HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 June 2010

REVOLADE 25 mg, film-coated tablets
B/14 (CIP code: 374 585-8)
B/28 (CIP code: 374 586-4)

REVOLADE 50 mg, film-coated tablets
B/14 (CIP code: 374 588-7)
B/28 (CIP code: 374 589-3)

Applicant: GLAXOSMITHKLINE

eltrombopag
ATC code: B02BX05

List I
Medicine for hospital prescription only.
Prescription restricted to specialists in haematology or internal medicine.
Medicine requiring special monitoring during treatment.

Orphan medicinal product (3 August 2007)

Date of Marketing Authorisation: 11 March 2010 (centralised procedure)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Eltrombopag

1.2. Background
REVOLADE is a thrombopoietin receptor (TPO-R) agonist.
It is the first TPO-R agonist for oral administration.

1.3. Indication

"REVOLADE is indicated for splenectomised adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
REVOLADE may be considered as second line treatment for non-splenectomised adult patients where surgery is contraindicated."

1.4. Dosage

"Eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts but to maintain platelet counts above the level for risk of bleeding e (> 50,000/µl).
In most patients, measurable elevations in platelet counts take 1-2 weeks.

Adults
The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily.

Monitoring and dose adjustment
After initiating eltrombopag, adjust the dose to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk of bleeding. Do not exceed a dose of 75 mg daily.

Clinical, haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag complete blood counts (CBCs), including platelet count and peripheral blood films, should be assessed weekly until a stable platelet count (≥ 50,000/µl for at least 4 weeks) has been achieved. CBCs including platelet counts and peripheral blood films should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table 1 Dose adjustments of eltrombopag

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
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg

Eltrombopag can be administered in addition to other ITP medicinal products. Modify the dose regimen of concomitant ITP medicinal products, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either upwards or downwards, should be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days may be required.

Discontinuation
Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The thrombocytopenia may recur when the treatment is stopped.

Renal impairment
No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and with close monitoring, for example by testing serum creatinine and/or performing urine analyses.

Hepatic impairment
Eltrombopag should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) unless the expected benefit outweighs the identified risk of portal venous thrombosis.

If the use of eltrombopag is deemed necessary, the starting dose must be 25 mg once daily.

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures.

Paediatric population
REVOLADE is not recommended for use in children and adolescents under the age of 18 due to insufficient data on tolerability and efficacy.

Elderly
There are limited data on the use of eltrombopag in patients aged 65 years and older. In the clinical studies on eltrombopag, overall no clinically significant differences in eltrombopag tolerability has been found between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the possibility that some older people may be more sensitive cannot be excluded..

East Asian patients
Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean). The patient's platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Method of administration
The tablets should be administered orally. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc)."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2010)
B : Blood and blood forming organs
B02 : Antihaemorrhagics
B02BX : Other systemic haemostatics
B02BX05 : Eltrombopag

2.2. Medicines in the same therapeutic category
2.2.1 Medicines that are strictly comparable
Not applicable
2.2.2 Medicines that are not strictly comparable
NPLATE (romiplostim): thrombopoietin receptor agonist for subcutaneous administration.

2.3. Medicines with a similar therapeutic aim
Corticosteroids, immunoglobulins, immunosuppressants (off-label).
Rituximab is currently used to treat ITP under a temporary treatment protocol.

3. ANALYSIS OF AVAILABLE DATA

The company has submitted 5 clinical studies, 3 of them randomised versus placebo (TRA 100773 A and B, and RAISE) and 2 open studies (REPEAT and EXTEND).

3.1. Efficacy

3.1.1 Study TRA 100773 A

Method

Phase II (dose-finding) randomised (1; 1; 1; 1), double-blind study in 4 parallel groups comparing the efficacy and tolerability of 3 doses of eltrombopag (30, 50 and 75 mg) versus placebo. Randomisation was stratified according to use of concomitant ITP treatments, platelet count (≤ or > 15 x 10^9/l) and whether or not splenectomy had been performed.

Inclusion criteria:

- adults (≥18 years) with chronic ITP for at least 6 months;
- platelet count < 30 x10^9/l;
- nonresponder or with relapse in the previous 3 months of at least one ITP treatment.

Treatment studied: eltrombopag 30, 50 or 75 mg/day for 6 weeks. Treatment was to be stopped if the platelet count was > 200 x10^9/l.

Endpoint: proportion of responder patients. Responder patients were defined as those with a platelet count ≥ 50 x 10^9/l on day 43 or who reached a count > 200 x 10^9/l during the study. The platelet count/l was measured each week during the study and 2, 4 and 6 weeks after treatment.

Statistics: the percentages of responders were compared between groups by logistic regression adjusted for the randomisation stratification variables.

Two interim analyses were scheduled: when the results for one third (90) and 2/3 (180) of the patients were available. The significance level was p ≤ 0.0113 (single-tailed test) for the 1st analysis. The study was stopped after this analysis.

