レボレード錠 12.5 mg, 25 mg に関する資料

ノバルティスファーマ株式会社

本資料に記載された情報に係る権利及び内容の責任は,
ノバルティスファーマ株式会社にあります。
当該製品の適正使用以外の営利目的に本資料を
利用することはできません。

1　起原又は発見の経緯

起原又は発見の経緯は 2.5 臨床に関する概括評価参照。

2　開発の経緯

エルトロンボパグ　オラミンの小児 AA に対する開発の経緯図を Figure 2-1 に示す。

Figure 2-1　小児 AA に対する開発の経緯図

試験項目	
臨床	国際共同/非対照試験/CETB115G2201
治験相談	医薬品申請前相談（オーファン）/P7217

[redacted]

1　外国における使用状況等

ETB115 は 2008 年 11 月に米国で「副腎皮質ステロイド，免疫グロブリン又は脾臓摘出で十分な効果が得られない成人慢性特発性血小板減少性紫斑病」の効能・効果で初めて承認されて以降，世界 100 ヵ国以上で承認されている。

免疫抑制療法抵抗性の成人の重症再生不良性貧血（SAA）に対し，米国では 2014 年 8 月に，欧州では 2015 年 9 月に承認を取得した。また，成人及び小児（2 歳以上）の SAA に対する免疫抑制療法との併用による一次治療として米国で 2018 年 11 月に承認されたが，欧州では承認されていない。再生不良性貧血に対する主要国での承認状況を，Table 1-1 に示す。

Table 1-1　再生不良性貧血に対する主要国での承認状況

国名	販売名	効能・効果	承認年月
米国	Promacta	免疫抑制療法抵抗性の SAA	2014 年 8 月
		成人及び小児（2 歳以上）SAA 患者に対する免疫抑制療法との併用による一次治療	2018 年 11 月
欧州	Revolade	免疫抑制療法抵抗性又は多数の前治療歴があり造血幹細胞移植が不適の成人後天性 SAA	2015 年 9 月

2　外国の添付文書等の概要

スイス・ノバルティス社の企業中核データシート（CCDS）を提出する。また 2023 年 10 月時点で最新の米国及び欧州の添付文書を提出する。

[redacted]

REVOLADE®/PROMACTA® (eltrombopag)
12.5 mg, 25 mg, 50 mg, 75 mg Film-coated tablets
12.5 mg, 25 mg Powder for oral suspension

Core Data Sheet (CDS)

[redacted]

P2-55は非公表とするため削除

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROMACTA safely and effectively. See full prescribing information for PROMACTA.

PROMACTA® (eltrombopag) tablets, for oral use
PROMACTA® (eltrombopag) for oral suspension
Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C and RISK OF HEPATOTOXICITY

See full prescribing information for complete boxed warning.

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. (5.1)

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended. (5.2)

----------INDICATIONS AND USAGE----------

PROMACTA is a thrombopoietin receptor agonist indicated:

- for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. (1.1)
- for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. (1.2)
- in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia. (1.3)
- for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)

Limitations of Use:

- PROMACTA is not indicated for the treatment of patients with myelodysplastic syndrome (MDS). (1.4)
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection. (1.4)

----------DOSAGE AND ADMINISTRATION----------

- Take PROMACTA without a meal or with a meal low in calcium (≤ 50 mg). Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements. (2.4, 7.1, 12.3)
- Persistent or Chronic ITP: Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older, and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9/L. Do not exceed 75 mg per day. (2.1, 8.6, 8.7)
- Chronic Hepatitis C-associated Thrombocytopenia: Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- First-line Severe Aplastic Anemia: Initiate PROMACTA once daily at 2.5 mg/kg (in pediatric patients aged 2 to 5 years old), 75 mg (pediatric patients aged 6 to 11 years old), or 150 mg for patients aged 12 years and older concurrently with standard immunosuppressive therapy. Reduce initial dose in patients of East-/Southeast-Asian ancestry. Modify dosage for toxicity or elevated platelet counts. (2.3, 8.7)
- Refractory Severe Aplastic Anemia: Initiate PROMACTA at 50 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 150 mg per day. (2.3, 8.6, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 12.5 mg, 25 mg, 50 mg, and 75 mg (3)
- For oral suspension: 12.5 mg and 25 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Monitor liver function before and during therapy. (5.2)
- Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia. (5.3)
- Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.4)

----------ADVERSE REACTIONS----------

Across all indications, the most common adverse reactions (≥ 20% in any indication) were: anemia, nausea, pyrexia, alanine aminotransferase increased, cough, fatigue, headache, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed during treatment. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C and RISK OF HEPATOTOXICITY

1 INDICATIONS AND USAGE
- 1.1 Treatment of Thrombocytopenia in Patients With Persistent or Chronic Immune Thrombocytopenia
- 1.2 Treatment of Thrombocytopenia in Patients With Hepatitis C Infection
- 1.3 Treatment of Severe Aplastic Anemia
- 1.4 Limitations of Use

2 DOSAGE AND ADMINISTRATION
- 2.1 Persistent or Chronic Immune Thrombocytopenia
- 2.2 Chronic Hepatitis C-Associated Thrombocytopenia
- 2.3 Severe Aplastic Anemia
- 2.4 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Hepatic Decompensation in Patients With Chronic Hepatitis C
- 5.2 Hepatotoxicity
- 5.3 Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia
- 5.4 Thrombotic/Thromboembolic Complications
- 5.5 Cataracts

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Polyvalent Cations (Chelation)
- 7.2 Transporters
- 7.3 Protease Inhibitors
- 7.4 Peginterferon Alfa-2a/b Therapy

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Ethnicity

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Pharmacology and/or Toxicology

14 CLINICAL STUDIES
- 14.1 Persistent or Chronic ITP
- 14.2 Chronic Hepatitis C-Associated Thrombocytopenia
- 14.3 Severe Aplastic Anemia

16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 Tablets
- 16.2 For Oral Suspension

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C and RISK OF HEPATOTOXICITY

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation *[see Warnings and Precautions (5.1)]*.

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of Thrombocytopenia in Patients With Persistent or Chronic Immune Thrombocytopenia

PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

1.2 Treatment of Thrombocytopenia in Patients With Hepatitis C Infection

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.

1.3 Treatment of Severe Aplastic Anemia

- PROMACTA is indicated in combination with standard immunosuppressive therapy (IST) for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
- PROMACTA is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

1.4 Limitations of Use

- PROMACTA is not indicated for the treatment of patients with myelodysplastic syndromes (MDS) *[see Warnings and Precautions (5.3)]*.
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

2 DOSAGE AND ADMINISTRATION

2.1 Persistent or Chronic Immune Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.4)]*. In clinical trials, platelet counts generally increased within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing PROMACTA *[see Clinical Studies (14.1)]*.

Initial Dose Regimen:

Adult and Pediatric Patients 6 Years and Older with ITP: Initiate PROMACTA at a dose of 50 mg once daily, except in patients who are of East-/Southeast-Asian ancestry or who have mild to severe hepatic impairment (Child-Pugh class A, B, C).

For patients of East-/Southeast-Asian ancestry with ITP, initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

For patients with ITP and mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

For patients of East-/Southeast-Asian ancestry with ITP and hepatic impairment (Child-Pugh class A, B, C), consider initiating PROMACTA at a reduced dose of 12.5 mg once daily *[see Clinical Pharmacology (12.3)]*.

Pediatric Patients with ITP Aged 1 to 5 Years: Initiate PROMACTA at a dose of 25 mg once daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 1. During therapy with PROMACTA, assess complete blood counts (CBCs) with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks, and then follow standard monthly monitoring.

Table 1. Dose Adjustments of PROMACTA in Patients With Persistent or Chronic Immune Thrombocytopenia

Platelet count result	Dose adjustment or response
< 50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥ 200 x 10^9/L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.
> 400 x 10^9/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
> 400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

In patients with ITP and hepatic impairment (Child-Pugh class A, B, C), after initiating PROMACTA or after any subsequent dosing increase, wait 3 weeks before increasing the dose.

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with PROMACTA. Do not administer more than one dose of PROMACTA within any 24-hour period.

Discontinuation: Discontinue PROMACTA if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with PROMACTA at the maximum daily dose of 75 mg.

Excessive platelet count responses, as outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*. Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

2.2 Chronic Hepatitis C-Associated Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.4)].* In clinical trials, platelet counts generally began to rise within the first week of treatment with PROMACTA *[see Clinical Studies (14.2)]*.

Initial Dose Regimen: Initiate PROMACTA at a dose of 25 mg once daily.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 25-mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy.

During antiviral therapy, adjust the dose of PROMACTA to avoid dose reductions of peginterferon. Monitor CBCs with differentials, including platelet counts, weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA.

For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Table 2. Dose Adjustments of PROMACTA in Adults With Thrombocytopenia Due to Chronic Hepatitis C

Platelet count result	Dose adjustment or response
$< 50 \times 10^9$/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$> 400 \times 10^9$/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $< 150 \times 10^9$/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
$> 400 \times 10^9$/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

Discontinuation: The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.

PROMACTA should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 2, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.3 Severe Aplastic Anemia

First-Line Severe Aplastic Anemia

Initiate PROMACTA concurrently with standard immunosuppressive therapy *[see Clinical Studies (14.3)]*.

Initial Dose Regimen

The recommended initial dose regimen is listed in Table 3. Do not exceed the initial dose of PROMACTA.

Table 3. Recommended Initial PROMACTA Dose Regimen in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose regimen
Patients 12 years and older	150 mg once daily for 6 months
Pediatric patients 6 to 11 years	75 mg once daily for 6 months
Pediatric patients 2 to 5 years	2.5 mg/kg once daily for 6 months

For patients with severe aplastic anemia of East-/Southeast-Asian ancestry or those with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, C), decrease the initial PROMACTA dose by 50% as listed in Table 4 *[see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]*.

If baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels are > 6 x upper limit of normal (ULN), do not initiate PROMACTA until transaminase levels are < 5 x ULN. Determine the initial dose for these patients based on Table 3 or Table 4.

Table 4. Recommended Initial PROMACTA Dose Regimen for Patients of East-/Southeast-Asian Ancestry or Those With Mild, Moderate, or Severe Hepatic Impairment (Child-Pugh class A, B, C) in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose regimen
Patients 12 years and older	75 mg once daily for 6 months
Pediatric patients 6 to 11 years	37.5 mg once daily for 6 months
Pediatric patients 2 to 5 years	1.25 mg/kg once daily for 6 months

Monitoring and Dose Adjustment for PROMACTA: Perform clinical hematology and liver tests regularly throughout therapy with PROMACTA *[see Warnings and Precautions (5.2)]*.

Modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 5.

Table 5. Dose Adjustments of PROMACTA for Elevated Platelet Counts in the First-Line Treatment of Severe Aplastic Anemia

Platelet count result	Dose adjustment or response
> 200 x 10^9/L to ≤ 400 x 10^9/L	Decrease the daily dose by 25 mg every 2 weeks to lowest dose that maintains platelet count ≥ 50 x 10^9/L. In pediatric patients under 12 years of age, decrease the dose by 12.5 mg.
> 400 x 10^9/L	Discontinue PROMACTA for one week. Once the platelet count is < 200 x 10^9/L, reinitiate PROMACTA at a daily dose reduced by 25 mg (or 12.5 mg in pediatric patients under 12 years of age).

Table 6 summarizes the recommendations for dose interruption, reduction, or discontinuation of PROMACTA in the management of elevated liver transaminase levels and thromboembolic events.

Table 6. Recommended Dose Modifications for PROMACTA for ALT or AST Elevations and Thromboembolic Events

Event	Recommendation
ALT or AST elevations	Increase in ALT or AST > 6 x ULN Discontinue PROMACTA. Once ALT or AST is < 5 x ULN, reinitiate PROMACTA at the same dose. Increase in ALT or AST > 6 x ULN after reinitiating PROMACTA Discontinue PROMACTA and monitor ALT or AST at least every 3 to 4 days. Once ALT or AST is < 5 x ULN, reinitiate PROMACTA at a daily dose reduced by 25 mg compared to the previous dose. If ALT or AST returns to > 6 x ULN on the reduced dose Reduce the daily dose of PROMACTA by 25 mg until ALT or AST is < 5 x ULN. In pediatric patients under 12 years of age, reduce the daily dose by at least 15% to the nearest dose that can be administered.
Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolus, stroke, myocardial infarction)	Discontinue PROMACTA but remain on horse antithymocyte globulin (h-ATG) and cyclosporine.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

The total duration of PROMACTA treatment is 6 months.

Refractory Severe Aplastic Anemia

Use the lowest dose of PROMACTA to achieve and maintain a hematologic response. Dose adjustments are based upon the platelet count. Hematologic response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting PROMACTA *[see Clinical Studies (14.3)]*.

Initial Dose Regimen: Initiate PROMACTA at a dose of 50 mg once daily.

For patients with severe aplastic anemia of East-/Southeast-Asian ancestry or those with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 50-mg increments every 2 weeks as necessary to achieve the target platelet count greater than or equal to 50 x 10^9/L as necessary. Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 7.

Table 7. Dose Adjustments of PROMACTA in Patients With Refractory Severe Aplastic Anemia

Platelet count result	Dose adjustment or response
< 50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 200 x 10^9/L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400 x 10^9/L	Stop PROMACTA for 1 week. Once the platelet count is < 150 x 10^9/L, reinitiate therapy at a dose reduced by 50 mg.
> 400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of PROMACTA may be reduced by 50% *[see Clinical Studies (14.3)]*. If counts remain stable after 8 weeks at the reduced dose, then discontinue PROMACTA and monitor blood counts. If platelet counts drop to less than 30 x 10^9/L, hemoglobin to less than 9 g/dL, or absolute neutrophil count (ANC) to less than 0.5 x 10^9/L, PROMACTA may be reinitiated at the previous effective dose.

Discontinuation: If no hematologic response has occurred after 16 weeks of therapy with PROMACTA, discontinue therapy. If new cytogenetic abnormalities are observed, consider discontinuation of PROMACTA *[see Adverse Reactions (6.1)]*. Excessive platelet count responses (as outlined in Table 7) or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.4 Administration

Administration of Tablets and Oral Suspension: Take PROMACTA without a meal or with a meal low in calcium (≤ 50 mg). Take PROMACTA at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (containing > 50 mg calcium e.g., dairy products, calcium-fortified juices, and certain fruits and vegetables), or supplements containing polyvalent cations, such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Do not split, chew, or crush tablets and mix with food or liquids.

Preparation of the Oral Suspension: Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration of PROMACTA for oral suspension.

Administer the oral suspension immediately after preparation. **Discard any suspension not administered within 30 minutes after preparation.**

Prepare the suspension with water only. NOTE: Do not use hot water to prepare the suspension.

For details on preparation and administration of the suspension, including the recommended duration of use of each oral dosing syringe, *[see Instructions for Use]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 12.5-mg tablets — round, biconvex, white, film-coated tablets debossed with “GS MZ1” and 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 12.5 mg of eltrombopag free acid.
- 25-mg tablets — round, biconvex, orange, film-coated tablets debossed with “GS NX3” and 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid.

