 100 mg tablet, GSK intends to manage the 100 mg dose proposed for use in the HCV indication with the available 25 mg, 50 mg and 75 mg tablets. GSK confirmed that the 100 mg tablet will not be supplied in Australia until the issues have been resolved. Given this new information, the quality evaluator recommended that the 100 mg tablet should not be registered and a new application for the 100 mg tablet will be required when the identified problems have been resolved.

Nonclinical

No new toxicology data were provided to support the new indication and the new maximum dose of 100 mg. The higher daily dose in the new patient group results in higher

exposures (2.1 times and 1.5 times the clinical AUC and C_{max}, respectively) compared with the currently registered dose for ITP patients. This indicates a potential increase in adverse effects compared with the currently registered indication. Toxicities observed in animal/*in vitro* studies at clinically relevant doses/concentrations included cardiotoxicity, hepatotoxicity, cataract formation and renal toxicity. Based on nonclinical data, an adequate safety profile was not considered to have been demonstrated for the proposed new indication and the new maximum dose of 100 mg.

The evaluator proposed a number of amendments to the proposed Product Information document should the extension of indication and the new maximum dose of 100 mg be approved on clinical grounds.

Clinical

Pharmacology

The PK of eltrombopag have been characterised in the previous registration submission. In the current submission, additional information was provided on the PK in the target population only. This information was obtained from the clinical efficacy studies and also encompassed the PK of the proposed two new strengths (75 mg and 100 mg).

See *Evaluator's overall conclusions on pharmacokinetics* above for details.

Plasma eltrombopag concentration-time data collected in 635 subjects with HCV in the Phase II study (TPL102357) and the two Phase III studies (TPL103922/ENABLE 1 and TPL108390/ENABLE 2) were combined with data from 28 healthy adult subjects (from Phase I study SB-497115/002) in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{0-\tau}$ estimates for subjects with HCV enrolled in the Phase III studies are presented for each dose studied below.

Table 8. Plasma exposure to eltrombopag

Eltrombopag Dose (once daily)	N	Geometric Mean (95% CI)	
		C_{max}, µg/ml	$AUC_{0-\tau}$, µg.h/ml
25 mg	330	6.40 (5.97, 6.86)	118 (109, 128)
50 mg	119	9.08 (7.96, 10.35)	166 (143, 192)
75 mg	45	16.71 (14.26, 19.58)	301 (250, 363)
100 mg	96	19.19 (16.81, 21.91)	354 (304, 411)

Note: AUC (0-τ) and Cmax based on population PK post-hoc estimates at the highest dose in the data for each subject.

The evaluator was of the view that plasma eltrombopag level over time was accurately predicted for all dosages, including the proposed 75 mg and 100 mg tablets.

The PK data on special populations including renal impairment, hepatic impairment, race, gender and elderly population was provided. This appears to be consistent with the previous experience with eltrombopag. Eltrombopag has the potential to affect the PK of co-administered drugs that are substrates of CYP2C8, CYP2C9, UGTs, OATP1B1 or BCRP. From the submitted efficacy studies, plasma eltrombopag exposure was not altered by concurrent administration of peginterferon alfa-2a + ribavirin or peginterferon alfa-2b + ribavirin, nor was plasma peginterferon alfa-2a and alfa-2b exposures altered by concurrent administration of eltrombopag.

A population PK/PD model was constructed to assess the PD of eltrombopag. Initially, a PK/PD model was developed based on data from eltrombopag mono-therapy to characterise the stimulatory effect of eltrombopag on platelet counts. The model was then extended to incorporate the inhibitory effects of peginterferon (alfa-2a and alfa-2b) by including data from antiviral therapy in the modelling. Due to a lack of serum concentrations of peginterferon alfa-2a and peginterferon alfa-2b in the majority of

patients, a kinetic-pharmacodynamic (KPD) modelling approach was used to characterise the inhibitory effect of interferon on platelet counts during antiviral therapy. The plasma eltrombopag concentration was related to the increase in KIN through an E_{max} relationship, with 50% of maximum stimulation achieved at the eltrombopag concentration (EC_{50}) of 29 µg/mL. The estimated maximum effect was a 15.4 fold increase in platelet production. The inhibitory effect of peginterferon on platelet production was linearly associated with peginterferon concentrations. This modelling allowed for a prediction of the required starting dose for eltrombopag and the requirement for dose adjustment during treatment. This modelling was then assessed in the pivotal efficacy studies.