Results:

Patients included: median age 50 years, 62% women, 32% were receiving ITP treatment at inclusion, 47% had failure of splenectomy and 48% had a platelet count of < 15 x 10^9/l.
The efficacy results are shown in *Table 1.*

Table 1: Efficacy of eltrombopag

Dose (n patients*)	Placebo (n = 27)	30 mg (n = 29	50 mg (n = 27)	75 mg (n = 26)
% responders (n)	11.1% (3)	27.6% (8)	70.4 % (19)	80.8 %(21)
Odds ratio for active treatment /placebo 95% CI p (single-tailed)	- - -	3.09 [0.69-13.75] 0.07	21.96 [4.72-102.23] <0.001	38.82 [7.62-197.73] < 0.001

* patients who received at least 1 dose of treatment and had an initial platelet count of < 30 x 10^9/l.

On the basis of these results, a dose of 50 mg/day was selected as the initial dose for the subsequent studies.

3.1.2 Study TRA 100773 B

Method

Phase III randomised (2:1), double-blind study in 2 parallel groups to evaluate the efficacy and tolerability of eltrombopag versus placebo. Randomisation was stratified using the same criteria as for study TRA 100773 A.

Main inclusion criteria:

- adults (≥ 18 years) with chronic ITP for at least 6 months, with a platelet count of < 30 x 10^9/l;
- not having responded to at least one ITP treatment or having had a recurrence within 3 months of the previous treatment.

Main exclusion criteria:

- venous thrombosis in the previous year;
- pre-existing heart disease, infarction in the previous 3 months or clinically significant abnormalities in the electrocardiogram.

Treatment studied: eltrombopag, 50 mg once/day for 6 weeks. The daily dose (active treatment or placebo) could be increased to 75 mg if the platelet count was < 50 x 10^9/l on day 22 or thereafter. Treatment was to be stopped if the platelet count was > 200 x 10^9/l.

Authorized concomitant ITP treatments: corticosteroids, azathioprine, danazol, ciclosporin A or mycophenolate mofetil at stable doses for at least 1 month.

Endpoints:

- primary endpoint: proportion of responder patients. Responder patients were defined as those with a platelet count ≥ 50 x 10^9/l on day 43 or who reached a count > 200 x 10^9/l during the study. The platelet count was measured each week during the study and 2, 4 and 6 weeks after treatment.
- Secondary endpoint:
  Incidence and severity of ITP symptoms (grade 1 to 4 bleeding on the WHO scale)

Statistics: the percentages of responders were compared between groups by logistic regression adjusted for the randomisation stratification variables.

Results

Patients included:

A total of 114 patients were included. Their characteristics on inclusion are shown in *Table 2.*

Table 2: Patients at inclusion

	Placebo (n = 38)	Eltrombopag n = 76
Age (years), median and range	51 (21-79)	47 (19-84)
Sex, % (n) - women - men	 71% (27) 29% (11)	 43% (57) 33% (43)
ITP treatments, % (n)	45% (17)	42% (32)
Previous splenectomy, % (n)	37% (14)	41% (31)
Platelet count ≤ 15 x 10^9/l-% (n)	45% (17)	50% (38)

Primary endpoint: the results are shown in *Table 3*.

Table 3: Efficacy of eltrombopag

	Placebo (n = 27)	Eltrombopag (n = 74)
n evaluable* % responders (n)	37 16.2% (6)	73 58.9 % (43)
Odds ratio for active treatment /placebo [95% CI] p (two-tailed)	9.6 [3.3-27.9] < 0.001	

* patients who received at least 1 dose of treatment, baseline platelet count < 30 x 10^9/l.

Secondary endpoint: effect on bleeding (WHO grades 1-4).

By day 43, 60% of the subjects in the placebo group had suffered a bleed compared to 39% of the treated group. The odds ratio of active treatment/placebo for the presence or absence of a bleed by day 43 was 0.27; 95% CI [0.09-0.88], p = 0.029 (logistic regression adjusted for the randomisation stratification variables).

3.1.3 RAISE study (TRA 102537)

Method

Phase III randomised (2:1), double-blind study in 2 parallel groups evaluating the efficacy and tolerability of eltrombopag against placebo. Randomisation was stratified using the same criteria as for study TRA 100773 A.

Main inclusion criteria:

Adults (≥ 18 years) with chronic ITP according to the criteria of the American Society of Hematology[1]/British Committee for Standards in Haematology[2]

- platelet count < 30 x 10^9/l;
- who had previously received at least one ITP treatment (corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide or rituximab)

Main exclusion criteria:

- history of venous or arterial thrombosis or ≥ 2 risk factors for venous or arterial thrombosis.
- known cardiovascular disease or arrhythmia increasing the thromboembolic risk or prolonging the QT interval.