- 50-mg tablets — round, biconvex, blue, film-coated tablets debossed with "GS UFU" and 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 50 mg of eltrombopag free acid.
- 75-mg tablets — round, biconvex, pink, film-coated tablets debossed with "GS FFS" and 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 75 mg of eltrombopag free acid.

For Oral Suspension

- 12.5-mg packet — contains a reddish-brown to yellow powder for reconstitution.
- 25-mg packet — contains a reddish-brown to yellow powder for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Decompensation in Patients With Chronic Hepatitis C

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy occurred more frequently on the arm receiving treatment with PROMACTA plus antivirals (7%) than the placebo plus antivirals arm (4%). Patients with low albumin levels (less than 3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score greater than or equal to 10 at baseline had a greater risk for hepatic decompensation on the arm receiving treatment with PROMACTA plus antivirals. Discontinue PROMACTA if antiviral therapy is discontinued.

5.2 Hepatotoxicity

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity *[see Adverse Reactions (6.1)]*. One patient (< 1%) with ITP treated with PROMACTA in clinical trials experienced drug-induced liver injury. Eleven patients (1%) with chronic hepatitis C treated with PROMACTA in clinical trials experienced drug-induced liver injury.

Treatment of ITP, Chronic Hepatitis C-associated Thrombocytopenia, and Refractory Severe Aplastic Anemia

Measure serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. PROMACTA inhibits UDP-glucuronosyltransferase (UGT)1A1 and organic anion-transporting polypeptide (OATP)1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or stabilized. Discontinue PROMACTA if ALT levels increase to greater than or equal to 3 x ULN in patients with normal liver function or greater than or equal to 3 x baseline (or greater than 5 x ULN, whichever is the lower) in patients with pre-treatment elevations in transaminases and are:

- progressively increasing, or
- persistent for greater than or equal to 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

If the potential benefit for reinitiating treatment with PROMACTA is considered to outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur if PROMACTA is reinitiated. If liver test abnormalities persist, worsen, or recur, then permanently discontinue PROMACTA.

First-Line Treatment of Severe Aplastic Anemia

Measure ALT, AST, and bilirubin prior to initiation of PROMACTA, every other day while hospitalized for h-ATG therapy, and then every 2 weeks during treatment. During treatment, manage increases in ALT or AST levels as recommended in Table 6.

5.3 Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia

A randomized, double-blind, placebo-controlled, multicenter trial in patients with International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2 or high risk MDS with thrombocytopenia, receiving azacitidine in combination with either PROMACTA (n = 179) or placebo (n = 177) was terminated due to lack of efficacy and safety reasons, including increased progression to acute myeloid leukemia (AML). Patients received PROMACTA or placebo at a starting dose of 200 mg once daily, up to a maximum of 300 mg once daily, in combination with azacitidine for at least six cycles. The incidence of death (overall survival) was 32% (57/179) in the PROMACTA arm versus 29% (51/177) in the placebo arm (HR [95% CI] = 1.42 [0.97, 2.08], showing an increased relative risk of death in this trial by 42% in the PROMACTA arm). The incidence of progression to AML was 12% (21/179) in the PROMACTA arm versus 6% (10/177) in the placebo arm (HR [95% CI] = 2.66 [1.31, 5.41], showing an increased relative risk of progression to AML in this trial by 166% in the PROMACTA arm).

5.4 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts.

Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet counts *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, 3% (31/955) treated with PROMACTA experienced a thrombotic event compared with 1% (5/484) on placebo. The majority of events were of the portal venous system (1% in patients treated with PROMACTA versus less than 1% for placebo).

In a controlled trial in patients with chronic liver disease and thrombocytopenia not related to ITP undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg of PROMACTA once daily. Seven thrombotic complications (six patients) were reported in the group that received PROMACTA and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received PROMACTA were portal vein thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the six patients in the group that received PROMACTA experienced a thrombotic complication within 30 days of completing treatment with PROMACTA and at a platelet count above 200 x 10^9/L. The risk of portal venous thrombosis was increased in thrombocytopenic patients with chronic liver disease treated with 75 mg of PROMACTA once daily for 2 weeks in preparation for invasive procedures.

5.5 Cataracts

In the three controlled clinical trials in adults with persistent or chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg of PROMACTA daily and 8 (7%) placebo-group patients. In the extension trial, cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. In the two controlled clinical trials in patients with chronic hepatitis C and

thrombocytopenia, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

Cataracts were observed in toxicology studies of eltrombopag in rodents *[see Nonclinical Toxicology (13.2)]*. Perform a baseline ocular examination prior to administration of PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and symptoms of cataracts.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions associated with PROMACTA are described in other sections.

- Hepatic Decompensation in Patients with Chronic Hepatitis C *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia *[see Warnings and Precautions (5.3)]*
- Thrombotic/Thromboembolic Complications *[see Warnings and Precautions (5.4)]*
- Cataracts *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Persistent or Chronic Immune Thrombocytopenia

Adults: In clinical trials, hemorrhage was the most common serious adverse reaction and most hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse reactions included thrombotic/thromboembolic complications *[see Warnings and Precautions (5.4)]*. The data described below reflect exposure of PROMACTA to patients with persistent or chronic ITP aged 18 to 85 years, of whom 66% were female, in three placebo-controlled trials and one open-label extension trial *[see Clinical Studies (14.1)]*. PROMACTA was administered to 330 patients for at least 6 months and 218 patients for at least 1 year.

Table 8 presents the most common adverse drug reactions (experienced by greater than or equal to 3% of patients receiving PROMACTA) from the three placebo-controlled trials, with a higher incidence in PROMACTA versus placebo.

Table 8. Adverse Reactions (≥ 3%) From Three Placebo-controlled Trials in Adults With Persistent or Chronic Immune Thrombocytopenia

Adverse reaction	PROMACTA 50 mg n = 241 (%)	Placebo n = 128 (%)
Nausea	9	3
Diarrhea	9	7
Upper respiratory tract infection	7	6
Vomiting	6	< 1
Urinary tract infection[a]	5	4
Increased ALT	5	3
Myalgia	5	2
Oropharyngeal pain	4	3
Increased AST	4	2
Pharyngitis	4	2
Back pain	3	2
Influenza	3	2
Paresthesia	3	2
Rash	3	2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Includes PTs of urinary tract infection, cystitis, urinary tract infection bacterial, and bacteriuria.

In the three controlled clinical persistent or chronic ITP trials, alopecia, musculoskeletal pain, blood alkaline phosphatase increased, and dry mouth were the adverse reactions reported in 2% of patients treated with PROMACTA and in no patients who received placebo.

Among 302 patients with persistent or chronic ITP who received PROMACTA in the single-arm extension trial, the adverse reactions occurred in a pattern similar to that seen in the placebo-controlled trials. Table 9 presents the most common treatment-related adverse reactions (experienced by greater than or equal to 3% of patients receiving PROMACTA) from the extension trial.

Table 9. Treatment-related Adverse Reactions (≥ 3%) From Extension Trial in Adults With Persistent or Chronic Immune Thrombocytopenia

Adverse reaction	PROMACTA 50 mg n = 302 (%)
Headache	10
ALT increased	5
AST increased	5
Cataract	5
Fatigue	5
Blood bilirubin increased	4
Nausea	4
Hyperbilirubinemia	3
Diarrhea	3

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

In the three controlled persistent or chronic ITP trials, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of patients for PROMACTA and placebo, respectively. Four patients (1%) treated with PROMACTA and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seventeen of the patients treated with PROMACTA in the controlled trials with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA in the extension

trial. Eight of these patients again experienced liver test abnormalities (less than or equal to Grade 3) resulting in discontinuation of PROMACTA in one patient. In the extension persistent or chronic ITP trial, six additional patients had PROMACTA discontinued due to liver test abnormalities (less than or equal to Grade 3).

In the three controlled persistent or chronic ITP trials, cataracts developed or worsened in 7% of patients treated with PROMACTA and 7% of patients in the placebo group. All patients had documented, preexisting risk factors for cataractogenesis, including corticosteroid use. In the extension trial, cataracts developed or worsened in 11% of patients who underwent ocular examination prior to therapy with PROMACTA. Seventy-two percent of patients had preexisting risk factors, including corticosteroid use.

The safety of PROMACTA was also assessed in all patients treated in 7 adult persistent or chronic ITP clinical trials (N = 763 PROMACTA-treated patients and 179 placebo-treated patients). Thromboembolic events were reported in 6% of PROMACTA-treated patients versus 0% of placebo-treated patients and thrombotic microangiopathy with acute renal failure was reported in < 1% of PROMACTA-treated patients versus 0% of placebo-treated patients.

In a placebo-controlled trial of PROMACTA in patients with chronic liver disease and thrombocytopenia not related to ITP, six patients treated with PROMACTA and one patient in the placebo group developed portal vein thromboses *[see Warnings and Precautions (5.4)]*.

Pediatric Patients: The data described below reflect median exposure to PROMACTA of 91 days for 107 pediatric patients (aged 1 to 17 years) with persistent or chronic ITP, of whom 53% were female, across the randomized phase of two placebo-controlled trials.

Table 10 presents the most common adverse drug reactions (experienced by greater than or equal to 3% of pediatric patients 1 year and older receiving PROMACTA) across the two placebo-controlled trials, with a higher incidence for PROMACTA versus placebo.

Table 10. Adverse Reactions (≥ 3%) With a Higher Incidence for PROMACTA Versus Placebo From Two Placebo-controlled Trials in Pediatric Patients 1 Year and Older With Persistent or Chronic Immune Thrombocytopenia

Adverse reaction	PROMACTA n = 107 (%)	Placebo n = 50 (%)
Upper respiratory tract infection	17	6
Nasopharyngitis	12	4
Cough	9	0
Diarrhea	9	2
Pyrexia	9	8
Abdominal pain	8	4
Oropharyngeal pain	8	2
Toothache	6	0
ALT increased[a]	6	0
Rash	5	2
AST increased	4	0
Rhinorrhea	4	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Includes adverse reactions or laboratory abnormalities > 3 x ULN.

In the two controlled clinical persistent or chronic ITP trials, cataracts developed or worsened in 2 (1%) patients treated with PROMACTA. Both patients had received chronic oral corticosteroids, a risk factor for cataractogenesis.

Chronic Hepatitis C-associated Thrombocytopenia: In the two placebo-controlled trials, 955 patients with chronic hepatitis C-associated thrombocytopenia received PROMACTA. Table 11 presents the most common

adverse drug reactions (experienced by greater than or equal to 10% of patients receiving PROMACTA compared with placebo).

Table 11. Adverse Reactions (≥ 10% and Greater Than Placebo) From Two Placebo-controlled Trials in Adults With Chronic Hepatitis C

Adverse reaction	PROMACTA + Peginterferon/Ribavirin n = 955 (%)	Placebo + Peginterferon/Ribavirin n = 484 (%)
Anemia	40	35
Pyrexia	30	24
Fatigue	28	23
Headache	21	20
Nausea	19	14
Diarrhea	19	11
Decreased appetite	18	14
Influenza-like illness	18	16
Insomnia[a]	16	15
Asthenia	16	13
Cough	15	12
Pruritus	15	13
Chills	14	9
Myalgia	12	10
Alopecia	10	6
Peripheral edema	10	5

[a]Includes PTs of insomnia, initial insomnia, and poor quality sleep.

Rash was reported in 9% and 7% of patients receiving PROMACTA and placebo, respectively.

In the two controlled clinical trials in patients with chronic hepatitis C, hyperbilirubinemia was reported in 8% of patients receiving PROMACTA compared with 3% for placebo. Total bilirubin greater than or equal to 1.5 x ULN was reported in 76% and 50% of patients receiving PROMACTA and placebo, respectively. ALT or AST greater than or equal to 3 x ULN was reported in 34% and 38% of patients for PROMACTA and placebo, respectively.

In the two controlled clinical trials in patients with chronic hepatitis C, cataracts developed or worsened in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

The safety of PROMACTA was also assessed in all patients treated with PROMACTA in the two controlled trials, including patients who initially received PROMACTA in the pre-antiviral treatment phase of the trial and were later randomized to the placebo arm (N = 1520 PROMACTA-treated patients). Hepatic failure was reported in 0.8% of PROMACTA-treated patients and 0.4% of placebo-treated patients.

Severe Aplastic Anemia

First-Line Treatment of Severe Aplastic Anemia

The safety of PROMACTA was established based upon a single-arm trial of 153 patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy. In this trial, PROMACTA was administered in combination with horse antithymocyte globulin (h-ATG) and cyclosporine *[see Clinical Studies (14.3)]*. Among the 153 patients who were dosed in this trial, 92 patients were evaluable for safety of the concurrent use of PROMACTA, h-ATG, and cyclosporine at the recommended dose and schedule.

In this cohort, PROMACTA was administered at up to 150 mg once daily on Day 1 to Month 6 (D1-M6) in combination with h-ATG on Days 1 to 4 and cyclosporine for 6 months, followed by low dose of cyclosporine

(maintenance dose) for an additional 18 months for patients who achieved a hematologic response at 6 months. The median duration of exposure to PROMACTA in this cohort was 183 days with 70% of patients exposed for > 24 weeks.

Table 12 presents the most common adverse reactions (experienced by greater than or equal to 5% of patients) associated with PROMACTA in the D1-M6 cohort.

Table 12. Adverse Reactions (≥ 5%) From One Open-label Trial in First-Line Treatment of Patients With Severe Aplastic Anemia

Adverse reaction	PROMACTA n = 92 (%)
ALT increased	29
AST increased	17
Blood bilirubin increased	17
Rash	8
Skin discoloration, including hyperpigmentation	5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

In the PROMACTA D1-M6 cohort, ALT increased (29%), AST increased (17%), and blood bilirubin increased (17%) were reported more frequently than in patients with refractory severe aplastic anemia (see Table 13).

New or worsening liver function laboratory abnormalities (CTCAE Grade 3 and Grade 4) in the PROMACTA D1-M6 cohort were 15% and 2% for AST, 26% and 4% for ALT, and 12% and 1% for bilirubin, respectively.

In this single-arm open-label clinical trial, ALT or AST > 3 x ULN with total bilirubin > 1.5 x ULN and ALT or AST > 3 x ULN with total bilirubin > 2 x ULN were reported in 44% and 32% of patients, respectively, in the PROMACTA D1-M6 cohort.

Pediatric Patients

A total of 34 pediatric patients (2 patients 2 to 5 years of age, 12 patients 6 to 11 years of age, and 20 patients 12 to 16 years of age) were enrolled in this single-arm trial of which 26 pediatric patients were enrolled in the PROMACTA D1-M6 cohort. In this cohort, the most frequent serious adverse reactions (experienced by ≥ 10% of patients) were upper respiratory tract infection (12% in patients age 2 to 16 years compared to 5% in patients 17 years of age and older, respectively) and rash (12% compared to 2%). The most common adverse reactions (experienced by ≥ 10% of patients) associated with PROMACTA were ALT increased (23% in patients age 2 to 16 years compared to 32% in patients 17 years of age and older, respectively), blood bilirubin increased (12% compared to 20%), AST increased (12% compared to 20%), and rash (12% compared to 6%).