Pharmacodynamic interactions were noted with rosuvastatin, lopinavir/ritonavir, polyvalent cations and food interactions. Eltrombopag demonstrated no clinically significant effect on cardiac repolarisation in patients with HCV infection.

Clinical efficacy

Two pivotal studies (ENABLE 1 and ENABLE 2) and one supporting study (TPL102357) were submitted to support the proposed indication. The two pivotal studies had identical designs and differed only in the pegylated interferon (peginterferon) used. They were multicenter, two-part studies that used a randomised withdrawal design. They consisted of an open-label (OL), Pre-Antiviral Treatment Phase (Part 1) and a randomised, double-blind (DB), placebo-controlled, Antiviral Treatment Phase (Part 2). Subjects entered into the studies with a platelet count of < 75 Gi/L and were stratified at baseline by platelet count, level of HCV RNA at screening and HCV genotype.

See *Evaluator's Conclusions on Clinical Efficacy* above for further details.

Clinical safety

Information on clinical safety was available from the pivotal efficacy studies, supporting efficacy study, information previously submitted to TGA and the postmarketing surveillance data. There was no specific safety studies submitted.

Interpretation of eltrombopag safety profile was complicated by the overall health status of the target population, especially those subjects with more severe baseline liver impairment and requiring more intensive therapy (and hence with more side-effects of treatment). In addition, the results from the efficacy studies indicated a proportion of patients who would have been unable to be treated previously because of low platelet counts, who could now be treated more aggressively.

See *Evaluator's Overall Conclusions on Clinical Safety* above for further details.

In terms of postmarketing data, approximately 6,664 patient years of eltrombopag therapy have been prescribed worldwide as of December 2011. A total of 5215 spontaneous and post marketing AEs (serious and non serious) have been received from the marketed use of eltrombopag (2261 cases). No significant trends were identified that would impact on the safety profile of eltrombopag.

Risk management plan

The submitted RMP has been evaluated by the OPR evaluator. A number of outstanding issues were identified by the evaluator, including further details on the educational program planned for Australia and a summary on the effectiveness of the educational program to be provided as part of the PSURs. The revised PI statements in relation to the recommendations on when to discontinue Revolade based on increases in ALT levels are considered acceptable by the RMP evaluator.

The evaluator raised concerns that TPO-R agonists may stimulate the progression of existing haematopoietic malignancies such as Myelodysplastic Syndromes (MDS). In the sponsor's response to TGA's RMP questions, GSK acknowledged that there is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematopoietic malignancies. However, it is considered that eltrombopag is a different medicine to romiplostim on the basis of its mechanism of action and nonclinical and clinical data. GSK also stated that a placebo-controlled data from a trial of eltrombopag in patients with advanced MDS and AML (study PMA112509) is now available and shows no evidence of harm in patients treated with eltrombopag and the data suggests a potential favourable outcome following treatment with eltrombopag compared to placebo. In light of the lack of evidence that eltrombopag stimulates progression of myeloid malignancies GSK considered that the following wording in the current Australian PI appropriately reflects the risk regarding haematological malignancies.

> *"There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS (see Carcinogenicity). Across the clinical trials in ITP (n = 493) and HCV (n = 1439) no difference in the incidence of malignancies or haematological malignancies was demonstrated between placebo- and Revolade treated patients."*

The response was reviewed by the RMP evaluator and the evaluator recommended to the Delegate that the additional information in regards to the clinical trial data should be added to the PI and that the prescribers should be advised in relation to ongoing monitoring and testing. The following statements are recommended to be included in the PI:

> *GSK has received post-marketing cases describing appearance or progression of Myelodysplastic Syndromes (MDS) in patients receiving eltrombopag. However, the information included in the post-marketing reports does not provide sufficient evidence to establish a causal relationship between treatment with eltrombopag and the appearance or worsening of MDS.*

Risk-benefit analysis

Delegate considerations

Multiple factors are involved in the aetiology of thrombocytopenia in HCV-infected patients and one of them is the impaired production of endogenous TPO in the liver. The severity of thrombocytopenia correlates with the severity of the liver disease. Thrombocytopenia is further aggravated by interferon-based antiviral therapy due to its myelosuppressive effects. The peginterferon labels advise that they should be used with caution in patients with low baseline platelet counts and should be discontinued in patients who develop severe decreases in platelet counts. The management of HCV-patients with thrombocytopenia receiving antiviral therapy relies on reducing the peginterferon dose. However, such dose reductions are associated with a reduced ability to achieve SVR.