Treatment studied: eltrombopag, 50 mg once a day for 6 months. The daily dose (active treatment or placebo) could be modified according to the platelet response:

- dose increased up to a maximum of 75 mg/day if the platelet count was < 50 x 10^9/l;
- dose maintained if the platelet count was between 50 x 10^9/l and 200 x 10^9/l;
- dose reduced if the platelet count was between 200 x 10^9/l and 400 x 10^9/l;
- treatment discontinued if the platelet count was greater than 400 x 10^9/l, resuming it at a lower dose if the platelet count fell to ≤ 150 x 10^9/l.

Authorized concomitant ITP treatments:

1 George JN, Woolf, SH, Raskob, GE, Wasser JS, Aledort LM, Ballem PJ et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3-40.

2 BCSH (British Committee for Standards in Haematology). Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120:574-596.

- corticosteroids or azathioprine in stable dosages for at least 4 weeks prior to randomisation.
- ciclosporin A, mycophenolate mofetil or danazol in stable dosages for at least 3 months prior to randomisation.
- these treatments had to be continued at stable dosages for the first 6 weeks of the study. A decision could then be taken to reduce the dosages or stop these treatments if the platelet count was greater than 100 x 10^9/l for at least 2 weeks.

Endpoints:

- primary endpoint:
  patient response profile: the aim was to compare, , the likelihood of obtaining a positive response during treatment between the groups.. The response was defined as positive if the platelet count was between 50 x 10^9/l and 400 x 10^9/l, otherwise it was defined as negative. The platelet count was measured once a week for the first 6 weeks then every 4 weeks if the dosage of eltrombopag and of any concomitant ITP medicines was stable.
- secondary endpoints:
  - maximum duration of response;
  - proportion of patients responding at at least 75% of evaluations;
  - incidence and severity of symptoms associated with ITP (bleeding, ecchymosis, petechiae, measured on the WHO bleeding scale);
  - proportion of patients receiving a “rescue” treatment: new ITP treatment and/or increase in the dose of the initial concomitant treatment and/or transfusion of platelets and/or splenectomy during the 6 months of the study;
  - proportion of patients who had a reduction in the dose of the initial concomitant ITP treatment.

Statistics:
A comparison of the response profiles during the 6 months of treatment between the 2 groups was made using a model for analysis of repeated measurements of binary data adjusted for randomisation stratification criteria, using the “generalized estimating equations” method.

Results
Patients included: 197 patients in total. Patient characteristics on inclusion are shown in *Table 4*.

Table 4: Patients at inclusion

	Placebo n = 62	Eltrombopag n = 135
Age (years), median and range	52.5 (18-77)	47 (18-85)
Sex, % (n) - women - men	 69% (43) 31% (19)	 69% (93) 31% (42)
ITP treatments, % (n)	50% (31)	47% (63)
Earlier splenectomy, % (n)	34% (21)	37% (50)
Platelet count = < 15 x 10^9/l-% (n)	48% (30)	50% (67)

Primary endpoint (ITT analysis):

- Comparison of the response profiles over 6 months of treatment: the odds ratio for eltrombopag/placebo was 8.2 (99% CI: 3.59-18.73; p < 0.001).
- The number and percentage of responder subjects at each evaluation is shown in *Table 5*

Table 5: Responder subjects

	Placebo n = 62		Eltrombopag n = 135	
	n evaluable*	% of responders (n)	n evaluable*	% of responders (n)
W 1	60	7% (4)	134	37% (50)
W 2	60	8% (5)	133	46% (61)
W 3	59	8% (5)	133	51% (68)
W 4	60	10% (6)	131	49% (64)
W 5	60	8% (5)	134	56% (75)
W 6	59	14% (8)	134	54% (73)
W 10	47	17% (8)	108	52% (56)
W 14	50	18% (9)	114	46% (52)
W 18	48	17% (8)	112	46% (52)
W 22	47	19% (9)	113	49% (55)
W 26	58	17% (10)	132	52% (68)
W 1 post-treatment	54	15% (8)	110	42% (46)
W 2 post-treatment	55	18% (10)	118	22% (26)
W 4 post-treatment	58	14% (8)	119	20% (24)

*: subjects present at the visit with an available result

Secondary endpoints: Results are shown in *Table 6*.

Table 6: Secondary endpoints

	Placebo n = 62	Eltrombopag n = 135	p
Duration of response (weeks): - Duration of continuous response - mean ± standard deviation median and range - Duration of cumulative response - mean ± standard deviation median and range	n = 60 2.2 ± 5.5 0 (0-25) 2.4 ± 5.9 0 (0-25)	n = 134 9.5 ± 8.9 8.1 (0-26) 11.3 ± 9.5 10.9 (0-26)	_
% of responder patients in at least 75% of evaluations (n);	7% (4)	38% (51)	<0.001*
Bleeding during the study: WHO grade 1-4 (%, n patients)	93% (56)	79% (106)	0.012*
Bleeding during the study: WHO grade 2-4 (%, n patients)	53% (32)	33% (44)	0.02
Use of rescue treatment (%, n patients)	40% (25)	18% (24)	0.001*
Reduction in dose or discontinuation of at least one concomitant ITP treatment (%, n patients)	n = 31 32% (10)	n = 63 59% (37)	0.016*

*: logistic regression adjusted for the randomisation stratification variables.