Cytogenetic Abnormalities

In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Seven patients in the PROMACTA D1-M6 cohort had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7; these 4 occurred within 6.1 months. Across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality: 7 patients had the loss of chromosome 7, 6 of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with PROMACTA.

Refractory Severe Aplastic Anemia

In the single-arm, open-label trial, 43 patients with refractory severe aplastic anemia received PROMACTA. Eleven patients (26%) were treated for greater than 6 months and 7 patients (16%) were treated for greater than

1 year. The most common adverse reactions (greater than or equal to 20%) were nausea, fatigue, cough, diarrhea, and headache.

Table 13. Adverse Reactions (≥ 10%) From One Open-label Trial in Adults With Refractory Severe Aplastic Anemia

Adverse reaction	PROMACTA n = 43 (%)
Nausea	33
Fatigue	28
Cough	23
Diarrhea	21
Headache	21
Pain in extremity	19
Pyrexia	14
Dizziness	14
Oropharyngeal pain	14
Abdominal pain	12
Muscle spasms	12
Transaminases increased	12
Arthralgia	12
Rhinorrhea	12

Rash and hyperbilirubinemia were reported in 7% of patients; cataract was reported in 2% of patients.

In this trial, concurrent ALT or AST greater than 3 x ULN with total bilirubin greater than 1.5 x ULN were reported in 5% of patients. Total bilirubin greater than 1.5 x ULN occurred in 14% of patients.

In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported on therapy, including 5 patients who had complex changes in chromosome 7.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of PROMACTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Skin discoloration, including hyperpigmentation and skin yellowing.

7 DRUG INTERACTIONS

7.1 Polyvalent Cations (Chelation)

Eltrombopag chelates polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids.

Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, dairy products, and mineral supplements to avoid significant reduction in absorption of PROMACTA due to chelation *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

7.2 Transporters

Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1 (e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, olmesartan, pitavastatin, pravastatin, rosuvastatin, repaglinide, rifampin, simvastatin acid, SN-38 [active metabolite of irinotecan], valsartan) or breast cancer resistance protein (BCRP) (e.g., imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin,

sulfasalazine, topotecan). Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or BCRP and consider reduction of the dose of these drugs, if appropriate. In clinical trials with PROMACTA, a dose reduction of rosuvastatin by 50% was recommended.

7.3 Protease Inhibitors

HIV Protease Inhibitors: No dose adjustment is recommended when PROMACTA is coadministered with lopinavir/ritonavir (LPV/RTV). Drug interactions with other HIV protease inhibitors have not been evaluated.

Hepatitis C Virus Protease Inhibitors: No dose adjustments are recommended when PROMACTA is coadministered with boceprevir or telaprevir. Drug interactions with other hepatitis C virus (HCV) protease inhibitors have not been evaluated.

7.4 Peginterferon Alfa-2a/b Therapy

No dose adjustments are recommended when PROMACTA is coadministered with peginterferon alfa-2a (PEGASYS®) or -2b (PEGINTRON®).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a small number of published case reports and postmarketing experience with PROMACTA use in pregnant women are insufficient to assess any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction and developmental toxicity studies, oral administration of eltrombopag to pregnant rats during organogenesis resulted in embryolethality and reduced fetal weights at maternally toxic doses. These effects were observed at doses resulting in exposures that were six times the human clinical exposure based on area under the curve (AUC) in patients with persistent or chronic ITP at 75 mg/day, and three times the AUC in patients with chronic hepatitis C at 100 mg/day *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an early embryonic development study, female rats received oral eltrombopag at doses of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Increased pre- and post-implantation loss and reduced fetal weight were observed at the highest dose which also caused maternal toxicity.

In an embryo-fetal development study eltrombopag was administered orally to pregnant rats during the period of organogenesis at doses of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Decreased fetal weights (6% to 7%) and a slight increase in the presence of cervical ribs were observed at the highest dose which also caused maternal toxicity. However, no evidence of major structural malformations was observed.

In an embryo-fetal development study eltrombopag was administered orally to pregnant rabbits during the period of organogenesis at doses of 30, 80, or 150 mg/kg/day (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the

human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). No evidence of fetotoxicity, embryolethality, or teratogenicity was observed.

In a pre- and post-natal developmental toxicity study in pregnant rats (F0), oral eltrombopag was administered from gestation Day 6 through lactation Day 20. No adverse effects on maternal reproductive function or on the development of the offspring (F1) were observed at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag was detected in the plasma of offspring (F1). The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

8.2 Lactation

Risk Summary

There are no data regarding the presence of eltrombopag or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. However, eltrombopag was detected in the pups of lactating rats 10 days postpartum suggesting the potential for transfer during lactation. Due to the potential for serious adverse reactions in a breastfed child from PROMACTA, breastfeeding is not recommended during treatment.

8.3 Females and Males of Reproductive Potential

Contraception

Based on animal reproduction studies, PROMACTA can cause fetal harm when administered to a pregnant woman. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using PROMACTA during treatment and for at least 7 days after stopping treatment with PROMACTA.

8.4 Pediatric Use

The safety and efficacy of PROMACTA have been established in pediatric patients 1 year and older with persistent or chronic ITP and in pediatric patients 2 years and older with IST-naïve severe aplastic anemia (in combination with h-ATG and cyclosporine). Safety and efficacy in pediatric patients below the age of 1 year with ITP have not been established. Safety and efficacy in pediatric patients with thrombocytopenia associated with chronic hepatitis C and refractory severe aplastic anemia have not been established.

The safety and efficacy of PROMACTA in pediatric patients 1 year and older with persistent or chronic ITP were evaluated in two double-blind, placebo-controlled trials *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*. The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily *[see Clinical Pharmacology (12.3)].* See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 1 year and older.

The safety and efficacy of PROMACTA in combination with h-ATG and cyclosporine for the first-line treatment of severe aplastic anemia in pediatric patients 2 years and older were evaluated in a single-arm, open-label trial *[see Adverse Reactions (6.1), Clinical Studies (14.3)]*. A total of 26 pediatric patients (ages 2 to < 17 years) were evaluated; 12 children (aged 2 to < 12 years) and 14 adolescents (aged 12 to < 17). See *Dosage and Administration (2.3)* for dosing recommendations for pediatric patients 2 years and older. The safety and efficacy of PROMACTA in combination with h-ATG and cyclosporine in pediatric patients younger than 2 years for the first-line treatment of severe aplastic anemia have not yet been established. In patients 2 to 16 years of age, 69% of patients experienced serious adverse events compared to 42% in patients 17 years and older. Among the 12 patients who were 2 to 11 years of age in the PROMACTA D1-M6 cohort and reached the 6-month assessment or withdrew earlier, the complete response rate at Month 6 was 8% versus 46% in patients age 12 to 16 years and 50% in patients 17 years of age and older.

8.5 Geriatric Use

Of the 106 patients in two randomized clinical trials of PROMACTA 50 mg in persistent or chronic ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. Of the 1439 patients in two randomized clinical trials of PROMACTA in patients with chronic hepatitis C and thrombocytopenia, 7% were 65 years of

age and over, while < 1% were 75 years of age and over. Of the 196 patients who received PROMACTA for the treatment of severe aplastic anemia, 18% were 65 years of age and over, while 3% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.6 Hepatic Impairment

Patients With Persistent or Chronic ITP and Severe Aplastic Anemia

Reduce the initial dose of PROMACTA in patients with persistent or chronic ITP (adult and pediatric patients 6 years and older only) or refractory severe aplastic anemia who also have hepatic impairment (Child-Pugh class A, B, C) *[see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

In a clinical trial in patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy, patients with baseline ALT or AST > 5 x ULN were ineligible to participate. If a patient with hepatic impairment (Child-Pugh class A, B, C) initiates therapy with PROMACTA for the first-line treatment of severe aplastic anemia, reduce the initial dose *[see Dosage and Administration (2.3), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

Patients With Chronic Hepatitis C

No dosage adjustment is recommended in patients with chronic hepatitis C and hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Ethnicity

Reduce the initial dose of PROMACTA for patients of East-/Southeast-Asian ancestry with ITP (adult and pediatric patients 6 years and older only) or severe aplastic anemia *[see Dosage and Administration (2.1, 2.3), Clinical Pharmacology (12.3)]*. No reduction in the initial dose of PROMACTA is recommended in patients of East-/Southeast-Asian ancestry with chronic hepatitis C *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications.

In one report, a subject who ingested 5000 mg of PROMACTA had a platelet count increase to a maximum of 929 x 10^9/L at 13 days following the ingestion. The patient also experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium, dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test abnormalities persisted for 3 weeks. After 2 months' follow-up, all events had resolved without sequelae.

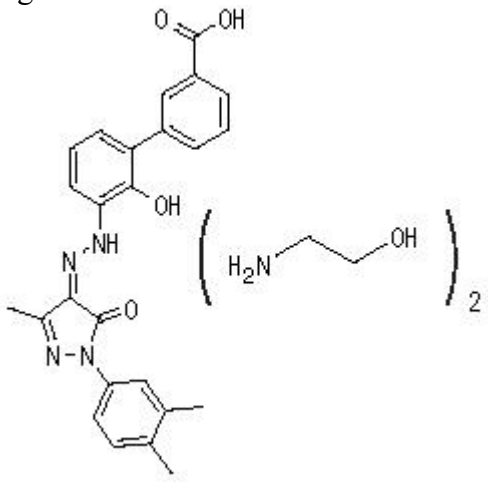
In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in accordance with dosing and administration recommendations *[see Dosage and Administration (2.1, 2.2)]*.

11 DESCRIPTION

PROMACTA (eltrombopag) tablets contain eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration.

Eltrombopag olamine is a biphenyl hydrazone. The chemical name for eltrombopag olamine is 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2). It has the molecular formula $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$. The

molecular weight is 564.65 g/mol for eltrombopag olamine and 442.5 g/mol for eltrombopag free acid. Eltrombopag olamine has the following structural formula:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

PROMACTA (eltrombopag) tablets contain eltrombopag olamine in the amount equivalent to 12.5 mg, 25 mg, 50 mg, or 75 mg of eltrombopag free acid. The inactive ingredients of PROMACTA tablets are:
Tablet Core: magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate.
Coating: FD&C Blue No. 2 aluminum lake (50-mg tablet), FD&C Yellow No. 6 aluminum lake (25-mg tablet), hypromellose, Iron Oxide Black and Iron Oxide Red (75-mg tablet), polyethylene glycol 400, polysorbate 80 (12.5-mg tablet), or titanium dioxide.

PROMACTA (eltrombopag) for oral suspension packets contain a reddish-brown to yellow powder which produces a reddish-brown suspension when reconstituted with water. Each packet delivers eltrombopag olamine equivalent to 12.5 mg or 25 mg of eltrombopag free acid. The inactive ingredients of PROMACTA for oral suspension are mannitol, sucralose, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eltrombopag is a TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor (also known as cMpl) and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes leading to increased platelet production.

12.2 Pharmacodynamics

In clinical trials, treatment with PROMACTA resulted in dose-dependent increases in platelet counts following repeated (daily) dosing. The increase in platelet counts reached a maximum approximately two weeks after the initiation of dosing, and returned to baseline within approximately two weeks after the last dose of PROMACTA.

Cardiac Electrophysiology

At doses up to 150 mg (the maximum recommended dose) daily for 5 days, PROMACTA did not prolong the QT/QTc interval to any relevant extent.

12.3 Pharmacokinetics

Eltrombopag demonstrated a dose-proportional increase in exposure between doses of 50 to 150 mg/day in healthy adult subjects. Eltrombopag AUC was approximately 1.7-fold higher in patients with persistent or chronic ITP and approximately 2.8-fold higher in patients with HCV compared to healthy subjects. Steady-state was achieved after approximately 1 week of once daily treatment, with geometric mean accumulation ratio of

1.56 (90% confidence interval 1.20, 1.63) at 75 mg/day. Eltrombopag AUC was approximately 3.2-fold higher in patients with definitive immunosuppressive therapy-naïve severe aplastic anemia compared to healthy subjects suggesting higher relative exposure compared to healthy subjects or patients with ITP and similar exposure compared to patients with chronic hepatitis C. Eltrombopag for oral suspension delivered 22% higher plasma $AUC_{0\text{-}INF}$ than the tablet formulation.

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Oral absorption of drug-related material following administration of a single 75-mg solution dose was estimated to be at least 52%.

Effect of Food

A standard high-fat breakfast (876 calories, 52 g fat, 71 g carbohydrate, 34 g protein, and 427 mg calcium) significantly decreased plasma eltrombopag $AUC_{0\text{-}INF}$ by approximately 59% and C_{max} by 65% and delayed T_{max} by 1 hour. The decrease in exposure is primarily due to the high calcium content.

A meal low in calcium (≤ 50 mg calcium) did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

The effect of administration of a single 25-mg dose of eltrombopag for oral suspension with a high-calcium, moderate-fat, moderate calorie meal on $AUC_{0\text{-}INF}$ and C_{max} in healthy adult subjects is presented in Table 14.

Table 14. Effect on Plasma Eltrombopag Pharmacokinetic Parameters After Administration of a Single 25-mg Dose of Eltrombopag for Oral Suspension With a High Calcium Meal[a] in Healthy Adult Subjects

Timing of eltrombopag for oral suspension dose	Mean (90% CI) reduction in plasma eltrombopag $AUC_{0\text{-}INF}$	Mean (90% CI) reduction in plasma eltrombopag C_{max}
With a high-calcium, moderate-fat, moderate-calorie meal	75% (71%, 88%)	79% (76%, 82%)
2 hours after the high-calcium, moderate-fat, moderate-calorie meal	47% (40%, 53%)	48% (40%, 54%)
2 hours before the high-calcium, moderate-fat, moderate-calorie meal	20% (9%, 29%)	14% (2%, 25%)

[a]372 calories, 9 g fat, and 448 mg calcium.

Distribution

The concentration of eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that eltrombopag is highly bound to human plasma proteins (greater than 99%). Eltrombopag is a substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

Elimination

The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26 to 35 hours in patients with ITP.

Metabolism: Absorbed eltrombopag is extensively metabolized, predominantly through pathways, including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag.

Excretion: The predominant route of eltrombopag excretion is via feces (59%), and 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for approximately 20% of the dose; unchanged eltrombopag is not detectable in urine.

Specific Populations

Ethnicity

Eltrombopag concentrations in East-/Southeast-Asian ancestry patients with ITP or chronic hepatitis C, were 50% to 55% higher compared with non-Asian subjects *[see Dosage and Administration (2.1, 2.3)]*.

Eltrombopag exposure in healthy African-American subjects was approximately 40% higher than that observed in Caucasian subjects in one clinical pharmacology trial and similar in three other clinical pharmacology trials. The effect of African-American ethnicity on exposure and related safety and efficacy of eltrombopag has not been established.