The two pivotal studies submitted were considered to be appropriately designed and conducted. Both studies met the primary endpoint: the addition of eltrombopag to standard antiviral therapy resulted in a statistically significant and clinically meaningful improvement in SVR (21%) compared with standard antiviral therapy + placebo (13%) ($p = 0.0004$). The response to eltrombopag during Open Label treatment was similar in both studies with 97% and 96% of subjects in ENABLE 1 and ENABLE 2, respectively, achieving a platelet count that would allow the initiation of antiviral therapy. Platelet counts began to rise within the first week of eltrombopag treatment. The median time to achieve the target platelet count was about 2 weeks, with over 75% of subjects achieving

these target platelet counts within the first 4 weeks of treatment. At the end of treatment, 48% (ENABLE 1) and 38% (ENABLE 2) of subjects randomised to the eltrombopag arm were HCV RNA negative, significantly more than in the respective placebo arms (37% for ENABLE 1and 23% for ENABLE 2). The benefit offered by eltrombopag treatment is that a certain proportion of patients who were previously ineligible or poor candidates for antiviral therapy achieved SVR and now has the opportunity to experience the long-term benefits of SVR.

The safety profile in the submitted studies appears to be consistent with the safety profile of peginterferon/ribavirin and the safety profile of eltrombopag. Thrombotic and thromboembolic events, including portal vein thrombosis and occurrence of cataracts are already described in the eltrombopag PI. Thrombotic events were reported 2% more frequently in the eltrombopag group versus the placebo group. There was no clear correlation between platelet counts, duration of eltrombopag therapy or other direct eltrombopag-specific risk factors and reports of thrombotic events. Hepatic decompensation is a known side effect of interferon therapy in patients with cirrhosis, and was observed in the pivotal studies. The safety profile was largely influenced by the degree of liver impairment prior to initiating treatment. Subjects with more severe baseline liver impairment had a higher incidence of hepatic decompensation and thromboembolic events. Interpretation of safety results was complicated by the nature of the target population. Nonetheless, the safety profile was comparable between treatment and placebo groups. Events suggestive of hepatic decompensation were observed more commonly in eltrombopag-treated subjects. Subjects with poor liver function at baseline had a greater risk of hepatic decompensation. The incidence and progression of cataracts occurred more frequently in the eltrombopag group. None of these issues were unexpected and surveillance for these conditions is recommended during treatment. Given the nature of the target population, all patients undergoing this treatment will require close monitoring to reduce morbidity and mortality from both the condition itself and any medication-related effects. HCV patients receiving eltrombopag therapy should be closely monitored for serum aspartate aminotransferase (AST)/ALT and bilirubin levels.

The use of a protease inhibitor (boceprevir or telaprevir) in addition to peginterferon alfa and ribavirin has now become the optimal treatment for genotype 1 HCV infection. It is noted that FDA has determined that only a clinical trial (rather than a nonclinical or observational study) would be sufficient to identify an unexpected serious risk of high drug exposure to eltrombopag when used with recommended protease inhibitors. The sponsor has been requested to conduct a PK study to evaluate the effect of boceprevir and telaprevir on eltrombopag PK and the effect of eltrombopag on boceprevir and telaprevir PK in healthy adult subjects. These studies were not available at the time of this submission and will need to be provided in a future submission.

The company's justification for not submitting bioequivalence studies on the 75 mg and 100 mg tablets versus the existing 25 mg and 50 mg tablets was considered acceptable from clinical perspective.

