13 December 2018
EMA/293205/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revolade

International non-proprietary name: eltrombopag / eltrombopag olamine

Procedure No. EMEA/H/C/001110/II/0050

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ASH: American Society of Hematology

BCSH: British Committee for Standards in Haematology

cITP: Chronic Immune thrombocytopenia

FDA: Food and Drug Administration

ITP: Immune thrombocytopenia

ITP Newly diagnosed: < 3-month duration

ITP Persistent: 3-12-month duration

ITP Chronic: >12-month duration

IVIg: intravenous immunoglobulin.

IWG: International Working Group

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 27 April 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Change of the Revolade indication of immune thrombocytopenic purpura to specify the duration of the disease. As a result, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 are being revised. The Package leaflet is being updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Not applicable, as the variation is not an extension of indication.

Information relating to orphan market exclusivity

Not applicable, as the variation is not an extension of indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	27 April 2018
Start of procedure:	23 June 2018
CHMP Rapporteur Assessment Report	9 August 2018
CHMP members comments	10 September 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 September 2018
Request for supplementary information (RSI)	20 September 2018
CHMP Rapporteur Assessment Report	26 November 2018
CHMP members comments	3 December 2018
Updated CHMP Rapporteur Assessment Report	5 December 2018
Opinion	13 December 2018

2. Scientific discussion

2.1. Introduction

Revolade (Eltrombopag) is an orally bioavailable, small-molecule thrombopoietin (TPO)-receptor agonist.

Revolade is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1). Revolade is also indicated for the treatment of thrombocytopenia associated to chronic hepatitis C virus (HCV) infection for the and for refractory acquired severe aplastic anaemia (SAA).

In the current variation application, the MAH proposes to modify the indication statement in ITP to address the changed disease terminology and definition of chronic ITP. The company states that studies enrolled patients greater than 6 months from initial diagnosis (definition of chronic ITP at the time the studies were conducted), and with the new accepted definition of chronic, > 12 months from ITP diagnosis [Rodeghiero *et al.* 2009], the designation of "chronic" no longer applies to this patient population. The MAH believes that the population under study is more appropriately defined as ≥ 6 months from diagnosis, rather than "chronic" ITP.

The MAH also proposes to delete the terms "idiopathic" and "purpura" from the indication, on the basis that the updated guidelines established by the International Working Group (IWG) also emphasised the uniform application of the acronym "ITP" to stand for "immune thrombocytopenia", and that it was advised to avoid the terms "idiopathic" and "purpura," in light of the immune-mediated mechanism of the disease and the absence of purpura in the majority of ITP cases [Rodeghiero *et al.* 2009].

The MAH has applied for a change of the indication which has been agreed with the CHMP as follows:

4.1 Therapeutic indications

> Revolade is indicated for the treatment of ~~chronic immune (idiopathic) thrombocytopenic purpura (ITP)~~ patients aged 1 year and above with immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

ITP can be defined by disease duration and the terms "acute" and "chronic" have been used to categorise patients based on the length of time from initial diagnosis. Historically, "chronic" disease referred to the persistence of symptoms beyond 6 months and "acute" was used to describe a self-limited form of the disease. In an effort to standardise definitions and response criteria, the IWG released updated guidelines in 2009 (Rodeghiero et al. 2009). The most recently established guidelines, the "International Consensus Report" (ICR) 2010 (Provan et al. 2010) and the "American Society of Hematology" (ASH) 2011 (Neunert et al, 2011), have recommended replacing "acute" with "newly diagnosed" for all cases at diagnosis, "persistent" to define the period between 3 and 12 months after diagnosis, and "chronic" to describe patients with ITP lasting beyond 12 months. Therefore, in currently accepted definitions in the 2010s, the period between 6 and 12 months is considered "persistent", while this period fell within the 2000s definition of "chronic" disease.