3.1.4 REPEAT study (TRA 108057)

Method

Open study comprising three 6-week treatment periods separated by 4-week periods without treatment.

Inclusion criteria:

- adult patients with chronic ITP defined according to the criteria of the American Society of Hematology/British Committee for Standards in Haematology,
- platelet count ≥ 20 x 10^9/l and ≤ 50 x 10^9/l.
- already having received at least one ITP treatment.

Treatment studied:

- the initial dose was 50 mg/day. This could be increased to 75 mg/day from day 22 in each cycle if the platelet count was < 50 x 10^9/l at 2 successive measurements. The following cycle was started with the daily dose used at the end of the preceding cycle.
- a treatment cycle was to be discontinued if the platelet count was ≥ 200 x 10^9/l. Patients resumed the following cycle when their platelet count reached < 20 x 10^9/l or was < 50 x 10^9/l in week 4 of the break in treatment.
- subjects who failed to respond during cycle 1 did not take part in the following cycles (2 and 3)
-

Stable concomitant treatments were permitted. Their dose and type could not be changed during the study.

Primary endpoint: proportion of responder patients in cycles 2 or 3. Response was defined as positive when the platelet count on day 43 was ≥ 50 x 10^9/l and at least twice the baseline value or, if treatment was stopped, a count > 200 x 10^9/l.
Statistics: descriptive.

Results
Patients included:
A total of 66 patients were included. The efficacy results are shown in *Table 7*.

Table 7: Proportion of responders

	Cycle 1 (n = 66)	Cycle 2 (n = 55*)	Cycle 3 (n = 51†)
n evaluable	65	54	51
% responders (n)	80% (52)	80% (n = 43)	76% (n = 39)

* including 1 non-responder and 1 not evaluable in cycle 1; †: including 8 non-responders in cycle 1 and 1 not evaluable in cycle 1

The 52 responders in cycle 1 were evaluable in cycles 2 or 3; 45 of these were responders in cycles 2 or 3.

Out of 48 responders in cycle 1 who were evaluable in cycles 2 or 3, 34 were responders in cycles 2 and 3.

3.1.5 EXTEND study (TRA 105325)

Method
Open extension study.

Inclusion criteria: patients with chronic ITP who are already included in a clinical study of eltrombopag, whether or not they are receiving a concomitant ITP treatment.

The study comprised 3 or 4 stages, depending on whether or not the patient was receiving concomitant ITP treatment:

- stage 1: initiation of treatment, intended to determine the dose with which a platelet count of ≥ 50 x 10^9/l could be achieved. If patients were receiving concomitant treatments, the target count was ≥ 100 x 10^9/l, which was deemed to be sufficient to allow a reduction in the concomitant treatments.
- stage 2: intended to reduce or stop concomitant treatments, maintaining a platelet count ≥ 50 x 10^9/l.
- stage 3: adjustment of the dose of eltrombopag to determine the minimum dose with which the platelet count could be maintained at ≥ 50 x 10^9/l, whether or not combined with minimal doses of concomitant ITP treatments.

- stage 4: study of the long-term tolerability and efficacy of eltrombopag and the minimum dose with which the platelet count could be maintained ≥ 50 x 10^9/l. if necessary in combination with concomitant treatments,

Treatment studied:
the initial dose was 50 mg/day. This could be adjusted or the frequency of doses reduced at each visit to keep the platelet count between 50 x 10^9/l and 400 x 10^9/l:

- the dose was to be reduced when the platelet count was > 200 x 10^9/l,
- the treatment was stopped for at least 7 days if the platelet count was > 400 x 10^9/l until it returned to < 150 x 10^9/l. The treatment was then resumed at a lower dose.
-

Primary endpoint: clinical and biological tolerability of treatment.

Main secondary endpoints:

- Proportion of subjects achieving a platelet count ≥ 50 x 10^9/l or ≥ 30 x 10^9/l;
- Maximum period for which the platelet count was maintained ≥ 50 x 10^9/l or ≥ 30 x 10^9/l during treatment;
- Proportion of responder patients during the earlier studies who again responded to treatment with a platelet count ≥ 50 x 10^9/l or ≥ 30 x 10^9/l;
- Effect of eltrombopag treatment on the reduction in concomitant treatments,maintaining a platelet count ≥ 50 x 10^9/l;
- Proportion of patients requiring rescue treatment (new concomitant treatment, need to increase the dose of a concomitant treatment, platelet transfusion or, splenectomy).