The submitted two pivotal studies were conducted utilising all four strengths of tablets and the doses were achieved through the use of 25 mg, 50 mg, 75 mg or 100 mg tablets. Both studies met the primary endpoint. As presented in the ITP application, the PK of eltrombopag are linear up to 150 mg and the relative bioavailability study demonstrated that $AUC_{(0-\infty)}$ and C_{max} were equivalent for a single 75 mg tablet compared to the combination of a single 25 mg plus a single 50 mg tablet and were lower for a single 100 mg tablet dose compared to two 50 mg tablets. From the data provided in the current submission, the dissolution rate for the 100 mg tablet is slower than the dissolution rates of the lower strength tablets until about 30 minutes, after which the dissolution rates are similar. As the eltrombopag dosing regimen is personalised based on the patient's response in platelet count, the clinical consequence of any potential differences in

bioavailability of the eltrombopag tablets is considered to be minimal because each patient is administered the minimum efficacious dose. The minimum toxic plasma concentration of eltrombopag has not been defined. However, no relationship between eltrombopag dose and adverse events was observed in the HCV studies.

The changes to the initially proposed PI have been recommended from various evaluation areas. The sponsor should include a revised version of the PI with the Pre Advisory Committee on Prescription Medicines (ACPM) response. In addition, it is recommended that the following statements should be included in the *Precautions* section:

> *Revolade should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon therapy or limits the ability to maintain optimal interferon-based therapy.*
>
> *Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C genotype 1 infection.*

Further changes to the PI may be required prior to the finalisation of this application, taking into account the discussion and the advice from the ACPM.

Delegate's pre-ACPM proposal

The Delegate proposed the registration approval of Revolade (eltrombopag) 25 mg, 50 mg, and 75 mg tables for the indication below:

> Revolade (eltrombopag) *is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy*

A separate application for the 100 mg tablet will be required when the identified problems are resolved. The text relating to 100 mg tablets in the PI should be deleted.

The implementation of the EU RMP Version 15 dated 02 May 2012 Data lock point 31 March 2012, with Australian Specific Annex Version 2 dated July 2012, and any future updates will be impose d as a condition of registration if this application is approved.

Request for ACPM advice

The ACPM was requested to advice on

- whether the benefits of Revolade (eltrombopag) in increasing platelet count and enabling chronic hepatitis C patients to receive peginterferon /ribavirin and to achieve SVR would outweigh the risks of the increased incidence of hepatic decompensation and thromboembolic events in the treating population?
- the risk of Revolade (eltrombopag) in stimulate the progression of existing haematopoietic malignancies such as Myelodysplastic Syndromes (MDS) and whether this information should be included in the Product Information?
- any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

GlaxoSmithKline (GSK) agreed with the Delegate's proposal to approve the following extension of indication for Revolade (eltrombopag) 25 mg, 50 mg, and 75 mg tablets:

> *Revolade is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.*

This indication is identical to that approved by the US FDA on 16th November 2012.

It was noted that the Delegate's recommendation is consistent with the clinical evaluator's finding that "*the benefit-risk balance, given the proposed usage, is favourable*".

GSK accepted the recommendation of the quality evaluator that the 100 mg tablets should not be registered with this submission. This is due to identified problems with tablet appearance and dissolution behaviour.

GSK's comments on Delegate's request for ACPM advice

Efficacy and safety profiles support a favourable benefit-risk ratio of Revolade in increasing platelet count and allowing chronic hepatitis C patients to receive peginterferon/ribavirin and to achieve Sustained Virological Response (SVR)

Summary of efficacy results

Two independent pivotal studies, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2), hereafter referred to as ENABLE 1 and ENABLE 2, demonstrated a statistically significant and clinically meaningful benefit, each meeting the predefined primary efficacy endpoint of SVR at 24 weeks post-completion of treatment.

Revolade treatment allows thrombocytopenic patients with HCV and advanced fibrosis/cirrhosis (that is, Metavir F3 or F4) to initiate and receive a more optimised antiviral treatment regimen. This in turn offers an increased probability of achieving SVR, which has been associated with better long-term clinical outcomes. The integrated efficacy data from ENABLE 1 and ENABLE 2 demonstrated the following:

Revolade enabled the initiation of antiviral therapy in 95% of patients who would otherwise have been ineligible or poor candidates for peginterferon-based therapy;

- The median time to achieve a platelet count of either ≥90 Gi/L or ≥100 Gi/L was about 2 weeks, with over 75% of patients achieving these target platelet counts within the first 4 weeks of treatment.
- Revolade enabled initiation of antiviral therapy for most patients at a dose of 25 mg or 50 mg Revolade.