Hepatic Impairment

Following a single dose of PROMACTA (50 mg), plasma eltrombopag $AUC_{0\text{-}INF}$ was 41% higher in patients with mild hepatic impairment (Child-Pugh class A) compared with subjects with normal hepatic function. Plasma eltrombopag $AUC_{0\text{-}INF}$ was approximately 2-fold higher in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) compared with subjects with normal hepatic function. The half-life of eltrombopag was prolonged 2-fold in these patients. This clinical trial did not evaluate protein-binding effects.

Chronic Liver Disease

Following repeat doses of eltrombopag in patients with thrombocytopenia and with chronic liver disease, mild hepatic impairment resulted in an 87% to 110% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ and moderate hepatic impairment resulted in approximately 141% to 240% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ values compared with patients with normal hepatic function. The half-life of eltrombopag was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical trial did not evaluate protein-binding effects.

Chronic Hepatitis C

Patients with chronic hepatitis C treated with PROMACTA had higher plasma $AUC_{(0\text{-}\tau)}$ values as compared with healthy subjects, and $AUC_{(0\text{-}\tau)}$ increased with increasing Child-Pugh score. Patients with chronic hepatitis C and mild hepatic impairment had approximately 100% to 144% higher plasma $AUC_{(0\text{-}\tau)}$ compared with healthy subjects. This clinical trial did not evaluate protein-binding effects.

Renal Impairment

Following a single dose of PROMACTA (50 mg), the average total plasma eltrombopag $AUC_{0\text{-}INF}$ was 32% to 36% lower in subjects with mild (estimated creatinine clearance (CLCr) by Cockcroft-Gault equation: 50 to 80 mL/min), to moderate (CLCr of 30 to 49 mL/min) renal impairment and 60% lower in subjects with severe (CLCr less than 30 mL/min) renal impairment compared with healthy subjects. The effect of renal impairment on unbound (active) eltrombopag exposure has not been assessed.

Pediatric Patients

The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily in two trials. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. East-/Southeast-Asian pediatric patients with ITP had approximately 43% higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ values as compared with non-Asian patients.

Plasma eltrombopag $AUC_{(0\text{-}\tau)}$ and C_{max} in pediatric patients aged 12 to 17 years was similar to that observed in adults. The pharmacokinetic parameters of eltrombopag in pediatric patients with ITP are shown in Table 15.

Table 15. Geometric Mean (95% CI) Steady-state Plasma Eltrombopag Pharmacokinetic Parameters[a] in Patients With ITP (Normalized to a Once-daily 50-mg Dose)

Age	C_{max}[b] (mcg/mL)	$AUC_{(0-\tau)}$[b] (mcg·hr/mL)
Adults (n = 108)	7.03 (6.44, 7.68)	101 (91.4, 113)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n = 68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

[a]PK parameters presented as geometric mean (95% CI).
[b]Based on population PK post-hoc estimates.

Drug Interaction Studies

Clinical Studies

Effect of Drugs on Eltrombopag

Effect of Polyvalent Cation-containing Antacids on Eltrombopag:

The coadministration of a single dose of PROMACTA (75 mg) with a polyvalent cation-containing antacid (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) decreased plasma eltrombopag AUC_{0-INF} and C_{max} by approximately 70%. The contribution of sodium alginate to this interaction is not known.

Effect of HIV Protease Inhibitors on Eltrombopag:

The coadministration of repeat-dose lopinavir 400 mg/ritonavir 100 mg (twice daily) with a single dose of PROMACTA (100 mg) decreased plasma eltrombopag AUC_{0-INF} by 17%.

Effect of HCV Protease Inhibitors on Eltrombopag:

The coadministration of repeat-dose telaprevir (750 mg every 8 hours) or boceprevir (800 mg every 8 hours) with a single dose of PROMACTA (200 mg) to healthy adult subjects in a clinical trial did not alter plasma eltrombopag AUC_{0-INF} or C_{max} to a significant extent.

Effect of Cyclosporine on Eltrombopag:

The coadministration of a single dose of PROMACTA (50 mg) with a single dose of an OATP and BCRP inhibitor cyclosporine (200 mg or 600 mg) decreased plasma eltrombopag AUC_{0-INF} by 18% to 24% and C_{max} by 25% to 39%.

Effect of Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b + Ribavirin on Eltrombopag:

The presence of pegylated interferon alfa + ribavirin therapy did not significantly affect the clearance of eltrombopag.

Effect of Eltrombopag on Other Drugs

Effect of Eltrombopag on Cytochrome P450 Enzymes Substrates:

The coadministration of multiple doses of PROMACTA (75 mg once daily for 7 days) did not result in the inhibition or induction of the metabolism of a combination of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) in humans.

Effect of Eltrombopag on Rosuvastatin:

The coadministration of multiple doses of PROMACTA (75 mg once daily for 5 days) with a single dose of rosuvastatin (OATP1B1 and BCRP substrate; 10 mg) increased plasma rosuvastatin $AUC_{0\text{-}INF}$ by 55% and C_{max} by 103%.

Effect of Eltrombopag on HCV Protease Inhibitors:

The coadministration of repeat-dose telaprevir (750 mg every 8 hours) or boceprevir (800 mg every 8 hours) with a single dose of PROMACTA (200 mg) to healthy adult subjects in a clinical trial did not alter plasma telaprevir or boceprevir $AUC_{0\text{-}INF}$ or C_{max} to a significant extent.

In vitro Studies

Eltrombopag Effect on Metabolic Enzymes

Eltrombopag has demonstrated the potential to inhibit CYP2C8, CYP2C9, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

Eltrombopag Effect on Transporters

Eltrombopag has demonstrated the potential to inhibit OATP1B1 and BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Eltrombopag does not stimulate platelet production in rats, mice, or dogs because of unique TPO receptor specificity. Data from these animals do not fully model effects in humans.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on C_{max} in patients with ITP at 75 mg/day and 7 times the human clinical exposure based on C_{max} in patients with chronic hepatitis C at 100 mg/day). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (less than 3-fold increase in mutation frequency).

Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).

13.2 Animal Pharmacology and/or Toxicology

Treatment-related cataracts were detected in rodents in a dose- and time-dependent manner. At greater than or equal to 6 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing. At greater than or equal to 4 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing *[see Warnings and Precautions (5.5)]*.

Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and 150 mg/kg/day. The exposure at the lowest dose was

1.2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.6 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day. No similar effects were observed in mice after 13 weeks at exposures greater than those associated with renal changes in the 2-year study, suggesting that this effect is both dose- and time-dependent.

14 CLINICAL STUDIES

14.1 Persistent or Chronic ITP

Adults: The efficacy and safety of PROMACTA in adult patients with persistent or chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label extension trial.

In Study TRA100773B and Study TRA100773A (referred to as Study 773B and Study 773A, respectively [NCT00102739]), patients who had completed at least one prior ITP therapy and who had a platelet count less than 30 x 10^9/L were randomized to receive either PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the trials, PROMACTA or placebo was discontinued if the platelet count exceeded 200 x 10^9/L.

The median age of the patients was 50 years and 60% were female. Approximately 70% of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the patients had undergone splenectomy. The median baseline platelet counts (approximately 18 x 10^9/L) were similar among all treatment groups.

Study 773B randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Of 60 patients with documented time since diagnosis, approximately 17% met the definition of persistent ITP with time since diagnosis of 3-12 months. Study 773A randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA, 30 mg, 50 mg, or 75 mg each administered daily. Of 51 patients with documented time since diagnosis, approximately 14% met the definition of persistent ITP.

The efficacy of PROMACTA in this trial was evaluated by response rate, defined as a shift from a baseline platelet count of less than 30 x 10^9/L to greater than or equal to 50 x 10^9/L at any time during the treatment period (Table 16).

Table 16. Studies 773B and 773A: Platelet Count Response (≥ 50 x 10^9/L) Rates in Adults With Persistent or Chronic Immune Thrombocytopenia

Study	PROMACTA 50 mg Daily	Placebo
773B	43/73 (59%)[a]	6/37 (16%)
773A	19/27 (70%)[a]	3/27 (11%)

[a] *p*-value < 0.001 for PROMACTA versus placebo.

The platelet count response to PROMACTA was similar among patients who had or had not undergone splenectomy. In general, increases in platelet counts were detected 1 week following initiation of PROMACTA and the maximum response was observed after 2 weeks of therapy. In the placebo and 50-mg–dose groups of PROMACTA, the trial drug was discontinued due to an increase in platelet counts to greater than 200 x 10^9/L in 3% and 27% of the patients, respectively. The median duration of treatment with the 50-mg dose of PROMACTA was 43 days in Study 773B and 42 days in Study 773A.

Of 7 patients who underwent hemostatic challenges, additional ITP medications were required in 3 of 3 placebo group patients and 0 of 4 patients treated with PROMACTA. Surgical procedures accounted for most of the hemostatic challenges. Hemorrhage requiring transfusion occurred in one placebo group patient and no patients treated with PROMACTA.

In the RAISE study (NCT00370331), 197 patients were randomized (2:1) to receive either PROMACTA 50 mg once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of PROMACTA could be adjusted based on individual platelet counts. Of 145 patients with documented time since diagnosis, 19% met

the definition of persistent ITP. Patients were allowed to taper or discontinue concomitant ITP medications after being treated with PROMACTA for 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as clinically indicated.

The median ages of the patients treated with PROMACTA and placebo were 47 years and 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and placebo (47% and 50%, respectively) were receiving concomitant ITP medication (predominantly corticosteroids) at randomization and had baseline platelet counts less than or equal to 15 x 10^9/L (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the odds of achieving a platelet count greater than or equal to 50 x 10^9/L and less than or equal to 400 x 10^9/L for patients receiving PROMACTA relative to placebo and was based on patient response profiles throughout the 6-month treatment period. In 134 patients who completed 26 weeks of treatment, a sustained platelet response (platelet count greater than or equal to 50 x 10^9/L and less than or equal to 400 x 10^9/L for 6 out of the last 8 weeks of the 26-week treatment period in the absence of rescue medication at any time) was achieved by 60% of patients treated with PROMACTA, compared with 10% of patients treated with placebo (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients: PROMACTA 66%, placebo 11%). The proportion of responders in the group of patients treated with PROMACTA was between 37% and 56% compared with 7% and 19% in the placebo treatment group for all on-therapy visits. Patients treated with PROMACTA were significantly more likely to achieve a platelet count between 50 x 10^9/L and 400 x 10^9/L during the entire 6-month treatment period compared with those patients treated with placebo.

Outcomes of treatment are presented in Table 17 for all patients enrolled in the trial.

Table 17. RAISE: Outcomes of Treatment in Adults With Persistent or Chronic Immune Thrombocytopenia

Outcome	PROMACTA n = 135	Placebo n = 62
Mean number of weeks with platelet counts ≥ 50 x 10^9/L	11.3	2.4
Requiring rescue therapy, n (%)	24 (18)	25 (40)

Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients treated with PROMACTA and 10 (32%) of 31 patients in the placebo group discontinued concomitant therapy at some time during the trial.

In the EXTEND study (NCT00351468), patients who completed any prior clinical trial with PROMACTA were enrolled in an open-label, single-arm trial in which attempts were made to decrease the dose or eliminate the need for any concomitant ITP medications. PROMACTA was administered to 302 patients in EXTEND; 218 patients completed 1 year, 180 patients completed 2 years, 107 patients completed 3 years, 75 patients completed 4 years, 34 patients completed 5 years, and 18 patients completed 6 years of therapy. The median baseline platelet count was 19 x 10^9/L prior to administration of PROMACTA. Median platelet counts at 1, 2, 3, 4, 5, 6, and 7 years on study were 85 x 10^9/L, 85 x 10^9/L, 105 x 10^9/L, 64 x 10^9/L, 75 x 10^9/L, 119 x 10^9/L, and 76 x 10^9/L, respectively.

Pediatric Patients: The efficacy and safety of PROMACTA in pediatric patients 1 year and older with persistent or chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. During the trials, doses could be increased every 2 weeks to a maximum of 75 mg once daily. The dose of PROMACTA was reduced if the platelet count exceeded 200 x 10^9/L and interrupted and reduced if it exceeded 400 x 10^9/L.

In the PETIT2 study (NCT01520909), patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 92) were stratified by age and randomized (2:1) to PROMACTA (n = 63) or placebo (n = 29). The starting dose for patients aged 6 to 17 years was 50 mg once daily for those at least 27 kg and 37.5 mg once daily for those less than 27 kg, administered as oral tablets. A reduced dose of

25 mg once daily was used for East-/Southeast-Asian patients aged 6 to 17 years regardless of weight. The starting dose for patients aged 1 to 5 years was 1.2 mg/kg once daily (0.8 mg/kg once daily for East-/Southeast-Asian patients) administered as oral suspension.

The 13-week, randomized, double-blind period was followed by a 24-week, open-label period where patients from both arms were eligible to receive PROMACTA.

The median age of the patients was 9 years and 48% were female. Approximately 62% of patients had a baseline platelet count less than or equal to 15 x 10^9/L, a characteristic that was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins) was 73% in the group treated with PROMACTA and 90% in the group treated with placebo. Four patients in the group treated with PROMACTA had undergone splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the proportion of subjects on PROMACTA achieving platelet counts ≥ 50 x 10^9/L (in the absence of rescue therapy) for at least 6 out of 8 weeks between Weeks 5 to 12 of the randomized, double-blind period (Table 18).

Table 18. PETIT2: Platelet Count Response (≥ 50 x 10^9/L Without Rescue) for 6 out of 8 Weeks (between Weeks 5 to 12) Overall and by Age Cohort in Pediatric Patients 1 Year and Older With Chronic Immune Thrombocytopenia

Age cohort	PROMACTA	Placebo
Overall	26/63 (41%)[a]	1/29 (3%)
12 to 17 years	10/24 (42%)	1/10 (10%)
6 to 11 years	11/25 (44%)	0/13 (0%)
1 to 5 years	5/14 (36%)	0/6 (0%)

[a] *p*-value = < 0.001 for PROMACTA versus placebo.

More pediatric patients treated with PROMACTA (75%) compared with placebo (21%) had at least one platelet count greater than or equal to 50 x 10^9/L during the first 12 weeks of randomized treatment in absence of rescue therapy. Fewer pediatric patients treated with PROMACTA required rescue treatment during the randomized, double-blind period compared with placebo-treated patients (19% [12/63] versus 24% [7/29]). In the patients who achieved a platelet response (≥ 50 x 10^9/L without rescue) for 6 out of 8 weeks (between weeks 5 to 12), 62% (16/26) had an initial response in the first 2 weeks after starting PROMACTA.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. Among 15 patients receiving other ITP therapy at baseline, 53% (8/15) reduced (n = 1) or discontinued (n = 7) concomitant therapy, mainly corticosteroids, without needing rescue therapy.

In the PETIT study (NCT00908037), patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 67) were stratified by age and randomized (2:1) to PROMACTA (n = 45) or placebo (n = 22). Approximately 15% of patients met the definition of persistent ITP. The starting dose for patients aged 12 to 17 years was 37.5 mg once daily regardless of weight or race. The starting dose for patients aged 6 to 11 years was 50 mg once daily for those greater than or equal to 27 kg and 25 mg once daily for those less than 27 kg, administered as oral tablets. Reduced doses of 25 mg (for those greater than or equal to 27 kg) and 12.5 mg (for those less than 27 kg), each once daily, were used for East-/Southeast-Asian patients in this age range. The starting dose for patients aged 1 to 5 years was 1.5 mg/kg once daily (0.8 mg/kg once daily for East-/Southeast-Asian patients) administered as oral suspension.