<u>Results (data frozen on 7 January 2008)</u>
Patients included: 207 patients received at least 1 dose of eltrombopag. Patient characteristics at inclusion are shown in *Table 8*.

Table 8: Patients at inclusion

	Eltrombopag n = 207
Age (years) mean ± standard deviation	48.8 ± 15.53
Sex, % (n) - women - men	 67% (138) 33% (69)
ITP treatments, % (n)	33% (69)
Earlier splenectomy, % (n)	40% (82)
Platelet count - % (n) < 30 x 10^9/l 30-50 x 10^9/l > 50 x 10^9/l	 70% (145) 18% (37) 12% (25)

The median duration of treatment (n = 206) was 91.5 days (2 to 523).

- Proportion of subjects achieving a platelet count ≥ 50 x 10^9/l or ≥ 30 x 10^9/l; by the time that data recording stopped, 79% of the patients (n = 159/201) had achieved a platelet count ≥ 50 x 10^9/l at least once during the study;16% of patients (n = 32/201) had a platelet count > 400 x 10^9/l; 86% of patients (n = 173/201) achieved a platelet count ≥ 30 x 10^9/l at least once during the study.
- Maximum period for which platelet count maintained ≥ 50 x10^9/l and at twice the baseline count: 51% of patients had a maximum period ≥ 4 weeks, 35% of the

patients treated ≥ 10 weeks had a maximum period ≥ 10 weeks, 24% of patients treated ≥ 25 weeks had a maximum period ≥ 25 weeks, 7% of the patients treated ≥ 52 weeks had a maximum period ≥ 52 weeks.

- Proportion of responder patients during earlier studies who again responded to treatment with a platelet count $\geq 50 \times 10^9$/l: according to earlier studies, 81 to 98% of patients who were previously responders had a platelet count ≥ 50×10^9/l at least once.
  Out of the 55 patients who had received placebo in earlier studies, and who had at least one follow-up visit, 73% (n = 40) had a platelet count ≥ 50×10^9/l at least once during the study.
- Effect of eltrombopag administration on the reduction in concomitant treatments:
  Out of 69 patients who had a concomitant treatment on inclusion, 23 (33%) stopped the treatment or maintained a reduction of at least one of the drugs without needing a rescue treatment up to when data recording stopped.
- Rescue treatments: 15% of patients (31/207) received rescue treatment.

3.2. Adverse effects

3.2.1 Study TRA 100773 A

The adverse events which occurred during the study are summarised in *Table 9*

Table 9: Adverse events occurring during the study*

	Placebo n = 29	30 mg n = 30	50 mg n = 30	75 mg n = 28
Adverse events, % (n patients)	62% (18)	67% (20)	57% (17)	68% (19)
Serious adverse events, % (n patients)	14% (4)	3% (1)	20% (6)	7% (2)
Adverse effects, % (n patients)	38% (11)	33% (10)	27% (8)	36% (10)
Adverse events which led to treatment being stopped, % (n patients)	10% (3)	0	7% (2)	4% (1)

*including the 6 weeks of monitoring after treatment

Headaches were the most common adverse event in all treatment groups. An increase in AST was reported in one patient in the 30 mg group and two in the 75 mg group.

3.2.2 Study TRA 100773 B

The adverse events which occurred during the study are summarised in *Table 10*

Table 10: Adverse events occuring during the study*

	Placebo n = 38	Eltrombopag, n = 76
Adverse events, % (n patients)	45% (17)	70% (53)
Serious adverse events, % (n patients)	11% (4)	8% (6)
Adverse effects, % (n patients)	13% (5)	30% (23)
Adverse events which led to treatment being stopped, % (n patients)	5% (2)	4% (3)

*including the 6 weeks of monitoring after treatment

Nausea (5%) and headaches (5%) were the most common adverse effects in the group treated.

3.2.3 RAISE study (TRA 102537)

The adverse events which occurred during the study are summarised in *Table 11*

Table 11: Adverse events during treatment

	Placebo n = 61*	Eltrombopag, n = 135*
Adverse events, % (n patients)	92% (56)	87% (118)
Serious adverse events, % (n patients)	18% (11)	11% (15)
Adverse effects, % (n patients)	30% (18)	36% (48)
Adverse events which led to treatment being stopped, % (n patients)	7% (4)	9% (12)

*: patients who received at least 1 dose of treatment.

Headaches were the most common adverse event in the 2 treatment groups (about 30% of subjects). Nausea (12% vs 7%) and vomiting (7% vs 2%) were more common in the eltrombopag group than in the placebo group.

Grade ≥ 3 adverse events of were distributed differently between the groups: bleeding was reported in 7% of patients in the placebo group and 2% of patients in the eltrombopag group; raised transaminases were reported in 2% of patients in the placebo group and 3% of patients in the eltrombopag group.