Based on the eligibility of the pivotal studies, the company believes that the current definition of chronic ITP (> 12 months according to the IWG 2009 guidelines) is not consistent with the definition of chronic disease that served as the basis for eligibility in the 3 double-blind, placebo-controlled clinical studies (TRA102537/RAISE, TRA100773A, TRA100773B) and 2 open-label studies (TRA108057/REPEAT, TRA105325/EXTEND), the pivotal studies that led to the original approval of eltrombopag for adult ITP, and the pivotal PETIT study that contributed to approval in the pediatric indication. In these pivotal

studies, patients were classified as having chronic ITP if their symptoms persisted beyond 6 months, consistent with the previously accepted ASH and BCSH definitions.

The updated guidelines established by the IWG (Rodeghiero *et al.* 2009) also emphasised the uniform application of the acronym "ITP" to stand for "immune thrombocytopenia." It was advised to avoid the terms "idiopathic" and "purpura," in light of the immune-mediated mechanism of the disease and the absence of purpura in the majority of ITP cases (Rodeghiero *et al.* 2009). Current variation application also contains changes in the product information in this respect.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

The applicant is asked to provide an updated ERA in compliance with the respective guidelines taking into account the final version of the ERA of Revolade EMEA/H/C/1110/II/49.

2.3. Clinical aspects

2.3.1. Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is an immune-mediated acquired disease of adults and children characterised by isolated thrombocytopenia and an increased tendency to bleed. The degree of bleeding in ITP is largely dependent on the degree of thrombocytopenia, with severe thrombocytopenia conferring the greatest risk of significant bleeding (Cooper & Bussel 2006).

Three double-blind, placebo-controlled clinical studies (TRA102537/RAISE, TRA100773A and TRA100773B) and 2 open-label studies (TRA108057/REPEAT, TRA105325/EXTEND) in adults, and one of two studies conducted in the paediatric population, PETIT, that served as the basis for the approval of eltrombopag for chronic ITP, classified patients as having chronic disease if their symptoms persisted beyond 6 months (Cheng et al. 2011). The PETIT2 study enrolled patients in accordance with the updated IWG 2009 guidelines, and therefore, eligible patients had chronic ITP >12 months in duration.

GCP

Not applicable as no new clinical trials have been submitted.

2.4. Clinical efficacy

Efficacy data of eltrombopag in adult and pediatric ITP were described in the original marketing authorisation application and are essentially unchanged. No additional information is provided in this application.

In order to support current variation application, the MAH has sent a very brief summary of adult and children ITP studies describing the number of patients recruited depending on time since ITP diagnosis, but without giving efficacy or safety data in these patients' subsets, as well as a small retrospective cohort study using MarketScan in order to assess the utilisation of eltrombopag in the real-world setting. The information provided is summarised below.

1) Adult cITP studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in adults with ITP is based principally on the results of three double-blind, placebo-controlled clinical studies (TRA102537/RAISE, TRA100773A and TRA100773B) and two open-label studies (TRA108057/REPEAT and TRA105325/EXTEND). In all five studies, the study population included adults (≥ 18 years) diagnosed with chronic ITP according to the American Society of Hematology (ASH) (George et al.1996) and British Committee for Standards in Haematology (BCSH) (BCSH 2003) guidelines and a baseline platelet count of <30 Gi/L. According to the ASH and BCSH guidelines established in 1996 and 2003 respectively, “chronic” ITP is defined as the persistence of thrombocytopenia for a period of 6 months or longer.

A total of 493 adult subjects with chronic ITP (> 6 months from diagnosis) were enrolled in the clinical program, of which 422 were exposed to eltrombopag. Demographic characteristics of the patient populations in all studies were similar and typical of the chronic ITP patient population described in the literature (Cines and Blanchette 2002). The median age in the studies was approximately 50 years and approximately two -thirds of subjects were female.

The majority of subjects were White (about 75%), followed by Asian (about 20%).