The 7-week, randomized, double-blind period was followed by an open-label period of up to 24 weeks where patients from both arms were eligible to receive PROMACTA.

The median age of the patients was 10 years and 60% were female. Approximately 51% of patients had a baseline platelet count less than or equal to 15 x 10^9/L. The percentage of patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins) was 84% in the group treated with PROMACTA and 86% in the group treated with placebo. Five patients in the group treated with PROMACTA had undergone splenectomy.

The efficacy of PROMACTA in this trial was evaluated by the proportion of patients achieving platelet counts greater than or equal to 50 x 10^9/L (in absence of rescue therapy) at least once between Weeks 1 and 6 of the randomized, double-blind period (Table 19). Platelet response to PROMACTA was consistent across the age cohorts.

Table 19. PETIT: Platelet Count Response (≥ 50 x 10^9/L Without Rescue) Rates in Pediatric Patients 1 Year and Older With Persistent or Chronic Immune Thrombocytopenia

Age cohort	PROMACTA	Placebo
Overall	28/45 (62%)[a]	7/22 (32%)
12 to 17 years	10/16 (62%)	0/8 (0%)
6 to 11 years	12/19 (63%)	3/9 (33%)
1 to 5 years	6/10 (60%)	4/5 (80%)

[a] *p*-value = 0.011 for PROMACTA versus placebo.

Fewer pediatric patients treated with PROMACTA required rescue treatment during the randomized, double-blind period compared with placebo-treated patients (13% [6/45] versus 50% [11/22]).

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the trial. Among 13 patients receiving other ITP therapy at baseline, 46% (6/13) reduced (n = 3) or discontinued (n = 3) concomitant therapy, mainly corticosteroids, without needing rescue therapy.

14.2 Chronic Hepatitis C-Associated Thrombocytopenia

The efficacy and safety of PROMACTA for the treatment of thrombocytopenia in adult patients with chronic hepatitis C were evaluated in two randomized, double-blind, placebo-controlled trials. The ENABLE1 study (NCT00516321) utilized peginterferon alfa-2a (PEGASYS®) plus ribavirin for antiviral treatment and the ENABLE2 study (NCT00529568) utilized peginterferon alfa-2b (PEGINTRON®) plus ribavirin. In both trials, patients with a platelet count of less than 75 x 10^9/L were enrolled and stratified by platelet count, screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of decompensated liver disease with Child-Pugh score greater than 6 (class B and C), history of ascites, or hepatic encephalopathy. The median age of the patients in both trials was 52 years, 63% were male, and 74% were Caucasian. Sixty-nine percent of patients had HCV genotypes 1, 4, 6, with the remainder genotypes 2 and 3. Approximately 30% of patients had been previously treated with interferon and ribavirin. The majority of patients (90%) had bridging fibrosis and cirrhosis, as indicated by noninvasive testing. A similar proportion (95%) of patients in both treatment groups had Child-Pugh class A (score 5 to 6) at baseline. A similar proportion of patients (2%) in both treatment groups had baseline international normalized ratio (INR) greater than 1.7. Median baseline platelet counts (approximately 60 x 10^9/L) were similar in both treatment groups. The trials consisted of 2 phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label PROMACTA to increase the platelet count to a threshold of greater than or equal to 90 x 10^9/L for ENABLE1 and greater than or equal to 100 x 10^9/L for ENABLE2. PROMACTA was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25-mg increments over 2- to 3-week periods to achieve the optimal platelet count to initiate antiviral therapy. The maximal time patients could receive open-label PROMACTA was 9 weeks. If threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of PROMACTA at the end of the pre-treatment phase or to placebo. PROMACTA was administered in combination with pegylated interferon and ribavirin per their respective prescribing information for up to 48 weeks.

The efficacy of PROMACTA for both trials was evaluated by sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count greater than or equal to 90 x 10^9/L was approximately 2 weeks. Ninety-five percent of patients were able to initiate antiviral therapy.

In both trials, a significantly greater proportion of patients treated with PROMACTA achieved SVR (see Table 20). The improvement in the proportion of patients who achieved SVR was consistent across subgroups

based on baseline platelet count (less than 50 x 10^9/L versus greater than or equal to 50 x 10^9/L). In patients with high baseline viral loads (greater than or equal to 800,000), the SVR rate was 18% (82/452) for PROMACTA versus 8% (20/239) for placebo.

Table 20. ENABLE1 and ENABLE2: Sustained Virologic Response (SVR) in Adults With Chronic Hepatitis C

	ENABLE1[a]		ENABLE2[b]	
Pre-antiviral treatment phase	**n = 715**		**n = 805**	
% Patients who achieved target platelet counts and initiated antiviral therapy[c]	95%		94%	
Antiviral treatment phase	**PROMACTA n = 450 %**	**Placebo n = 232 %**	**PROMACTA n = 506 %**	**Placebo n = 253 %**
Overall SVR[d]	23	14	19	13
HCV genotype 2,3	35	24	34	25
HCV genotype 1, 4, 6	18	10	13	7

Abbreviation: HCV, hepatitis C virus.

[a]PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg daily in 2 divided doses orally).

[b]PROMACTA given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg daily in 2 divided doses orally).

[c]Target platelet count was ≥ 90 x 10^9/L for ENABLE1 and ≥ 100 x 10^9/L for ENABLE2.

[d]*p*-value < 0.05 for PROMACTA versus placebo.

The majority of patients treated with PROMACTA (76%) maintained a platelet count greater than or equal to 50 x 10^9/L compared with 19% for placebo. A greater proportion of patients on PROMACTA did not require any antiviral dose reduction as compared with placebo (45% versus 27%).

14.3 Severe Aplastic Anemia

First-Line Treatment of Severe Aplastic Anemia

PROMACTA in combination with h-ATG and cyclosporine was investigated in a single-arm, single-center, open-label sequential cohort trial (Study ETB115AUS01T, referred to as Study US01T [NCT01623167]) in patients with severe aplastic anemia who had not received prior immunosuppressive therapy (IST) with any ATG, alemtuzumab, or high dose cyclophosphamide. A total of 153 patients received PROMACTA in Study US01T in three sequential cohorts and an extension of the third cohort. The multiple cohorts received the same PROMACTA starting dose but differed by treatment start day and duration. The starting dose of PROMACTA for patients 12 years and older was 150 mg once daily (a reduced dose of 75 mg was administered for East-/Southeast-Asians), 75 mg once daily for pediatric patients aged 6 to 11 years (a reduced dose of 37.5 mg was administered for East-/Southeast-Asians), and 2.5 mg/kg once daily for pediatric patients aged 2 to 5 years (a reduced dose of 1.25 mg/kg was administered for East-/Southeast-Asians).

- Cohort 1 (n = 30): PROMACTA on Day 14 to Month 6 (D14-M6) plus h-ATG and cyclosporine
- Cohort 2 (n = 31): PROMACTA on Day 14 to Month 3 (D14-M3) plus h-ATG and cyclosporine
- Cohort 3 + Extension cohort [PROMACTA D1-M6 cohort] (n = 92): PROMACTA on Day 1 to Month 6 (D1-M6) plus h-ATG and cyclosporine (with all patients eligible to receive low dose of cyclosporine (maintenance dose) if they achieved a hematologic response at 6 months)

PROMACTA dose reductions were conducted for elevated platelet counts and hepatic impairment. Table 21 includes the dosages of h-ATG and cyclosporine administered in combination with PROMACTA in Study US01T.

Data from the Cohort 3 + Extension cohort support the efficacy of PROMACTA for the first-line treatment of patients with severe aplastic anemia (Table 22). The results presented in this section represent the findings from the Cohort 3 and Extension cohort (n = 92).

Table 21. Dosages of Immunosuppressive Therapy Administered With PROMACTA in Study US01T

Agent	Dose Administered in the Pivotal Trial
Horse antithymocyte globulin (h-ATG)	40 mg/kg/day, based on actual body weight, administered intravenously on Days 1 to 4 of the 6-month treatment period
Cyclosporine[a] (therapeutic dose for 6 months, from Day 1 to Month 6, adjusted to obtain a target therapeutic trough level between 200 mcg/L and 400 mcg/L)	Patients 12 years and older (total daily dose of 6 mg/kg/day) 3 mg/kg, based on actual body weight, orally every 12 hours for 6 months, starting on Day 1 *Patients > 20 years of age with a body mass index > 35 or patients 12 to 20 years of age with a body mass index > 95th percentile*: 3 mg/kg, based on adjusted body weight[b], orally every 12 hours for 6 months, starting on Day 1 Patients 2 to 11 years of age (total daily dose of 12 mg/kg/day) 6 mg/kg, based on actual body weight, orally every 12 hours for 6 months, starting on Day 1 *Patients 2 to 11 years of age with a body mass index > 95th percentile*: 6 mg/kg, based on adjusted body weight[b], orally every 12 hours for 6 months, starting on Day 1
Cyclosporine (maintenance dose, from Month 6 to Month 24)	For patients who achieve a hematologic response at 6 months 2 mg/kg/day administered orally at a fixed dose for an additional 18 months

[a]Dose of cyclosporine was adjusted to achieve the above recommended target trough levels; refer to the appropriate cyclosporine prescribing information.

[b] Calculated as the midpoint between the ideal body weight and actual body weight.

In the PROMACTA D1-M6 cohort, the median age was 28 years (range, 5 to 82 years) with 16% and 28% of patients ≥ 65 years of age and < 17 years of age, respectively. Forty-six percent of patients were male and the majority of patients were White (62%). Patients weighing 12 kg or less or patients with ALT or AST > 5x upper limit of normal were excluded from the trial.

The efficacy of PROMACTA in combination with h-ATG and cyclosporine was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) > 1000/mcL, platelet count > 100 x 10^9/L and hemoglobin > 10 g/dL. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC > 500/mcL, platelet count > 20 x 10^9/L, or reticulocyte count > 60,000/mcL. Overall response rate is defined as the number of partial responses plus complete responses.

Table 22. Study US01T: Hematologic Response in First-Line Treatment of Patients With Severe Aplastic Anemia

	PROMACTA D1-M6 + h-ATG + cyclosporine n = 92
Month 6, n[a]	**87**
Overall response, n (%) [95% CI]	69 (79) [69, 87]
Complete response, n (%) [95% CI]	38 (44) [33, 55]
Median duration of overall response, n[b]	**70**
Months (95% CI)	24.3 (21.4, NE)
Median duration of complete response, n[b]	**46**
Months (95% CI)	24.3 (23.0, NE)

Abbreviation: NE, not estimable.
[a]The number of patients who reached the 6-month assessment or withdrew earlier is the denominator for percentage calculation.
[b]Number of responders at any time.

The overall and complete hematological response rates at Year 1 (n = 78) are 56.4% and 38.5% and at Year 2 (n = 62) are 38.7% and 30.6%, respectively.

Pediatric Patients

Thirty-four patients 2 to 16 years of age were enrolled in Study US01T. In the D1-M6 cohort, 7 and 17 out of 25 pediatric patients achieved a complete and overall response, respectively, at 6 months.

Refractory Severe Aplastic Anemia

PROMACTA was studied in a single-arm, single-center, open-label trial (Study ETB115AUS28T, referred to as Study US28T [NCT00922883]) in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count less than or equal to 30 x 10^9/L. PROMACTA was administered at an initial dose of 50 mg once daily for 2 weeks and increased over 2-week periods up to a maximum dose of 150 mg once daily. The efficacy of PROMACTA in the study was evaluated by the hematologic response assessed after 12 weeks of treatment. Hematologic response was defined as meeting 1 or more of the following criteria: 1) platelet count increases to 20 x 10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5 g/dL, or a reduction in greater than or equal to 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) ANC increase of 100% or an ANC increase greater than 0.5 x 10^9/L. PROMACTA was discontinued after 16 weeks if no hematologic response was observed. Patients who responded continued therapy in an extension phase of the trial.

The treated population had median age of 45 years (range, 17 to 77 years) and 56% were male. At baseline, the median platelet count was 20 x 10^9/L, hemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L, and absolute reticulocyte count was 24.3 x 10^9/L. Eighty-six percent of patients were red blood cell (RBC) transfusion dependent and 91% were platelet transfusion dependent. The majority of patients (84%) received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

Table 23 presents the efficacy results.

Table 23. Study US28T: Hematologic Response in Patients With Refractory Severe Aplastic Anemia

Outcome	**PROMACTA n = 43**
Response rate[a], n (%) 95% CI (%)	17 (40) (25, 56)
Median of duration of response in months (95% CI)	NR[b] (3.0, NR[b])

[a]Includes single- and multi-lineage.
[b]NR = not reached due to few events (relapsed).

In the 17 responders, the platelet transfusion-free period ranged from 8 to 1096 days with a median of 200 days, and the RBC transfusion-free period ranged from 15 to 1082 days with a median of 208 days.

In the extension phase, 8 patients achieved a multi-lineage response; 4 of these patients subsequently tapered off treatment with PROMACTA and maintained the response (median follow up: 8.1 months, range, 7.2 to 10.6 months).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Tablets

- The 12.5-mg tablets are round, biconvex, white, film-coated tablets debossed with "GS MZ1" and 12.5 on one side and are available in bottles of 30: NDC 0078-0684-15
- The 25-mg tablets are round, biconvex, orange, film-coated tablets debossed with "GS NX3" and 25 on one side and are available in bottles of 30: NDC 0078-0685-15
- The 50-mg tablets are round, biconvex, blue, film-coated tablets debossed with "GS UFU" and 50 on one side and are available:
  - Bottles of 14 NDC 0078-0686-55
  - Bottles of 30 NDC 0078-0686-15
- The 75-mg tablets are round, biconvex, pink, film-coated tablets debossed with "GS FFS" and 75 on one side and are available in bottles of 30: NDC 0078-0687-15

Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Dispense in original bottle.

16.2 For Oral Suspension

- The 12.5-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, copackaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes.

  Each kit (NDC 0078-0972-61) contains 30 packets: NDC 0078-0972-19

- The 25-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, copackaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes.

  Each kit (NDC 0078-0697-61) contains 30 packets: NDC 0078-0697-19

Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Throw away (discard) the mixture if not used within 30 minutes.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Prior to treatment, patients should fully understand and be informed of the following risks and considerations for PROMACTA:

Risks

Hepatotoxicity

- Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities *[see Warnings and Precautions (5.2)]*.
- Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic decompensation when receiving PROMACTA with alfa interferon therapy *[see Warnings and Precautions (5.1)]*.
- Advise patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away *[see Warnings and Precautions (5.2)]*.
  - yellowing of the skin or the whites of the eyes (jaundice)
  - unusual darkening of the urine
  - unusual tiredness
  - right upper stomach area pain
  - confusion
  - swelling of the stomach area (abdomen)

Risk of Bleeding Upon PROMACTA Discontinuation

- Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing PROMACTA, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents. Advise patients that during therapy with PROMACTA, they should continue to avoid situations or medications that may increase the risk for bleeding.