Two patients had a thromboembolic adverse event in the eltrombopag group and none in the placebo group.

3.2.4 REPEAT study (TRA 108057)

A total of 68% of patients had at least one adverse event. Headaches were the commonest adverse event.

No serious adverse event was deemed to be related to the treatment.

3.2.5 EXTEND study (TRA 105325)

The adverse events which occurred during the study are summarised in *Table 12*.

Table 12: Adverse events during treatment

	n = 207
Adverse events, % (n patients)	72% (150)
Serious adverse events, % (n patients)	8% (17)
Adverse effects, % (n patients)	25% (51)
Adverse events which led to treatment being stopped, % (n patients)	4% (9)

The commonest adverse effects were headaches and nausea.

Twelve patients (5.8%) had an abnormality in the liver function tests (increase in ALT, AST, bilirubin or alkaline phosphatase).

Seven patients (3.4%) had a thromboembolic adverse event.

3.2.6 Deaths during the development of eltrombopag

Eight deaths occurred in the studies presented, including 1 on placebo. None was deemed to be related to the treatment.

3.2.7 Main risks of adverse effects (see SPC and EPAR[3])

The main risks of identified or potential adverse effects during the development of REVOLADE are: disturbances in liver parameters, thromboembolic events, recurrence of thrombocytopenia after treatment, formation of reticulin deposits in the bone marrow, risk of fibrosis of the bone marrow, malignant haematological disorders, cataract and tachyphylaxis.

- Increases in AST, ALT and bilirubin were reported in the clinical studies. These were mostly mild and reversible.
- Thromboembolic events (deep vein thrombosis, pulmonary embolism, myocardial infarction, embolism, strokes) were recorded in 17 patients out of 446 treated during clinical development in chronic ITP.
  The risk of thromboembolic events was reported to be increased in patients with chronic liver disease.
- Recurrence of thrombocytopenia after treatment: in most patients, the platelet counts return to baseline levels within 2 weeks after the end of treatment
- Formation of reticulin deposits in the bone marrow and risk of bone marrow fibrosis: limited data suggest that the administration of eltrombopag may be associated with reticulin formation in the bone marrow. However, it has not been established whether this has any long-term clinical consequences.
- Risk of malignant haematological disorders:
  there is a theoretical risk of the progression of existing malignant haematological disorders being triggered by thrombopoietin receptor agonists.
- Cataract: the clinical relevance of this risk, which was identified in animals, is not known.

The risk management plan provides for the monitoring and evaluation of these risks. In particular, it envisages the following measures concerning the potential risk of reticulin deposits in the bone marrow: aperipheral blood film to be performed before treatment is started to establish the baseline profile of morphological cellular abnormalities; a complete blood count to be performed every month once a stable dosage has been established; if immature or dysplastic cells are found, peripheral blood films must then be performed in order to detect any new morphological abnormality or aggravation of existing abnormalities or cytopenia; if the patient develops new abnormalities or aggravation of existing abnormalities or cytopenia, treatment with REVOLADE must be stopped and a bone marrow biopsy including fibrosis markers must be considered.

The company stipulated centralised examination of the medullary biopsies comparing samples before and after 1 and 2 years of treatment in 150 patients.

3.3. Conclusion

Three randomised studies have shown a statistically significant difference in favour of eltrombopag compared to placebo in patients with chronic ITP who were not responders or had relapsed after at least one medical treatment for ITP, whether or not they were splenectomised.

In the first 2 randomised studies (TRA 100773 A and B), the efficacy of eltrombopag was evaluated after 6 weeks of treatment. In study TRA 100773 A, a dose-ranging study, the responder rate was 11.1% in the placebo group and between 27.6 and 80.8% and the active medication/placebo odds ratio was between 3.09 and 38.82 in the eltrombopag groups, depending on the dose administered (30, 50 and 75 mg). In study TRA 100773 B, the initial

3 http://www.ema.europa.eu/humandocs/PDFs/EPAR/revolade/H-1110-en6.pdf

dose of 50 mg was adjusted according to response to treatment. The percentage responder ratewas 58.9% in the treated group compared to 16.2% in the placebo group; active medication/placebo odds ratio 9.6 (95% CI: 3.3-27.9).

In the 3rd randomised study (RAISE), the initial dose of 50 mg was adjusted according to the response to treatment. The main aim was to compare the groups as regards the response profiles during the 6 months of treatment; the platelet count was measured every week for 6 weeks then once a month. The eltrombopag/placebo odds ratio was 8.2 (99% CI: 3.59-18.73); over the 6 months of treatment, the percentage of responders was between 37 and 56% in the eltrombopag group and between 7 and 19% in the placebo group.