Revolade treatment delayed and reduced the number of peginterferon dose reductions and reduced the incidence of antiviral therapy cessation compared with placebo;

- A significantly greater proportion of Revolade treated patients (45%) required no antiviral therapy dose reductions compared with placebo (27%) ($p<0.0001$).
  - The median cumulative dose for each peginterferon was ≥60% greater for the Revolade treatment group than for the placebo treatment group.
  - For ribavirin there was also a longer cumulative duration of treatment and a higher (37%) cumulative dose for the Revolade group compared with the placebo group.

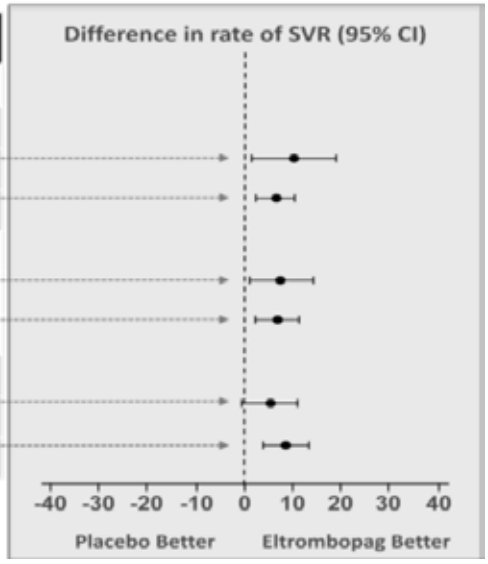
Revolade treatment in the DB phase enabled maintenance of platelet counts at a level sufficient to avoid dose reductions of antiviral therapy compared with placebo:

- Median platelet counts by Week 4 were approximately 97 Gi/L for the Revolade group and 48 Gi/L for the placebo group; median platelet counts remained near the Week 4 values for the remainder of DB treatment.
- More Revolade-treated patients (76%) had platelet counts that remained ≥50 Gi/L during antiviral therapy compared with placebo (19%); the approved peginterferon labels recommend dose reduction when platelet counts fall <50 Gi/L.

Revolade-treated patients had a statistically significant and clinically meaningful improvement in SVR compared with placebo (21% versus 13%) ($p=0.0004$); SVR was consistent across studies (randomisation strata and predefined subgroups (Figure 2).

Figure 2. Forest Plot of SVR rates by stratification factor (Pooled data, ITT Population).

Subgroup	Eltrombopag	Placebo
	No. of subjects (%)	
Actual HCV genotype		
Genotype 2/3	102 (35)	37 (25)
Non–genotype 2/3	99 (15)	28 (8)
Actual platelet level		
<50Gi/L	53 (20)	15 (11)
≥50Gi/L	148 (21)	50 (14)
Actual HCV RNA		
<800,000IU/mL	119 (24)	45 (18)
≥800,000IU/mL	82 (18)	20 (8)



Summary of safety results

The Delegate has stated that "*the safety profile in the submitted studies appears to be consistent with the safety profile of peginterferon/ribavirin and the safety profile of eltrombopag*." GSK reiterated that no new safety findings were identified that are not already described in the Product Information for Revolade, peginterferon or ribavirin.

GSK highlights the following key points:

- The overall safety profile of Revolade in patients with advanced fibrosis/cirrhosis and thrombocytopenia due to chronic HCV infection has been well characterised in >1500 patients and GSK consider it manageable with appropriate monitoring and intervention when indicated.
- During the DB Phase of the pivotal studies, the median cumulative duration of treatment for peginterferon and ribavirin was longer in the Revolade group compared with the placebo group (circa 60% more peginterferon and circa 37% more ribavirin), and the intensity of peginterferon and ribavirin dosing was higher in Revolade treated patients compared with placebo treated patients.
- The incidence of (S)AEs leading to drug discontinuation or withdrawal and the incidence of Grade 3/Grade 4 AEs were similar between the treatment groups
- The incidence (placebo 1%, Revolade 2%) and incidence rate for death were similar between the treatment groups (2.93/100 patient-years (confidence interval [CI]: 1.86, 4.00) for the Revolade group and 2.30/100 patient-years (CI: 0.88, 3.72) for the placebo group).
- The causes of death were consistent with the disease under study and with what would be expected in this study population receiving peginterferon based therapy.