The approximate time since ITP diagnosis was collected for the RAISE study, which may serve as an estimate of the chronicity of symptoms. As seen in Table 4.1, out of 197 patients enrolled in the study, 39 patients (19.8%) had ITP for 6 months to < 12 months, consistent with the definition of “chronic” disease reflected in the ASH/BCSH guidelines. Furthermore, among the 39 patients with ITP for a duration of 6 months to < 12 months, 25 patients (64.1%) were randomized to receive eltrombopag.

Corresponding data about "time since ITP diagnosis" from TRA100773A, TRA100773B, TRA108057/REPEAT, and TRA105325/EXTEND are not available.

Table 4-1 Summary of approximate time since ITP diagnosis in RAISE study

Approximate time since diagnosis	**Eltrombopag (N=135)**	**Placebo (N=62)**	**Total (N=197)**
	n (%)	n (%)	n (%)
0 to <6 months	27 (20)	6 (10)	33 (17%)
6 to <12 months	25 (19)	14 (23)	39 (20%)
1 to <2 years	21 (16)	7 (11)	28 (14)
2 to <3 years	15 (11)	7 (11)	22 (11)
3 to <4 years	5 (4)	3 (5)	8 (4)
4 to <5 years	7 (5)	5 (8)	12 (6)
5 to <10 years	13 (10)	8 (13)	21 (11)
10 plus year	22 (16)	11 (18)	33 (17)
Missing	0	1 (2)	1 (<1)

2) Pediatric cITP studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in pediatric patients with ITP is based principally on the results of two studies (TRA108062/PETIT and TRA115450/PETIT2) in paediatric patients with previously treated ITP.

PETIT was a Phase II three part, staggered cohort, open-label and double-blind, randomized, placebo-controlled study to investigate the efficacy, safety, tolerability and pharmacokinetics of eltrombopag in previously treated pediatric patients with chronic ITP. The study enrolled male and female patients between 1 year and < 18 years of age with a diagnosis of chronic ITP, defined as the persistence of thrombocytopenia for a least 6 months, according to the ASH/BCSH guidelines and a baseline platelet count of < 30 Gi/L consistent with the older definition of "chronic."

The approximate time since ITP diagnosis was collected for the PETIT study, which may serve as an estimate of the chronicity of symptoms. As seen in Table 4-2, out of 67 patients enrolled in the study, 10 patients (14.9%) had a diagnosis of ITP for less than 12 months, which includes the definition of "chronic" disease reflected in the ASH/BCSH guidelines. Furthermore, among the 10 patients with ITP for a duration of < 12 months, 8 patients (80%) were randomized to receive eltrombopag.

Table 4-2 Time since ITP diagnosis in PETIT Study

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		All Cohorts		
Time since ITP diagnosis, n (%)	**Placebo (N=8)**	**Eltrombopag (N=16)**	**Placebo (N=9)**	**Eltrombopag (N=19)**	**Placebo (N=5)**	**Eltrombopag (N=10)**	**Placebo (N=22)**	**Eltrombopag (N=45)**	**Total (N=67)**
<12 months	0	1 (6.3)	2 (22.2)	2 (10.5)	0	5 (50.0)	2 (9.1)	8 (17.8)	10 (14.9)
≥12 months	8 (100.0)	15 (93.8)	7 (77.8)	17 (89.5)	5 (100.0)	5 (50.0)	20 (90.9)	37 (82.2)	57 (85.1)

Data Source: PETIT CSR Table 6.3005, ITP=Idiopathic thrombocytopenia

Eligibility criteria were similar in PETIT2, a Phase III two-part, double-blind, randomized, placebo-controlled and open-label study to investigate the efficacy, safety and tolerability of eltrombopag in pediatric patients with previously treated chronic ITP, except that patients were required to have a confirmed diagnosis of chronic ITP for at least 12 months, consistent with updated ASH guidelines established in 2011.