The main adverse effects reported in the 5 clinical studies (including the open studies) were disturbances in liver parameters, thromboembolic events, recurrence of thrombocytopenia when the treatment was stopped, formation of reticulin deposits in the bone marrow, a risk of myelofibrosis, a risk of malignant haemopathies progressing and of cataracts developing. The risk management plan provides for the monitoring and evaluation of these risks.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease leading to the peripheral destruction of platelets and central inhibition of platelet production. The chronic forms mostly affect adults.

ITP usually manifests itself as a cutaneous haemorrhagic (purpura, ecchymosis) and/or mucosal (nosebleed, bleeding gums, endobuccal bullae, menorrhagia) bleeding which usually occurs only when the platelet count is below 30 x 10^9/l. In rare cases and when the platelet count is very low (< 10 x 10^9/l), serious visceral bleeding (haematuria, gastro-intestinal or cerebromeningeal haemorrhage) may occur.

ITP has a major impact on patients' quality of life; the risk of bleeding is ever-present and forces them to restrict their activities.

This medicine is intended as curative therapy.

The efficacy/adverse effects ratio for this medicine is high.

Public health benefit

Idiopathic thrombocytopenic purpura is a serious condition but represents a small public health burden because of its rarity. The burden of the disease corresponding to the more limited population covered by the therapeutic indication for REVOLADE (chronic idiopathic thrombocytopenic purpura in adults which is refractory to splenectomy or where splenectomy is contraindicated) can therefore only be small.

An improvement in the management of idiopathic thrombocytopenic purpura is a public health need which is already an established priority (Law of 9 August 2004 on Public Health Policy, Rare Diseases Plan).

In view of the available clinical data and the current treatment strategies, the medicinal product REVOLADE is expected to have a low impact in terms of morbidity.

The impact of the treatment on the quality of life is not documented.

Applicability of the results of clinical studies to practice is however not assured, given the comparator used (placebo) and the limited duration of the pivotal study performed (24 weeks).

Thus, the medicinal product REVOLADE should therefore provide only a partial response to the identified public health need.

Finally, it is possible that, by reducing the need for immunoglobulins in emergency situations, the medicinal product REVOLADE could reduce use of the healthcare system. However, the reduction in the need for immunoglobulins in the population treated with the medicinal product REVOLADE is difficult to quantify at this stage.

Consequently, in the same way as with Nplate, there is expected to be a public health benefit from the medicinal product REVOLADE in this indication. This benefit is at best small.

This medicinal product is a rescue treatment in the treatment of chronic ITP in adults where the usual treatments have failed in refractory splenectomised patients and in non-splenectomised patients when surgery is contraindicated.

There is a treatment alternative (NPLATE).

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

Shares the improvement in actual benefit (IAB II) of NPLATE in the context of rescue treatment for chronic ITP in adults where the usual treatments have failed in refractory splenectomised patients and in non-splenectomised patients when surgery is contraindicated.

4.3. Therapeutic use[4, 5, 6, 7]

4.3.1 Treatment strategy

The treatment strategy in ITP depends on three factors:
- the severity of the haemorrhagic syndrome
- the extent of the thrombocytopenia
- patient characteristics (age, sex, associated diseases, etc.)

There is usually thought to be no need for treatment when the platelet count is higher than 30 x 10^9/l in the absence of bleeding. Only patients below 30 x 10^9/l are therefore treated. This threshold can nevertheless be raised according to the situation (elderly patients, presence of comorbidities). The aim of treatment in the acute phase of the disease is to increase the platelet count as quickly as possible to protect the patient from bleeding complications in the hope that they will recover within the next 12 months.

- In the acute phase, first line treatment involves administration of corticosteroids and/or intravenous immunoglobulins the respective indications for which are influenced by the severity of bleeding and whether or not the patient has previously responded to one or other of these two treatments. Transfusions of platelets are indicated only in exceptional life-threatening cases.

- In chronic ITP (persisting for more than 12 months), the aim of treatment is to increase the platelet count to over 30 to 50 x 10^9/l and to maintain it above this threshold. Splenectomy is the reference treatment despite the risks associated with surgery (long-term response rate about 65%). The contraindications to splenectomy (fewer than 20% of cases) relate to comorbidities or advanced age.

Patients with extreme thrombocytopenia may benefit from pre-splenectomy treatments aimed at increasing their platelet levels (corticosteroids or immunoglobulins).

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4 Godeau B, Provan D, Bussel J. Immune thrombocytopenic purpura in adults. Current Opinion Hematol 2007;14:535-56

5 Orphanet [homepage on the Internet]. Paris : Purpura Thrombopénique Auto-immun. [updated Jul 2006 ; cited 2008 Dec 10]. Available from : http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=FR&Expert=3002

6 Diagnosis and Treatment of Idiopathic Thrombocytopenic Purpura: Recommendations of the American Society of Hematology Ann Intern Med 1997;126:319-26

7 Groupe d'Etude des Cytopénies Auto-Immunes. Le Purpura Thrombopénique Immunologique (PTI) [monograph on the Internet]. Créteil; 2007 Nov [cited 2009 Feb 09]. Available from: http://www.lesmedecins.org/gecai/files/Purpura_Thrombopenique.pdf

Rituximab is also used in a short-term treatment protocol.