Thrombotic/Thromboembolic Complications

- Advise patients that too much PROMACTA may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications *[see Warnings and Precautions (5.4)]*.

Cataracts

- Advise patients to have a baseline ocular examination prior to administration of PROMACTA and be monitored for signs and symptoms of cataracts during therapy *[see Warnings and Precautions (5.5)]*.

Drug Interactions

- Advise patients to take PROMACTA at least 2 hours before or 4 hours after calcium-rich foods, mineral supplements, and antacids which contain polyvalent cations, such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Dosage and Administration (2.4), Drug Interactions (7.1)]*.

Lactation

- Advise women not to breastfeed during treatment with PROMACTA *[see Use in Specific Populations (8.2)]*.

Administration of PROMACTA

- For patients with persistent or chronic ITP, therapy with PROMACTA is administered to achieve and maintain a platelet count greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding *[see Indications and Usage (1.1)]*.
- For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin *[see Indications and Usage (1.2)]*.
- Advise patients to take PROMACTA without a meal or with a meal low in calcium (≤ 50 mg) and at least 2 hours before or 4 hours after other medications (e.g., antacids) and calcium-rich foods *[see Dosage and Administration (2.4)]*.

- Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration *[see Dosage and Administration (2.4)]*.
- Inform patients or caregivers how many packets to administer to get the full dose *[see Instructions for Use]*.
- Inform patients or caregivers to use a new oral dosing syringe to prepare each dose of PROMACTA for oral suspension *[see Instructions for Use]*.

The following are registered trademarks of their respective owners: PEGASYS/Hoffmann-La Roche Inc.; PEGINTRON/Schering Corporation.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

© Novartis

MEDICATION GUIDE

PROMACTA® (pro-MAC-ta)
(eltrombopag)
tablets

PROMACTA® (pro-MAC-ta)
(eltrombopag)
for oral suspension

What is the most important information I should know about PROMACTA?

PROMACTA can cause serious side effects, including:

Liver problems:

- If you have chronic hepatitis C virus and take PROMACTA with interferon and ribavirin treatment, PROMACTA may increase your risk of liver problems. If your healthcare provider tells you to stop your treatment with interferon and ribavirin, you will also need to stop taking PROMACTA.
- PROMACTA may increase your risk of liver problems that may be severe and possibly life threatening. Your healthcare provider will do blood tests to check your liver function before you start taking PROMACTA and during your treatment. Your healthcare provider may stop your treatment with PROMACTA if you have changes in your liver function blood tests.

Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the urine
- unusual tiredness
- right upper stomach area (abdomen) pain
- confusion
- swelling of the stomach area (abdomen)

See "What are the possible side effects of PROMACTA?" for other side effects of PROMACTA.

What is PROMACTA?

PROMACTA is a prescription medicine used to treat adults and children 1 year of age and older with low blood platelet counts due to persistent or chronic immune thrombocytopenia (ITP), when other medicines to treat ITP or surgery to remove the spleen have not worked well enough.

PROMACTA is also used to treat people with:

- low blood platelet counts due to chronic hepatitis C virus (HCV) infection before and during treatment with interferon.
- severe aplastic anemia (SAA) in combination with other medicines to treat SAA, as the first treatment for adults and children 2 years of age and older.
- severe aplastic anemia (SAA) when other medicines to treat SAA have not worked well enough.

PROMACTA is used to try to raise platelet counts in order to lower your risk for bleeding.

PROMACTA is not used to make platelet counts normal.

PROMACTA is not for use in people with a pre-cancerous condition called myelodysplastic syndrome (MDS), or in people with low platelet counts caused by certain other medical conditions or diseases.

It is not known if PROMACTA is safe and effective when used with other antiviral medicines to treat chronic hepatitis C.

It is not known if PROMACTA is safe and effective in children:

- younger than 1 year with ITP
- with low blood platelet counts due to chronic hepatitis C
- whose severe aplastic anemia (SAA) has not improved after previous treatments.
- younger than 2 years when used in combination with other medicines to treat SAA as the first treatment for SAA.

Before you take PROMACTA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have a precancerous condition called MDS or a blood cancer
- have or had a blood clot
- have a history of cataracts
- have had surgery to remove your spleen (splenectomy)
- have bleeding problems
- are of East-/Southeast-Asian ancestry. You may need a lower dose of PROMACTA.

- are pregnant or plan to become pregnant. It is not known if PROMACTA will harm an unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with PROMACTA.
    - Females who are able to become pregnant, should use effective birth control (contraception) during treatment with PROMACTA and for at least 7 days after stopping treatment with PROMACTA. Talk to your healthcare provider about birth control methods that may be right for you during this time.
- are breastfeeding or plan to breastfeed. You should not breastfeed during your treatment with PROMACTA. Talk to your healthcare provider about the best way to feed your baby during this time.
- **Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. PROMACTA may affect the way certain medicines work. Certain other medicines may affect the way PROMACTA works.

Especially tell your healthcare provider if you take:

- certain medicines used to treat high cholesterol, called “statins”
- a blood thinner medicine

Certain medicines may keep PROMACTA from working correctly. Take PROMACTA at least 2 hours before or 4 hours after taking these products:

- antacid medicine used to treat stomach ulcers or heartburn
- multivitamins or products that contain iron, calcium, aluminum, magnesium, selenium, and zinc which may be found in mineral supplements

Ask your healthcare provider if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take PROMACTA?

- Take PROMACTA exactly as your healthcare provider tells you to take it. Your healthcare provider will prescribe the dose of PROMACTA tablets or PROMACTA for oral suspension that is right for you.
- If your healthcare provider prescribes PROMACTA tablets, take PROMACTA tablets whole. **Do not split, chew, or crush PROMACTA tablets and do not mix with food or liquids.**
- If your healthcare provider prescribes PROMACTA for oral suspension, see the **“Instructions for Use”** that comes with your medicine for instructions on how to correctly mix and take a dose of PROMACTA.
- Use a new single-use oral dosing syringe to prepare each dose of PROMACTA for oral suspension. **Do not re-use the oral dosing syringe**.
- **Do not** stop taking PROMACTA without talking with your healthcare provider first. Do not change your dose or schedule for taking PROMACTA unless your healthcare provider tells you to change it.
- Take PROMACTA without a meal or with a meal low in calcium (50 mg or less) and at least 2 hours before or 4 hours after eating calcium-rich foods, such as dairy products, calcium-fortified juices, and certain fruits and vegetables.
- If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do not take more than 1 dose of PROMACTA in 1 day.
- If you take too much PROMACTA, you may have a higher risk of serious side effects. Call your healthcare provider right away.
- Your healthcare provider will check your platelet count during your treatment with PROMACTA and change your dose of PROMACTA as needed.
- Tell your healthcare provider about any bruising or bleeding that happens while you take and after you stop taking PROMACTA.
- If you have SAA, your healthcare provider may do tests to monitor your bone marrow during treatment with PROMACTA.

What should I avoid while taking PROMACTA?

Avoid situations and medicines that may increase your risk of bleeding.

What are the possible side effects of PROMACTA?

PROMACTA may cause serious side effects, including:

- See **"What is the most important information I should know about PROMACTA?"**
- **Increased risk of worsening of a precancerous blood condition called myelodysplastic syndrome (MDS) to acute myelogenous leukemia (AML).** PROMACTA is not for use in people with a precancerous condition called myelodysplastic syndromes (MDS). See "**What is PROMACTA**?" If you have MDS and receive PROMACTA, you have an increased risk that your MDS condition may worsen and become a blood cancer called AML. If your MDS worsens to become AML, you may have an increased risk of death from AML.
- **High platelet counts and higher risk for blood clots.** Your risk of getting a blood clot is increased if your platelet count is too high during treatment with PROMACTA. Your risk of getting a blood clot may also be increased during treatment with PROMACTA if you have normal or low platelet counts. You may have severe problems or die from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. Your healthcare provider will check your blood platelet counts, and change your dose or stop PROMACTA if your platelet counts get too high. Tell your healthcare provider right away if you have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in your leg.

  People with chronic liver disease may be at risk for a type of blood clot in the stomach area (abdomen). Tell your healthcare provider right away if you have stomach-area (abdomen) pain, nausea, vomiting, or diarrhea as these may be symptoms of this type of blood clot.
- **New or worsened cataracts (a clouding of the lens in the eye).** New or worsened cataracts can happen in people taking PROMACTA. Your healthcare provider will check your eyes before and during your treatment with PROMACTA. Tell your healthcare provider about any changes in your eyesight while taking PROMACTA.

The most common side effects of PROMACTA in adults and children include:

- low red blood cell count (anemia)
- nausea
- fever
- abnormal liver function tests
- cough
- tiredness
- headache
- diarrhea

Laboratory tests may show abnormal changes to the cells in your bone marrow.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of PROMACTA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROMACTA tablets and PROMACTA for oral suspension?

Tablets:

- Store PROMACTA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PROMACTA in the bottle given to you.

For oral suspension:

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

Keep PROMACTA and all medicines out of the reach of children.

General information about the safe and effective use of PROMACTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROMACTA for a condition for which it was not prescribed. Do not give PROMACTA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about PROMACTA that is written for health professionals.

What are the ingredients in PROMACTA?

Tablets

Active ingredient: eltrombopag olamine

Inactive ingredients:

- **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate.
    - **Coating:** FD&C Blue No. 2 aluminum lake (50-mg tablet), FD&C Yellow No. 6 aluminum lake (25-mg tablet), hypromellose, Iron Oxide Black and Iron Oxide Red (75-mg tablet), polyethylene glycol 400, polysorbate 80 (12.5-mg tablet), or titanium dioxide.

For oral suspension

Active ingredient: eltrombopag olamine

Inactive ingredients: mannitol, sucralose, and xanthan gum

Distributed by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936

© Novartis

For more information about PROMACTA, go to www.PROMACTA.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: March 2023

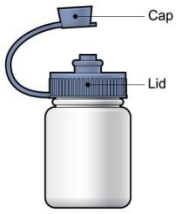
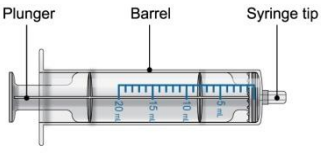
INSTRUCTIONS FOR USE
PROMACTA® [pro-MAC-ta]
(eltrombopag)
for oral suspension

Read all the Instructions for Use and follow the steps below to mix and give a dose of PROMACTA for oral suspension.

Important information you need to know before taking PROMACTA for oral suspension:

- **Do not take PROMACTA for oral suspension or give it to someone else until you have been shown how to properly mix and give a dose of PROMACTA for oral suspension.** Your healthcare provider or nurse will show you how to mix and give a dose of PROMACTA for oral suspension properly.
- **PROMACTA for oral suspension must be mixed with cool or cold water only.** Do not use hot water to prepare the oral suspension.
- Give the dose of suspension right away after mixing with water. **If the medicine is not given within 30 minutes, you will have to mix a new dose.** Throw away (discard) the unused mixture into the trash. Do not pour it down the drain.
- If PROMACTA for oral suspension comes in contact with your skin, wash the skin right away with soap and water. Call your healthcare provider if you have a skin reaction or if you have any questions. If you spill any powder or liquid, follow the clean-up instructions in **Step 12**.
- Contact your healthcare provider or pharmacist if you have any questions about how to mix or give PROMACTA to your child, or if you damage or lose any of the supplies in your kit.
- **Do not** re-use the oral dosing syringe. Use a new single-use oral dosing syringe to prepare each dose of PROMACTA for oral suspension.
- After you have used all 30 packets, throw all the remaining supplies (mixing bottle, lid with cap, and oral dosing syringe) away in the trash.

Each PROMACTA for oral suspension kit contains the following supplies:

30 packets of PROMACTA for oral suspension	
1 Reusable mixing bottle with lid and cap	
30 Single-use 20-mL oral dosing syringes (Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension)	

You will need the following to give a dose of PROMACTA for oral suspension.

From the kit:

- prescribed number of packets
- 1 reusable mixing bottle with lid and cap. **Note:** Due to its small size, the cap may pose a danger of choking to small children.

- 1 single-use 20-mL oral dosing syringe (Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension)

Not included in the kit:
- 1 clean glass or cup filled with drinking water
- scissors to cut packet
- paper towels or disposable cloth
- disposable gloves (optional)

How do I prepare a dose of PROMACTA for oral suspension?

Step 1. Make sure that the mixing bottle, cap, lid and oral dosing syringe are dry before use. Remove the lid from the mixing bottle.

- **Prepare a clean, flat work surface.**
- **Wash and dry your hands before preparing the medicine.**

Step 2. Fill the oral dosing syringe with 20 mL of drinking water from the glass or cup.

- Start with the plunger pushed all the way into the syringe.
- Place the tip of the oral dosing syringe all the way into the water and pull back on the plunger to the 20 mL mark on the barrel of the oral dosing syringe.

Note: Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension.

Figure 1.



Step 3. Place the tip of the oral dosing syringe into the open mixing bottle. Empty water into open mixing bottle by slowly pushing the plunger all the way into the oral dosing syringe.

Figure 2.



Step 4. Take only the prescribed number of packets for one dose out of the kit. You may need to use more than one packet to prepare the entire dose.

12.5 mg packets

Dose	Number of 12.5 mg Packets Needed
12.5 mg dose	1 packet
25 mg dose	2 packets
50 mg dose	4 packets
75 mg dose	6 packets

25 mg packets

Dose	Number of 25 mg Packets Needed
12.5 mg dose	1 packet (Note: See Step 9 for instructions on how to give a 12.5-mg dose using a 25-mg packet.)
25 mg dose	1 packet
50 mg dose	2 packets
75 mg dose	3 packets

Step 5. Add the prescribed number of packets to the mixing bottle.

- Tap the top of each packet to make sure the contents fall to the bottom.
- Cut off the top of the packet with scissors and empty the entire contents of the packet into the mixing bottle.
- Make sure not to spill the powder outside the mixing bottle.

Figure 3.

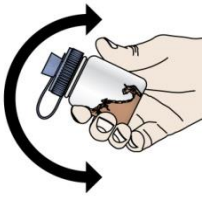


Step 6. Screw the lid tightly onto the mixing bottle. Make sure the cap is pushed onto the lid.

Step 7. Gently and slowly shake the mixing bottle back and forth for at least 20 seconds to mix the water with the powder.

- To prevent the mixture from foaming, do not shake the mixing bottle hard.

Figure 4.



How should I give a dose of PROMACTA for oral suspension?

Step 8. Make sure the plunger is pushed all the way into the oral dosing syringe. Pull cap off the mixing bottle lid and insert the tip of the oral dosing syringe into the hole in the lid.

Step 9. Transfer the mixture into the oral dosing syringe. The liquid will be dark brown in color.