The company states that studies enrolled patients greater than 6 months from initial diagnosis, and with the new accepted definition of chronic, > 12 months, the designation of "chronic" no longer applies to this patient population. Based on the data presented above, the company believes that the population under study is more appropriately defined as ≥ 6 months from diagnosis, rather than "chronic" ITP.

3) Retrospective cohort utilization study

In order to assess the utilisation of eltrombopag in the real-world setting, a retrospective cohort study was conducted using MarketScan - Commercial and Medicare Supplemental Database, and PharmetricsPlusTM Adjudicated Claims Database. The objective of the study was to characterise when patients were initiating eltrombopag in relation to their ITP diagnoses.

Objective: The objective of this study was to evaluate the use of eltrombopag in a real world setting. More specifically, to assess the percent of patients initiating treatment with eltrombopag ≤ 3 months, 4 to ≤ 6 months, 7 to ≤ 12 months and > 12 months after their index ITP diagnosis. This information provides real world evidence regarding the interpretation of "chronic" ITP as it applies to the timing of

initiation of treatment with eltrombopag in the real world setting and potentially provides support for initiating treatment earlier.

Methods: This study was conducted using data from the following claims databases:

- Truven Health MarketScan Research Databases (referred to as MarketScan in this document):
  - Commercial Claims and Encounters Database (Commercial)
  - Medicare Supplemental and Coordination of Benefits Database (Medicare Supplemental)
- IMS PharmetricsPlus Adjudicated Claims Data (referred to as PharMetrics in this document).

Patients with at least 2 non-diagnostic outpatient claims separated by ≥ 30 days (but ≤ 365 days) or ≥ 1 inpatient claim carrying an ICD-9-CM diagnosis code for ITP in any position during the enrollment window (July 1, 2010 through December 31, 2013) were eligible for inclusion. The index date was deemed the date of the first ITP diagnosis. Patients were excluded if they were < 18 years of age on the index date, had continuous enrollment in medical and pharmacy benefits for < 24 months prior to the index date and < 18 months following the index date, or had a medical claim with an ICD-9-CM diagnosis code for any another condition associated with thrombocytopenia (secondary thrombocytopenia) during the pre-index period.

Timing of eltrombopag treatment initiation was calculated from the index date to the date of first claim for eltrombopag. Patients were categorised into one of four cohorts, those initiating treatment 0 to 3 months, 4 to 6 months, 7 to 12 months and > 12 months after index date.

Results

Included population

Between Jul 1, 2010 and Dec 31, 2013, 39,816 and 22,827 patients with ITP were identified in the MarketScan and PharMetrics databases, respectively. After applying all selection criteria, 3,264 (8.2%) patients in MarketScan and 3,804 (16.7%) patients in PharMetrics qualified for the study. Among these patients, treatment with eltrombopag was initiated in 98 (3.0%) patients and 135 (3.5%) patients in MarketScan and PharMetrics, respectively.

Table 4-3. Sample Attrition

	MarketScan		**PharMetrics**	
	N	%	N	%
Target Population				
Patients with ≥2 non-diagnostic outpatient claims separated by ≥30 days (but ≤365 days) or ≥1 inpatient claim carrying an ICD-9-CM diagnosis code for ITP in any position during the enrollment window	39,816		22,827	
Exclusion Criteria				
Age <18 year on index date	4,407	11.1%	1,771	7.8%
Continuous enrollment in medical and pharmacy benefits for ≥24 months prior to the index date	23,988	60.2%	8,812	38.6%
Continuous enrollment in medical and pharmacy benefits for ≥18 months post the index date	5,145	12.9%	4,448	19.5%
Medical claim with an ICD-9-CM diagnosis code for another condition associated with thrombocytopenia (secondary	3,012	7.6%	3,992	17.5%