Specific adverse events of interest

Thromboembolic events (TEEs)

Thromboembolic/thrombotic complications were observed more frequently in the Revolade treatment group than in the placebo treatment group.

- Reported TEEs included both arterial and venous events, including portal vein thrombosis.

- There was no clear correlation between platelet counts, duration of treatment with Revolade or other direct Revolade specific risk factors and reports of thrombotic events. The majority of TEEs in Revolade patients resolved and most on-treatment events did not lead to discontinuation from antiviral treatment.
- The TEE data from the ENABLE program is consistent with the information described in the current Revolade Product Information.

The majority of the TEEs resolved and did not lead to discontinuation from antiviral treatment. In the ENABLE studies anticoagulation appeared to increase the likelihood of TEE resolution, especially for portal vein thrombosis (PVTs). This is consistent with the recent American Association for the Study of Liver Diseases practice guideline on vascular disorders of the liver. [12]

Hepatic decompensation

As noted by the Delegate, *"hepatic decompensation is a known risk in cirrhotic HCV patients receiving peginterferon therapy"*. Events suggestive of hepatic decompensation were observed in the ENABLE study population and more commonly in Revolade treated patients.

- Patients with poor liver function (albumin ≤35 g/L or MELD >10) at baseline had a greater risk of hepatic decompensation.

Physicians experienced in the treatment of patients with chronic HCV know how to treat ascites and encephalopathy and these were effectively treated in the ENABLE studies. Compared with the placebo group, a lower proportion of the events in the Revolade group were fatal, led to withdrawal of study medication or led to withdrawal from study. A higher proportion of events suggestive of hepatic decompensation were reported as resolved in the Revolade group. Ultimately, a higher proportion of patients with hepatic decompensation achieved SVR in the Revolade group (10%) compared with the placebo group (3%). Hepatic decompensation is an identified risk in HCV associated thrombocytopenia and is included as a *Precaution* in the proposed Product Information.

Benefit: Risk summary

When compared to the alternative of no treatment, the risks associated with Revolade and antiviral therapy are not considered excessive and can be managed. Therefore, despite the higher risk for liver decompensation events and TEEs, GSK believes Revolade supported interferon-based therapy can be an important therapy option in these patients. The patient population eligible for treatment with Revolade should reflect the population enrolled in the ENABLE studies, where a favourable benefit/risk has been demonstrated.

Text in the precautions section of the Australia PI for "Malignancies and progressions of malignancies"

In response to the TGA's request that GSK provided a detail justification for why the current *Precautions* section of Australian PI appropriately addresses the theoretical concern that TPO-R agonists may stimulate the progression of existing haematopoietic malignancies. Subsequently, the *Risk Management Plan advice – Round 2 Assessment* recommended that the Delegate consider addition of the following sentence to the Revolade PI:

> *GSK has received post-marketing cases describing appearance or progression of MDS in patients receiving eltrombopag. However, the information included in the post-marketing reports does not provide sufficient evidence to establish a causal*

[12] DeLeve LD, Valla D-C, Garcia-Tsao G. Vascular Disorders of the liver (AASLD Practice Guidelines). Hepatology 2009; 49(5): 1729-1764

relationship between treatment with eltrombopag and the appearance or worsening of MDS.

GSK continues to closely monitor this potential safety concern and agrees to include the proposed text subject to the following minor changes:

GSK has received There have been post-marketing cases describing appearance or progression of MDS in patients receiving eltrombopagRevolade. However, the information included in the post-marketing reports does not provide sufficient evidence to establish a causal relationship between treatment with eltrombopagRevolade and the appearance or worsening of MDS.

In response to Question 8 from the RMP evaluator, GSK provided a summary of study TRC114968 (ASPIRE). ASPIRE is a worldwide, three-part, multi-centre study to evaluate the effect of eltrombopag in patients with MDS or AML who have thrombocytopenia due to bone marrow insufficiency from their underlying disease or prior therapy. Patients must have MDS or AML, bone marrow blasts ≤50% and Grade 4 thrombocytopenia (<25Gi/L).