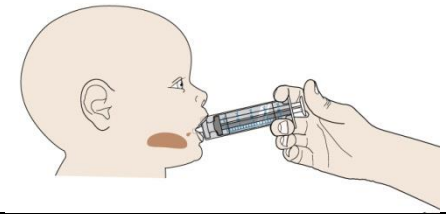
- Turn the mixing bottle upside down along with the oral dosing syringe.
- Pull back the plunger:
  12.5-mg packet
  - until all the medicine is in the oral dosing syringe (12.5-mg, 25-mg, 50-mg, or 75-mg dose)

  25-mg packet
  - to the 10 mL mark on the oral dosing syringe for a **12.5-mg dose only**

    OR
  - until all the medicine is in the oral dosing syringe (25-mg, 50-mg, or 75-mg dose).

Figure 5.



Step 10. Return the mixing bottle to the upright position and remove the oral dosing syringe from the mixing bottle.	**Figure 6.** 
Step 11. Giving a dose of PROMACTA for oral suspension to a child. • Place the tip of the oral dosing syringe into the inside of the child's cheek. • Slowly push the plunger all the way down to give the entire dose. Make sure the child has time to swallow the medicine.	**Figure 7.** 

How should I clean up?

Step 12. Carefully clean up any spill of the powder or suspension with a damp paper towel or disposable cloth.

- To avoid possibly staining your skin, consider using disposable gloves.
- Throw away (discard) used paper towel or disposable cloth and gloves in the trash.

Step 13. Clean the mixing supplies.

- **Do not reuse any of the mixture remaining in the mixing bottle.**
- Throw away (discard) any mixture remaining in the mixing bottle in the trash. Do not pour down the drain.
- Throw away (discard) the used oral dosing syringe. Use a new (single-use) oral dosing syringe to prepare each dose of PROMACTA for oral suspension.
- Rinse the mixing bottle and lid under running water and air dry. The mixing bottle may become stained from the medicine. This is normal.
- Wash hands with soap and water.

How should I store PROMACTA for oral suspension?

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

Keep PROMACTA and all medicines out of the reach of children.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

© Novartis

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: April 2020

T2020-61

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets
Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Revolade 12.5 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

Revolade 25 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

Revolade 50 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

Revolade 75 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Revolade 12.5 mg film-coated tablets
White, round, biconvex film-coated tablet (approximately 7.9 mm in diameter) debossed with 'GS MZ1' and '12.5' on one side.

Revolade 25 mg film-coated tablets
White, round, biconvex film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS NX3' and '25' on one side.

Revolade 50 mg film-coated tablets
Brown, round, biconvex film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS UFU' and '50' on one side.

Revolade 75 mg film-coated tablets
Pink, round, biconvex film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS FFS' and '75' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Revolade is indicated for the treatment of paediatric 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).

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

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.

The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation (see section 5.2). When switching between the tablet and the powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Immune (primary) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥50 000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric population aged 6 to 17 years
The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Paediatric population aged 1 to 5 years
The recommended starting dose of eltrombopag is 25 mg once daily.

Monitoring and dose adjustment
After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥50 000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

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 full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50 000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

Table 1 Dose adjustments of eltrombopag in ITP patients

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.

* For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.
♦ For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

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

It is necessary to 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 decrease or increase, would be 25 mg once daily.

Discontinuation
Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 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. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50 000-75 000/µl. Platelet counts >75 000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen
Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment
The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50 000-75 000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. It is recommended to wait for 2 weeks to assess the effects of this and any subsequent dose adjustments.

A dose of 100 mg eltrombopag once daily must not be exceeded.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

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 100 mg/day.
≥50 000/µl to ≤100 000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon.
>100 000/µl to ≤150 000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
>150 000/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*.

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

♦ On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation
If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe aplastic anaemia

Initial dose regimen
Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment
Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥50 000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
<50 000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥50 000/µl to ≤150 000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
>150 000/µl to ≤250 000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>250 000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤100 000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders
For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to <30 000/µl, haemoglobin drops to < 9 g/dl or absolute neutrophil count (ANC) <0.5 x 10^9/l, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation
If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate *(*see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment
No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment
Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 3 weeks should be observed before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events (TEEs), in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly
There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between patients aged at least 65 years and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East-/Southeast-Asian patients
For adult and paediatric patients of East-/Southeast-Asian ancestry, including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population
Revolade is not recommended for use in children under the age of one year with ITP due to insufficient data on safety and efficacy. The safety and efficacy of eltrombopag has not been established in children and adolescents (<18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.

Method of administration

Oral use.
The tablets should be taken at least two hours before or four hours 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) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤35 g/l or model for end stage liver disease (MELD) score ≥10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤35g/l) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct-acting antiviral agents

Safety and efficacy have not been established in combination with direct-acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening (see section 4.8).

Serum alanine aminotransferase (ALT), aspartate aminotrasferase (AST) and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥3 times the upper limit of normal [x ULN] in patients with normal liver function, or ≥3 x baseline or >5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) 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.

Caution is required when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients a lower starting dose of eltrombopag should be used. Close monitoring is required when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤35 g/l) or with MELD score ≥10 at baseline.

Chronic HCV patients with liver cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In two controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) occurred more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/l) or with a MELD score ≥10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤35 g/l) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1 439), 38 out of 955 patients (4%) treated with eltrombopag and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus <1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤35 g/l) or MELD ≥10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for 2 weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count >200 000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical studies in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of TEEs of any aetiology.

No case of TEE was identified from a clinical study in refractory SAA, however the risk of these events cannot be excluded in this patient population due to the limited number of exposed patients. As the highest authorised dose is indicated for patients with SAA (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical studies, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin-receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome (MDS)

There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS. 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.

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 SAA 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 Revolade have not been established for the treatment of thrombocytopenia due to MDS. Revolade should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

In clinical studies with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1 439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical studies of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Paediatric population

The above warnings and precautions for ITP also apply to the paediatric population.

Interference with laboratory tests

Eltrombopag is highly coloured and so has the potential to interfere with some laboratory tests. Serum discolouration and interference with total bilirubin and creatinine testing have been reported in patients taking Revolade. If the laboratory results and clinical observations are inconsistent, re-testing using another method may help in determining the validity of the result.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% confidence interval [CI]: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilising human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20%, and decreased C_{min} by 32%. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Ciclosporin

A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor). The co-administration of 200 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 39% and 24%, respectively. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section 4.2). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1 524 mg aluminium hydroxide and 1 425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of a single 100 mg dose of eltrombopag with repeat dose lopinavir/ritonavir 400/100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{0-\infty}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with lopinavir/ritonavir takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations, whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV protease inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Food interaction

The administration of eltrombopag tablet or powder for oral suspension formulations with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [<50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent (see section 4.2).

Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 59% and mean C_{max} by 65%.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high-calcium, moderate-fat and moderate-calorie meal reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 75% and mean C_{max} by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%).

Food low in calcium (<50 mg calcium), including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain, did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

Immune thrombocytopenia in adult and paediatric patients

The safety of Revolade was assessed in adult patients (N=763) using the pooled double-blind, placebo-controlled studies TRA100773A and B, TRA102537 (RAISE) and TRA113765, in which 403 patients were exposed to Revolade and 179 to placebo, in addition to data from the completed open-label studies (N=360) TRA108057 (REPEAT), TRA105325 (EXTEND) and TRA112940 (see section 5.1). Patients received study medication for up to 8 years (in EXTEND). The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included nausea, diarrhoea, increased alanine aminotransferase and back pain.

The safety of Revolade in paediatric patients (aged 1 to 17 years) with previously treated ITP has been demonstrated in two studies (N=171) (see section 5.1). PETIT2 (TRA115450) was a two-part, double-blind and open-label, randomised, placebo-controlled study. Patients were randomised 2:1 and received Revolade (n=63) or placebo (n=29) for up to 13 weeks in the randomised period of the study. PETIT (TRA108062) was a three-part, staggered-cohort, open-label and double-blind, randomised, placebo-controlled study. Patients were randomised 2:1 and received Revolade (n=44) or placebo (n=21), for up to 7 weeks. The profile of adverse reactions was comparable to that seen in adults with some additional adverse reactions, marked ♦ in the table below. The most common adverse reactions in paediatric ITP patients 1 year and older (≥3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain, oropharyngeal pain, toothache and rhinorrhoea.

Thrombocytopenia with HCV infection in adult patients

ENABLE 1 (TPL103922 n=716, 715 treated with eltrombopag) and ENABLE 2 (TPL108390 n=805) were randomised, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of Revolade in thrombocytopenic patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies the safety population consisted of all randomised patients who received double-blind study medicinal product during Part 2 of ENABLE 1 (Revolade treatment n=450, placebo treatment n=232) and ENABLE 2 (Revolade treatment n=506, placebo treatment n=252). Patients are analysed according to the treatment received (total safety double-blind population, Revolade n=955 and placebo n=484). The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included headache, anaemia, decreased appetite, cough, nausea, diarrhoea, hyperbilirubinaemia, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and oedema.

Severe aplastic anaemia in adult patients

The safety of Revolade in severe aplastic anaemia was assessed in a single-arm, open-label study (N=43) in which 11 patients (26%) were treated for >6 months and 7 patients (16%) were treated for >1 year (see section 5.1). The most common adverse reactions occurring in at least 10% of patients included headache, dizziness, cough, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, arthralgia, pain in extremity, muscle spasms, fatigue and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=763), paediatric ITP studies (N=171), the HCV studies (N=1 520), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA system organ class and by frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); not known (cannot be estimated from the available data).

ITP study population

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Nasopharyngitis♦, upper respiratory tract infection♦
	Common	Pharyngitis, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection, gingivitis
	Uncommon	Skin infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Rectosigmoid cancer
Blood and lymphatic system disorders	Common	Anaemia, eosinophilia, leukocytosis, thrombocytopenia, haemoglobin decreased, white blood cell count decreased
	Uncommon	Anisocytosis, haemolytic anaemia, myelocytosis, band neutrophil count increased, myelocyte present, platelet count increased, haemoglobin increased
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Hypokalaemia, decreased appetite, blood uric acid increased
	Uncommon	Anorexia, gout, hypocalcaemia
Psychiatric disorders	Common	Sleep disorder, depression
	Uncommon	Apathy, mood altered, tearfulness
Nervous system disorders	Common	Paraesthesia, hypoaesthesia, somnolence, migraine
	Uncommon	Tremor, balance disorder, dysaesthesia, hemiparesis, migraine with aura, neuropathy peripheral, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache
Eye disorders	Common	Dry eye, vision blurred, eye pain, visual acuity reduced
	Uncommon	Lenticular opacities, astigmatism, cataract cortical, lacrimation increased, retinal haemorrhage, retinal pigment epitheliopathy, visual impairment, visual acuity tests abnormal, blepharitis, keratoconjunctivitis sicca
Ear and labyrinth disorders	Common	Ear pain, vertigo
Cardiac disorders	Uncommon	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged

Vascular disorders	Common	Deep vein thrombosis, haematoma, hot flush
	Uncommon	Embolism, thrombophlebitis superficial, flushing
Respiratory, thoracic and mediastinal disorders	Very common	Cough♦
	Common	Oropharyngeal pain♦, rhinorrhoea♦
	Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, sinus disorder, sleep apnoea syndrome
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Mouth ulceration, toothache♦, vomiting, abdominal pain*, mouth haemorrhage, flatulence * Very common in paediatric ITP
	Uncommon	Dry mouth, glossodynia, abdominal tenderness, faeces discoloured, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Hepatobiliary disorders	Very common	Alanine aminotransferase increased†
	Common	Aspartate aminotransferase increased†, hyperbilirubinaemia, hepatic function abnormal
	Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Rash, alopecia, hyperhidrosis, pruritus generalised, petechiae
	Uncommon	Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Common	Myalgia, muscle spasm, musculoskeletal pain, bone pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Proteinuria, blood creatinine increased, thrombotic microangiopathy with renal failure‡
	Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, blood urea increased, urine protein/creatinine ratio increased
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Pyrexia*, chest pain, asthenia *Very common in paediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	Common	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	Uncommon	Sunburn

♦ Additional adverse reactions observed in paediatric studies (aged 1 to 17 years).

† Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

‡ Grouped term with preferred terms acute kidney injury and renal failure

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes
	Uncommon	Gastroenteritis, pharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Hepatic neoplasm malignant
Blood and lymphatic system disorders	Very common	Anaemia
	Common	Lymphopenia
	Uncommon	Haemolytic anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hyperglycaemia, abnormal loss of weight
Psychiatric disorders	Common	Depression, anxiety, sleep disorder
	Uncommon	Confusional state, agitation
Nervous system disorders	Very common	Headache
	Common	Dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia
Eye disorders	Common	Cataract, retinal exudates, dry eye, ocular icterus, retinal haemorrhage
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitations
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastrooesophagal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal
	Uncommon	Oesophageal varices haemorrhage, gastritis, aphthous stomatitis
Hepatobiliary disorders	Common	Hyperbilirubinaemia, jaundice, drug-induced liver injury
	Uncommon	Portal vein thrombosis, hepatic failure

Skin and subcutaneous tissue disorders	Very common	Pruritus
	Common	Rash, dry skin, eczema, rash pruritic, erythema, hyperhidrosis, pruritus generalised, alopecia
	Uncommon	Skin lesion, skin discolouration, skin hyperpigmentation, night sweats
Musculoskeletal and connective tissue disorder	Very common	Myalgia
	Common	Arthralgia, muscle spasms, back pain, pain in extremity, musculoskeletal pain, bone pain
Renal and urinary disorders	Uncommon	Thrombotic microangiopathy with acute renal failure[†], dysuria
General disorders and administration site conditions	Very common	Pyrexia, fatigue, influenza-like illness, asthenia, chills
	Common	Irritability, pain, malaise, injection site reaction, non-cardiac chest pain, oedema, oedema peripheral
	Uncommon	Injection site pruritus, injection site rash, chest discomfort
Investigations	Common	Blood bilirubin increased, weight decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, international normalised ratio increased, activated partial thromboplastin time prolonged, blood glucose increased, blood albumin decreased
	Uncommon	Electrocardiogram QT prolonged

[†] Grouped term with preferred terms oliguria, renal failure and renal impairment

SAA study population

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Neutropenia, splenic infarction
Metabolism and nutrition disorders	Common	Iron overload, decreased appetite, hypoglycaemia, increased appetite
Psychiatric disorders	Common	Anxiety, depression
Nervous system disorders	Very common	Headache, dizziness
	Common	Syncope
Eye disorders	Common	Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters
Respiratory, thoracic and mediastinal disorders	Very common	Cough, oropharyngeal pain, rhinorrhoea
	Common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, gingival bleeding, abdominal pain
	Common	Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence
Hepatobiliary disorders	Very common	Transaminases increased
	Common	Blood bilirubin increased (hyperbilirubinemia), jaundice
	Not known	Drug-induced liver injury* * Cases of drug-induced liver injury have been reported in patients with ITP and HCV
Skin and subcutaneous tissue disorders	Common	Petechiae, rash, pruritus, urticaria, skin lesion, rash macular
	Not known	Skin discolouration, skin hyperpigmentation
Musculosketal and connective tissue disorders	Very common	Arthralgia, pain in extremity, muscle spasms
	Common	Back pain, myalgia, bone pain
Renal and urinary disorders	Common	Chromaturia
General disorders and administration site conditions	Very common	Fatigue, pyrexia, chills
	Common	Asthenia, oedema peripheral, malaise
Investigations	Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies among adult ITP patients receiving eltrombopag (n=446), 17 patients experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1) (see section 4.4).