	MarketScan		PharMetrics	
	N	%	N	%
thrombocytopenia) during the pre-index window				
FINAL SAMPLE	3,264	8.2%	3,804	16.6%
Initiating treatment with eltrombopag	***98***	***3.0%***	**135**	**3.5%**
Data Source: Truven Health MarketScan® Research Databases - Commercial Claims and Encounters Database (Commercial) and the Medicare Supplemental and Coordination of Benefits Database (Medicare Supplemental), and the IMS' PharmetricsPlus™ Adjudicated Claims Data				

Timing of eltrombopag initiation

Among the patients who initiated eltrombopag, 65.3% (64/98) and 58.5% (79/135) of patients initiated eltrombopag prior to 12 months from their index diagnosis in MarketScan and PharMetrics, respectively.

Data Source: Truven Health MarketScan Research Databases - Commercial Claims and Encounters Database (Commercial) and the Medicare Supplemental and Coordination of Benefits Database (Medicare Supplemental), and the IMS' PharmetricsPlus Adjudicated Claims Data

2.4.1. Discussion on clinical efficacy

No new efficacy data have been submitted with this application. The following comments are related to the MAH's justification of the proposed SmPC changes to the indication in relation to the use of eltrombopag and the efficacy/safety data already available with eltrombopag from clinical trials and publications.

Section a) is related to the change in time since diagnosis, and section b) is related to the change in terminology from "immune (idiopathic) thrombocytopenic purpura" to "Immune thrombocytopenia (ITP)".

a) Change from "chronic ITP to ITP lasting 6 months or longer from diagnosis":

No new clinical studies have been provided to support the change in the wording of the indication from "chronic ITP" to "ITP lasting 6 months or longer from diagnosis".

Data in adults: Five clinical trials supported the initial MAA of eltrombopag in chronic ITP, but the time since diagnosis was only available from one study (TRA102537/RAISE study). In that study, the experience available is for 52 patients treated with eltrombopag started <12 months since IPT diagnosis (25 patients starting < 6 months since ITP diagnosis and 27 patients started 6-12 months since ITP diagnosis).

Corresponding data about "time since ITP diagnosis" from the remaining four adult studies (TRA100773A, TRA100773B, TRA108057/REPEAT, and TRA105325/EXTEND) are not available.

Data in children: The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in pediatric patients with ITP is based principally on the results of two studies (TRA108062/PETIT and TRA115450/PETIT2) in pediatric patients with previously treated ITP. The approximate time since ITP diagnosis was collected for the PETIT study (n=67). Only 8 children received eltrombopag started < 12 months since ITP diagnosis. While limited, data suggest similar response rate in persistent ITP compared to chronic ITP. This is in line with the data observed in adults for whom response rate was independent of the time since diagnosis of ITP. There is no sound reason to think that the drug effect observed in adults cannot be expected in children. Overall, in practice few children with persistent ITP are expected to

receive eltrombopag since in this short time window (6-12 months since diagnosis) first line options need to be tested (and eventually failed) before eltrombopag being administered. In addition, these patients will be treated and monitored by physicians with experience in this disease who carefully consider the need of pharmacological treatment.

Post-marketing data:

In order to assess the utilisation of eltrombopag in the real-world setting, a retrospective cohort study was conducted using MarketScan - Commercial and Medicare Supplemental Database, and PharmetricsPlusTM Adjudicated Claims Database. The objective of the study was to characterise when patients were initiating eltrombopag in relation to their ITP diagnoses. The study included adults only, and children were excluded by protocol.

Among the adults patients who initiated eltrombopag, 65.3% (64/98) and 58.5% (79/135) of patients started treatment prior to 12 months from their index diagnosis in MarketScan and PharMetrics, respectively. The MAH states that these data support that eltrombopag is being prescribed to patients prior to 12 months from their initial ITP diagnosis and suggest that clinicians and patients perceive a benefit of initiating treatment earlier in the course of their disease. The adult studies with eltrombopag enrolled approximately 15% of patients diagnosed 6 to 12 months prior to first dose. Although the sample size is limited, data comparing the subset of patients with ITP for 6 to 12 months to those with ITP for >12 months show that the response rate in patients treated with eltrombopag as compared to placebo are independent of the time since diagnosis. After 6 months since ITP diagnosis, these patients continued to experience grade 1 and 2 bleeding events, thus reflecting the need to treat these patients.