GSK informed the TGA and ACPM of the following updated information for ASPIRE:

On the 28 June 2013 the Independent Data Monitoring Committee (IDMC) reviewed un-blinded safety data from 54 subjects in ASPIRE (as of 5 April 2013) and recommended to temporarily pause recruitment.

During their review, the IDMC observed an imbalance in the number of cases of disease progression, however the clinical significance remains unknown until the detailed baseline characteristics (such as percentage of blast counts, poor risk cytogenetics) have been reviewed for the patients who progressed at the time of the review. The IDMC recommended a temporary pause on screening in the study until this additional information is reviewed. Until then, the specific recommendations made by the IDMC regarding the ASPIRE trial are as follows:

- Patients currently in the trial may continue with treatment
- Patients currently in screening may continue with randomisation, if eligible
- No new patients should be consented or screened until further notice.

The final IDMC recommendation was expected imminently. GSK would provide an update to the Delegate once available.

In summary, GSK agreed to include the additional precautionary text in the PI. Haematological malignancies are listed an *Important Identified Risk* in the RMP and continue to be closely monitored.

Conclusion

Thrombocytopenia restricts access to interferon-based antiviral therapy and can result in dose reductions and premature discontinuations. This leads to reduced viral clearance and lower rates of cure from HCV infection. There is currently no approved medicinal agent for the treatment of thrombocytopenia in patients with HCV infection. Furthermore, there are currently no interferon-free regimens approved for use to treat HCV infection. The patients studied in the ENABLE clinical trials (HCV patients with advanced based therapy fibrosis/cirrhosis and thrombocytopenia) have a great and urgent need for interferon. The ENABLE studies showed that Revolade enables access to this potentially curative interferon-based antiviral therapy. The risks of Revolade therapy are well characterised, short term and manageable by physicians experienced in treating HCV and its complications. The benefit of therapy (cure from HCV infection) continues to accrue over time. When compared to the alternative of no treatment, the benefit risk assessment is favourable.

GSK considered that platelet boosting with Revolade would be an appropriate treatment option for this fragile compensated cirrhotic population with poor prognostic factors requiring antiviral treatment. Revolade should be made available to treat thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection whose degree of thrombocytopenia prevents the initiation or limits the ability to maintain optimal interferon-based therapy. As long as interferon has a role in the treatment of HCV patients with thrombocytopenia, there will be a need for Revolade to support platelet counts.

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, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Revolade film coated tablets containing 25 mg, 50 mg and 75 mg of eltrombopag (as olamine) to have an overall positive benefit–risk profile for the delegate's amended indication**;**

> *Revolade (eltrombopag) is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy*

The ACPM noted the lack of data with protease inhibitors which is a major deficiency as this is the standard of care for genotype 1. However, data is to be provided.

TheA CPM advised that the benefit-risk profile was finely balanced in the patient group with end stage liver disease who will need close monitoring.

The ACPM noted and agreed with the Delegate that a separate application for the 100 mg tablet is required when the identified pharmaceutical and manufacturing problems are resolved. The text relating to 100 mg tablets in the Product Information (PI) should be deleted.

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 PI and CMI and specifically advised on the inclusion of the following:

- A discussion in the PI of the risk of progression of myelodysplastic syndromes (MDS), which may be a class effect associated with thrombopoietin receptor (TPO-R) agonists (particularly that MDS may be misdiagnosed as immune thrombocytopenic purpura (ITP)) including eltrombopag specific data..
- A statement in the *Precautions* section of the PI and relevant sections of the CMI to ensure cross referencing of the data on renal impairment in the Precautions section.
- Suitable precautionary statements on the lack of evidence on safety for use in renal impairment.

The ACPM advised that the 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

It was noted that the sponsor has accepted the TGA recommendation that the additional strength of Revolade eltrombopag 100 mg film coated tablets blister pack should not be registered with this submission.

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

> *Revolade is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.*

The full indications are now:

> *Revolade is indicated for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.*
>
> *Revolade is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.*

Specific conditions applying to these therapeutic goods

Risk management plan

The Revolade film coated tablets containing eltrombopag olamine Risk Management Plan (EU RMP), version 15 dated 2 May 2012 Data lock point 31 March 2012, with Australian Specific Annex Version 2 dated July 2012 included with submission PM-2012-01934-3-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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