Patients who continue to suffer from thrombocytopenia after splenectomy in whom rituximab fails are at greater risk than the general population (mortality close to 10% in the most severe cases).

Thrombopoietin receptor agonists are indicated in patients who do not respond to splenectomy or in whom splenectomy is contraindicated.

In cases of refractory ITP (thrombocytopenia which persists after several lines of treatment including splenectomy have been tried, and in whom an effective treatment is needed to keep platelet levels above 20-30 x 10^9/l), the treatment options are limited.

It is proposed that if splenectomy fails, patients should be retreated with treatments which were ineffective before splenectomy, particularly by giving a further short course of corticosteroids. Intensification of treatment, and in particular the use of immunosuppressant therapies (off-label), may be justified in the most severe forms of disease. The potential severity of the adverse effects of immunosuppressants (cyclophosphamide, azathioprine, ciclosporin and mycophenolate mofetil) are such that they must be reserved for patients who fail on splenectomy, rituximab and TPO receptor agonists and who have severe, symptomatic thrombocytopenia.

4.3.2 Role of the medicinal product

This medicinal product is rescue treatment in the treatment of chronic ITP in adults where the usual treatments have failed in refractory splenectomised patients and in non-splenectomised patients when surgery is contraindicated.

4.4. Target population

The target population for REVOLADE is defined by two groups of patients:

- splenectomised adults with chronic ITP who are refractory to or unable to tolerate other treatments (such as corticosteroids or immunoglobulins).
- non-splenectomised adults with chronic ITP who do not respond satisfactorily to or are unable to tolerate corticosteroids and immunoglobulins and in whom surgery is medically contraindicated.

The annual incidence of ITP in adults differs between studies depending on how the ITP is defined and the threshold platelet countused.

In a prospective study based on a cohort of adults (northern region of the United Kingdom) with newly diagnosed ITP and a platelet count of < 50 x 10^9/l for a period of more than 5 years[8], the annual incidence of ITP in adults was estimated to be 1.6 cases per 100,000 per year.

Extrapolating this incidence to the adult French population[9], the incident population of adults with ITP is estimated to be about 792 patients.

The European data are mixed and show a prevalence ranging from 21 to 35 patients per 100,000 people. According to Orphanet, the mean prevalence of ITP is 25/100,000[10].

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8 Neylon A. J. et al. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. British Journal of Haematology, 2003, 122, 966-974

9 Insee report of 1 January 2008

10 Orphanet Reports – November 2008

On this basis, the prevalent adult population is estimated to be 12,375 patients.

ITP becomes a chronic disease in 70% of these patients, or about 8660 adults, 80% of whom are treated, i.e. 6930 adults.

Among these, several subgroups of patients can be identified (expert opinion):

- **First group** (50% of patients, i.e. 3465 patients):

This consists of patients treated with rituximab under the temporary treatment protocol granted by the French Healthcare Product Safety Agency (AFSSAPS). On the basis of the long-term data quoted[11], about 70% of patients are non-responders after treatment with rituximab, i.e. approximately 2425 patients.

After failure of rituximab, it is thought that 85% of patients are eligible for splenectomy, i.e. about 2060 patients. The failure rate for splenectomy is about 30%[12]: consequently, about 620 patients are eligible for treatment with REVOLADE.

The other patients (15%) who do not respond to rituximab and who cannot benefit from splenectomy thus total about 365 patients.

- **Second group** (20% of patients, i.e. about 1390 patients):

This consists of patients managed with specific treatments, particularly corticosteroids given intermittently to maintain their platelet count at a suitable level. Consequently, these patients are not eligible for treatment with REVOLADE.

- **Third group** (30% of patients, i.e. 2080 patients):

These patients need treatment but are not treated with rituximab. 85% (1767 patients) and are eligible for splenectomy. Of these, and as described previously, about 30%, i.e. about 530 patients, will not respond to surgery and will benefit from treatment with REVOLADE as a last resort.

The remaining 15% of patients are not eligible for surgery because of contraindications: consequently, these 312 patients may benefit from treatment with REVOLADE.

In total, the target population for REVOLADE can be estimated to be about 670 non-splenectomised patients and about 1150 splenectomised patients, i.e. 1820 patients.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The transparency Committee would like to be kept informed of the results of the Risk Management Plan, particularly the potential risk of reticulin deposits and bone marrow fibrosis.

4.5.1 Packaging: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65%

11 Godeau B et al. Immune thrombocytopenic purpura in adults. Current Opinion Hematol 2007;14:535-56

12 Kumar S, Diehn FE, Gertz MA, Tefferi A. Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. Ann Hematol 2002; 81:312–319.