A simple bibliographic search would have been able to identify several studies, not company-sponsored, but providing data with eltrombopag, like for instance in newly diagnosed ITP as an adjunct to dexametasone (Gómez-Almaguer D, et al. 2014). It is disappointing that the company has not made efforts in further investigating eltrombopag in newly-diagnosed/persistent ITP despite it is evident from the post-marketing data provided that there is a significant and predominant off-label use in the earlier stages of the ITP disease compared with the chronic phase. The MAH did not address this, however considering that data from clinical trials suggest a similar effect of eltrombopag regardless of time since ITP diagnosis in adults, this issue was considered resolved.

b) Change from to "idiopathic thrombocytopenic purpura (ITP" to "Immune thrombocytopenia (ITP)": The company also proposes to delete the terms "idiopathic" and "purpura" from the indication, on the basis that the updated guidelines established by the IWG also emphasised the uniform application of the acronym “ITP” to stand for “immune thrombocytopenia”, and that it was advised to avoid the terms “idiopathic” and “purpura” in light of the immune-mediated mechanism of the disease and the absence of purpura in the majority of ITP cases [Rodeghiero et al. 2009].

On the basis of current knowledge of the disease, it is accepted that the term "immune thrombocytopenia (ITP)" is more accurate than "thrombocytopenic purpura". According to the International Consensus Report, ITP can be primary or secondary [Provan et al.2010]. Secondary ITP is associated with underlying disorders, such as autoimmune disease (systemic lupus erythematosus or rheumatoid arthritis), HIV, Helicobacter pylori, or underlying immune dysregulation syndromes, such as common variable immunodeficiency. The majority of adults with ITP (≈80%) have primary ITP. Hence, the term “primary” is appropriate to be included in the proposed wording of the indication, as the pivotal trials that served as the basis for approval of eltrombopag were conducted in chronic ITP excluded patients with a diagnosis of secondary ITP.

2.4.2. Conclusions on the clinical efficacy

No new data have been provided. According to the SmPC information, eltrombopag increases platelet counts, which is considered a reliable surrogate outcome measure in ITP correlated to a decreased bleeding risk and the basis for clinical practice guidelines recommendations [Rhodegiero & Ruggery, 2014].

A recent meta-analysis of eltrombopag in ITP examined 6 randomized controlled trials [Elgebaly et al. 2017]. Eltrombopag significantly improved platelet counts (RR, 3.42; 95% CI, 2.51-4.65) and decreased incidence of bleeding (RR, 0.74; 95%CI, 0.66-0.83). In the reported clinical trials about 80% of patients had platelet response even among highly refractory and multiply treated patients [Provan et al.2015]. In clinical practice, the response rate is somewhat lower [Mazza et al. 2016] [González-López et al. 2016], reflecting perhaps the increased heterogeneity of a nonclinical trial population [Lambert & Gemsheimer, 2017].

2.5. Clinical safety

Introduction

The safety of eltrombopag was described for ITP in the original marketing authorisation application and no new data are provided. According to the SmPC information, unfavourable effects of eltrombopag include: a relapse of thrombocytopenia in most patients within 2 weeks following discontinuation of eltrombopag; risk of thromboembolic complications in about 4% of patients; risk of liver toxicity generally mild but requiring monitoring of transaminase levels before and after starting treatment; and potential unfavourable effects of bone marrow fibrosis and malignancies that cannot be ruled out with the data available.

2.5.1. Discussion on clinical safety

A recent integrated analysis of TPO-RAs in ITP reported in 994 patients from 13 clinical trials treated with romiplostim [Cines et al.2015]. In this analysis, the median study duration was 75 to 77 weeks (depending on splenectomy status), and the most frequent dose was 5 mg/kg and 4.6 mg/kg (postsplenectomy and unsplenectomized, respectively). The most frequent AEs were headache, contusion, epistaxis, and nasopharyngitis. The rate of thromboembolism (TE) was 5.5 per 100 patient-years in both romiplostim and placebo-treated patients, and occurred over a wide range of platelet counts [Cines et al. 2015]. The incidence of bone marrow reticulin fiber formation has been reported to be;3%for romiplostim with higher rates and grades in patients who exceed the currently recommended maximum dose of 10 mg/kg. The incidence of reticulin fiber formation was 1.3/100 patient-years.

2.5.2. Conclusions on clinical safety

Safety data of eltrombopag in adult and pediatric ITP were described in the initial marketing authorisation application and remain unchanged.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH has applied for the following change in the indication: “Revolade is indicated for the treatment of patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).”

3.1.2. Available therapies and unmet medical need

There are several guidelines including treatment approaches in ITP, with the ASH-2011 and ICR being the more relevant ones. Inferences regarding the efficacy of treatments are mainly based on platelet counts as the more reliable surrogate outcome measure.

In newly diagnosed ITP (first 3 months), treatment is aimed at rapidly obtaining a safe platelet count (> 30 x 10^9 /L) to prevent or stop hemorrhages and to ensure an acceptable quality of life, avoiding as much as possible treatment-related adverse effects. Corticosteroids, intravenous immunoglobulin (IVIg) or anti-D Ig are considered first-line treatments by both guidelines, and prednisone 1 mg/day for 3-4 weeks followed by tapering in another 2-3 weeks is a general standard approach.

Patients still remaining thrombocytopenic after 3 months from diagnosis or initial treatment are classified in persistent (between 3 to 12 months) or chronic (after at least 12 months). None of the available guidelines specifically addresses patients with persistent ITP (between 3 to 12 months) due to lack of robust efficacy/safety data. In both guidelines, patients not responding to first-line treatments (corticosteroids, IVIg, anti-D) are lumped together in a single heterogeneous category irrespective of the different phases of the disease (newly diagnosed, persistent or chronic ITP). This precludes separate considerations for patients failing initial OCS but still with a short disorder duration, and thus at a more favorable prognosis, from those with a more advanced disease and thus probably already exposed to more lines of medical treatments. Both guidelines just suggest that, if splenectomy is deemed necessary, surgery should be deferred for at least 6 months (ICS) or 12 months (ASH 2011) from diagnosis.

Considering that 50-80% of initially treated patients will relapse after first line therapies (i.e.: after initial corticosteroids), the most appropriate treatment of patients with persistent ITP represents an area of major clinical interest burdened by unacceptable uncertainty [Rodeghiero & Ruggeri, 2014]. Second line therapies include short treatment with rituximab, long-term treatment with danazol, dapsone, or immune suppressants like azathioprine, cyclosporine A, mycophenolate mofetil and vinca alkaloid. A general rule is to spare these patients treatments with long-term adverse effects such as prolonged use of OCS, inmmunosuppresive drugs or chemotherapy. Sometimes, on demand therapy is the only treatment used at the time of, or in anticipation of high risk bleeding situations. In other cases, the lowest effective dose of corticosteroids is maintained for weeks or months.

It is worth mentioning that two of the second line treatments (splenectomy and rituximab) are "single shot" and may produce long-term or indefinite remission in a significant proportion of patients, while the effect of eltrombopag is transient while on-treatment. Splenectomy could produce up to 66% of sustained

responses after 5 years, while "single shot" rituximab (100 mg once weekly at a maximum of 4 doses, drug stopped after first remission), may also confer long-term or indefinite remission in about two thirds of patients [Dolai *et al.* 2016].

On the contrary, there is a need for long-term maintenance treatment with eltrombopag, and a relapse of thrombocytopenia occurs in most patients within 2 weeks following drug discontinuation. The more comparable second-line therapies to eltrombopag, in terms of need for long-term oral treatment, are danazol and dapsone. These drugs could be useful to spare corticosteroids until a decision on splenectomy has, eventually, been taken. Danazol and dapsone have shown to induce an overall 58% and 55% response rate, respectively, in a recent systematic review including 200 patients in 11 studies with danazol and 80 patients in 7 studies with dapsone [Weber *et al.* 2017].

3.1.3. Main clinical studies

No new clinical studies have been provided.

3.2. Favourable effects

The favourable effects of the product are already included in section 5.1 of the approved SmPC. No new favourable efficacy or safety data have been provided.

3.3. Uncertainties and limitations about favourable effects

No new uncertainties on the favourable effects have been provided.

3.4. Unfavourable effects

No new unfavourable safety data have been provided. The unfavourable effect of the product are already included in sections 4.4, 4.8 and 5.1 of the approved SmPC.

3.5. Uncertainties and limitations about unfavourable effects

No new uncertainties on the unfavourable effects have been provided.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

No new favourable or unfavourable efficacy or safety data have been submitted.

3.6.2. Balance of benefits and risks

This variation application pertains to a change in the wording of the indication to replace "chronic ITP" to "ITP lasting 6 months or longer from diagnosis". The company also proposes to delete the terms "idiopathic" and "purpura" from the indication.

No new clinical studies have been submitted to ascertain whether the favourable effect of eltrombopag (increase in platelet count and subsequent decreased risk of bleeding) may differ depending on chronic ITP definition (i.e.: > 6 months since ITP diagnosis vs. >12 months since ITP diagnosis). Given the revised definition of “chronic” within the medical community, the current accepted definition of chronic ITP according to the IWG 2009 guidelines is not consistent with the accepted definition of chronic disease that served as the basis for eligibility in the three double-blind, placebo-controlled clinical studies

(TRA102537/RAISE, TRA100773A and TRA100773B) and two open label studies (TRA108057/REPEAT and TRA105325/EXTEND), the pivotal studies that led to the original approval of eltrombopag for adult ITP, and the pivotal PETIT study that contributed to approval in the pediatric indication.

In these pivotal studies, patients were classified as having chronic ITP if their symptoms persisted beyond 6 months, consistent with the previously accepted ASH and BCSH definitions and modified the indication statement to allow physicians the opportunity to treat patients according to current medical practice and the patient population that is consistent with the original approval.

The MAH's approach of limiting the variation to wording changes is, in principle, descriptive and reasonable. The inclusion of "ITP lasting 6 months or longer from diagnosis" is consistent with the population studied in pivotal studies supporting initial MAA. However, the population included in current indication is primary ITP, which is reflected with the term "idiopathic". The initial MAH's proposal of deleting "idiopathic" means widening the indication to any kind of ITP, which has not been considered acceptable. Therefore, the term "primary" has been included by the MAH in the revised wording of the indication provided during the evaluation of this procedure which is considered acceptable.

The MAH has also provided some support that including the 6-month threshold since diagnosis could be also applicable to children, in addition to adults, although spontaneous remissions are more frequently observed in children than in adults. Therefore, it is reasonable to expect that the efficacy observed in adults can be extrapolated to children.

3.7. Conclusions

The overall B/R of Revolade is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Change of the Revolade indication of immune thrombocytopenic purpura to specify the duration of the disease. As a result, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been revised. The Package leaflet has been updated accordingly. Furthermore, minor editorial changes have been introduced in the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Change of the Revolade indication of immune thrombocytopenic purpura to specify the duration of the disease. As a result, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been revised. The Package leaflet has been updated accordingly. Furthermore, minor editorial changes have been introduced in the PI.

Summary

Please refer to the Scientific Discussion document: Revolade H-1110-II-50