In a placebo-controlled study (n=288, Safety population), following 2 weeks' treatment in preparation for invasive procedures, 6 of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1%) patients in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count >200 000/µl

No specific risk factors were identified in those patients who experienced a TEE with the exception of platelet counts ≥200 000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1 439), 38 out of 955 patients (4%) treated with eltrombopag experienced a TEE and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/l) or MELD ≥10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤35 g/l) or MELD score ≥10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Hepatotoxicity

In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum ALT, AST and bilirubin were observed (see section 4.4).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo-controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥3 x ULN was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

In the single-arm phase II monotherapy refractory SAA study, concurrent ALT or AST >3 x ULN with total (indirect) bilirubin >1.5 x ULN were reported in 5% of patients. Total bilirubin >1.5 x ULN occurred in 14% of patients.

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

Haematologic malignancies

In the single-arm, open-label study in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) patient has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the patient ingested 5 000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin. The platelet counts were 672 000/µl on Day 18 after ingestion and the maximum platelet count was 929 000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Immune (primary) thrombocytopenia (ITP) studies

Two phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year. The single-arm phase II study TAPER (CETB115J2411) evaluated the safety and efficacy of eltrombopag and its ability to induce sustained response after treatment discontinuation in 105 adult ITP patients who relapsed or failed to respond to first-line corticosteroid treatment.

Double-blind placebo-controlled studies
RAISE:
197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6-month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag-treated patients were maintained on ≤25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16 000/µl for both treatment groups and in the eltrombopag group were maintained above 50 000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained <30 000/µl throughout the study.

Platelet count response between 50 000-400 000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6-month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 4 Secondary efficacy results from RAISE

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥50 000-400 000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥75% of assessments in the target range (50 000 to 400 000/µl), n (%)	51 (38)	4 (7)
p-value [a]	<0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
p-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
p-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
p-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
p-value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33%) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70% of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6-month treatment period.

TRA100773B:
The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥50 000/µl at Day 43 from a baseline of <30 000/µl; patients who withdrew prematurely due to a platelet count >200 000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated ITP were randomised 2:1 eltrombopag (n=76) to placebo (n=38).

Table 5 Efficacy results from TRA100773B

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥50 000/µl after up to 42 days of dosing (compared to a baseline count of <30 000/µl), n (%)	43 (59)	6 (16)
p-value[a]	<0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
p-value[a]	0.029	

a Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤15 000/µl, >15 000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤15 000/µl the median platelet counts did not reach the target level (>50 000/µl), although in both studies 43% of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count ≤15 000/µl treated with eltrombopag responded at the end of the 6-month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

Open-label non-controlled studies
REPEAT (TRA108057):
This open-label, repeat-dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

EXTEND (TRA105325):
Eltrombopag was administered to 302 ITP patients in this open-label extension study, 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19 000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85 000/µl, 85 000/µl, 105 000/µl, 64 000/µl, 75 000/µl, 119 000/µl and 76 000/µl, respectively.

TAPER (CETB115J2411):
This was a single-arm phase II study including ITP patients treated with eltrombopag after first-line corticosteroid failure irrespective of time since diagnosis. A total of 105 patients were enrolled on the study and started eltrombopag treatment on 50 mg once daily (25 mg once daily for patients of East-/Southeast-Asian ancestry). The dose of eltrombopag was adjusted during the treatment period based on individual platelet counts with the goal to achieve a platelet count ≥100 000/µl.

Of the 105 patients who were enrolled in the study and who received at least one dose of eltrombopag, 69 patients (65.7%) completed treatment and 36 patients (34.3%) discontinued treatment early.

Analysis of sustained response off treatment
The primary endpoint was the proportion of patients with sustained response off treatment until Month 12. Patients who reached a platelet count of ≥100 000/µl and maintained platelet counts around 100 000/µl for 2 months (no counts below 70 000/µl) were eligible for tapering off eltrombopag and treatment discontinuation. To be considered as having achieved a sustained response off treatment, a patient had to maintain platelet counts ≥30 000/µl, in the absence of bleeding events or the use of rescue therapy, both during the treatment tapering period and following discontinuation of treatment until Month 12.

The duration of tapering was individualised depending on the starting dose and the response of the patient. The tapering schedule recommended dose reductions of 25 mg every 2 weeks if the platelet counts were stable. After the daily dose was reduced to 25 mg for 2 weeks, the dose of 25 mg was then only administered on alternate days for 2 weeks until treatment discontinuation. The tapering was done in smaller decrements of 12.5 mg every second week for patients of East-/Southeast-Asian ancestry. If a relapse (defined as platelet count <30 000/µl) occurred, patients were offered a new course of eltrombopag at the appropriate starting dose.

Eighty-nine patients (84.8%) achieved a complete response (platelet count ≥100 000/µl) (Step 1, Table 6) and 65 patients (61.9%) maintained the complete response for at least 2 months with no platelet counts below 70 000/µl (Step 2, Table 6). Forty-four patients (41.9%) were able to be tapered off eltrombopag until treatment discontinuation while maintaining platelet counts ≥30 000/µl in the absence of bleeding events or the use of rescue therapy (Step 3, Table 6).

The study met the primary objective by demonstrating that eltrombopag was able to induce sustained response off treatment, in the absence of bleeding events or the use of rescue therapy, by Month 12 in 32 of the 105 enrolled patients (30.5%; p<0.0001; 95% CI: 21.9, 40.2) (Step 4, Table 6). By Month 24, 20 of the 105 enrolled patients (19.0%; 95% CI: 12.0, 27.9) maintained sustained response off treatment in the absence of bleeding events or the use of rescue therapy (Step 5, Table 6).

The median duration of sustained response after treatment discontinuation to Month 12 was 33.3 weeks (min-max: 4-51), and the median duration of sustained response after treatment discontinuation to Month 24 was 88.6 weeks (min-max: 57-107).

After tapering off and discontinuation of eltrombopag treatment, 12 patients had a loss of response, 8 of them re-started eltrombopag and 7 had a recovery response.

During the 2-year follow-up, 6 out of 105 patients (5.7%) experienced thromboembolic events, of which 3 patients (2.9%) experienced deep vein thrombosis, 1 patient (1.0%) experienced superficial vein thrombosis, 1 patient (1.0%) experienced cavernous sinus thrombosis, 1 patient (1.0%) experienced cerebrovascular accident and 1 patient (1.0%) experienced pulmonary embolism. Of the 6 patients, 4 patients experienced thromboembolic events that were reported at or greater than Grade 3, and 4 patients experienced thromboembolic event that were reported as serious. No fatal cases were reported.

Twenty out of 105 patients (19.0%) experienced mild to severe haemorrhage events on treatment before tapering started. Five out of 65 patients (7.7%) who started tapering experienced mild to moderate haemorrhage events during tapering. No severe haemorrhage event occurred during tapering. Two out of 44 patients (4.5%) who tapered off and discontinued eltrombopag treatment experienced mild to moderate haemorrhage events after treatment discontinuation until Month 12. No severe haemorrhage event occurred during this period. None of the patients who discontinued eltrombopag and entered the second year follow-up experienced haemorrhage event during the second year. Two fatal intracranial haemorrhage events were reported during the 2-year follow-up. Both events occurred on treatment, not in the context of tapering. The events were not considered to be related to study treatment.

The overall safety analysis is consistent with previously reported data and the risk-benefit assessment remained unchanged for the use of eltrombopag in patients with ITP.

Table 6 Proportion of patients with sustained response off treatment at Month 12 and at Month 24 (full analysis set) in TAPER

	All patients N=105		Hypothesis testing	
	n (%)	95% CI	p-value	Reject H0
Step 1: Patients who reached platelet count ≥100 000/µl at least once	89 (84.8)	(76.4, 91.0)		
Step 2: Patients who maintained stable platelet count for 2 months after reaching 100 000/µl (no counts <70 000/µl)	65 (61.9)	(51.9, 71.2)		
Step 3: Patients who were able to be tapered off eltrombopag until treatment discontinuation, maintaining platelet count ≥30 000/µl in the absence of bleeding events or use of any rescue therapy	44 (41.9)	(32.3, 51.9)		
Step 4: Patients with sustained response off treatment until Month 12, with platelet count maintained ≥30 000/µl in the absence of bleeding events or use of any rescue therapy	32 (30.5)	(21.9, 40.2)	<0.0001*	Yes
Step 5: Patients with sustained response off treatment from Month 12 to Month 24, maintaining platelet count ≥30 000/µl in the absence of bleeding events or use of any rescue therapy	20 (19.0)	(12.0, 27.9)		

N: The total number of patients in the treatment group. This is the denominator for percentage (%) calculation.
n: Number of patients in the corresponding category.
The 95% CI for the frequency distribution was computed using Clopper-Pearson exact method. Clopper-Pearson test was used for testing whether the proportion of responders was >15%. CI and p-values are reported.
* Indicates statistical significance (one-sided) at the 0.05 level.

Results of response on treatment analysis by time since ITP diagnosis
An ad-hoc analysis was conducted on the n=105 patients by time since ITP diagnosis to assess the response to eltrombopag across four different ITP categories by time since diagnosis (newly diagnosed ITP <3 months, persistent ITP 3 to <6 months, persistent ITP 6 to ≤12 months, and chronic ITP >12 months). 49% of patients (n=51) had an ITP diagnosis of <3 months, 20% (n=21) of 3 to <6 months, 17% (n=18) of 6 to ≤12 months and 14% (n=15) of >12 months.

Until the cut-off date (22-Oct-2021), patients were exposed to eltrombopag for a median (Q1-Q3) duration of 6.2 months (2.3-12.0 months). The median (Q1-Q3) platelet count at baseline was 16 000/µl (7 800-28 000/µl).

Platelet count response, defined as a platelet count ≥50 000/µl at least once by Week 9 without rescue therapy, was achieved in 84% (95% CI: 71% to 93%) of newly diagnosed ITP patients, 91% (95% CI: 70% to 99%) and 94% (95% CI: 73% to 100%) of persistent ITP patients (i.e. with ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and in 87% (95% CI: 60% to 98%) of chronic ITP patients.

The rate of complete response, defined as platelet count ≥100 000/µl at least once by Week 9 without rescue therapy, was 75% (95% CI: 60% to 86%) in newly diagnosed ITP patients, 76% (95% CI: 53% to 92%) and 72% (95% CI: 47% to 90%) in persistent ITP patients (ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and 87% (95% CI: 60% to 98%) in chronic ITP patients.

The rate of durable response, defined as a platelet count ≥50 000/µl for at least 6 out of 8 consecutive assessments without rescue therapy during the first 6 months on study, was 71% (95% CI: 56% to 83%) in newly diagnosed ITP patients, 81% (95% CI: 58% to 95%) and 72% (95% CI: 47% to 90.3%) in persistent ITP patients (ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and 80% (95% CI: 52% to 96%) in chronic ITP patients.

When assessed with the WHO Bleeding Scale, the proportion of newly diagnosed and persistent ITP patients without bleeding at Week 4 ranged from 88% to 95% compared to 37% to 57% at baseline. For chronic ITP patients it was 93% compared to 73% at baseline.

The safety of eltrombopag was consistent across all ITP categories and in line with its known safety profile.

Clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)
The safety and efficacy of eltrombopag in paediatric patients have been investigated in two studies.

TRA115450 (PETIT2):
The primary endpoint was a sustained response, defined as the proportion of patients receiving eltrombopag, compared to placebo, achieving platelet counts ≥50 000/µl for at least 6 out of 8 weeks (in the absence of rescue therapy), between weeks 5 to 12 during the double-blind randomised period. Patients were diagnosed with chronic ITP for at least 1 year and were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count <30 000/µl. Ninety-two patients were randomised by three age cohort strata (2:1) to eltrombopag (n=63) or placebo (n=29). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag patients (40%) compared with placebo patients (3%) achieved the primary endpoint (Odds Ratio: 18.0 [95% CI: 2.3, 140.9] p <0.001) which was similar across the three age cohorts (Table 7).

Table 7 Sustained platelet response rates by age cohort in paediatric patients with chronic ITP

	Eltrombopag n/N (%) [95% CI]	Placebo n/N (%) [95% CI]
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

Statistically fewer eltrombopag patients required rescue treatment during the randomised period compared to placebo patients (19% [12/63] vs. 24% [7/29], p=0.032).

At baseline, 71% of patients in the eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of eltrombopag patients reporting any bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo patients reported any bleeding.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of patients were able to reduce (n=1) or discontinue (n=7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT):
The primary endpoint was the proportion of patients achieving platelet counts ≥50 000/µl at least once between weeks 1 and 6 of the randomised period. Patients were diagnosed with ITP for at least 6 months and were refractory or relapsed to at least one prior ITP therapy with a platelet count <30 000/µl (n=67). During the randomised period of the study, patients were randomised by three age cohort strata (2:1) to eltrombopag (n=45) or placebo (n=22). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag patients (62%) compared with placebo patients (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p=0.011).

Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT study.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled studies. ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of <75 000/µl were enrolled and stratified by platelet count (<50 000/µl and ≥50 000/µl to <75 000/µl), screening HCV RNA (<800 000 IU/ml and ≥800 000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64%) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59 500/µl in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts <20 000/µl, <50 000/µl and ≥50 000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label eltrombopag to increase the platelet count to ≥90 000/µl for ENABLE 1 and ≥100 000/µl for ENABLE 2. The median time to achieve the target platelet count ≥90 000/µl (ENABLE 1) or ≥100 000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 8). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (<50 000 vs. >50 000), viral load (<800 000 IU/ml vs. ≥800 000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 8 Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts and initiating antiviral therapy [c]	1 439/1 520 (95%)		680/715 (95%)		759/805 (94%)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering antiviral treatment phase	**n=956**	**n=485**	**n=450**	**n=232**	**n=506**	**n=253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/l	11	8				
> 35g/l	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 µg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1 200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 µg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1 400 mg orally in 2 divided doses)

c Target platelet count was ≥90 000/µl for ENABLE 1 and ≥100 000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 patients then withdrew consent prior to receiving antiviral therapy

d *p*-value <0.05 for eltrombopag versus placebo

e 64% patients participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following: significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p=<0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45% vs. 27%). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label study in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤30 000/µl.

The majority of patients, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 patients had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anaemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ⩾50%, where excluded from participation.

At baseline the median platelet count was 20 000/µl, haemoglobin was 8.4 g/dl, ANC was 0.58 x 10^9/l and absolute reticulocyte count was 24.3 x 10^9/l. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20 000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by >1.5g/dl, or a reduction in ≥4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase >0.5 x 10^9/l.

The haematological response rate was 40% (17/43 patients; 95% CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion-free period for non-responders was 27 days (median). The longest platelet transfusion-free period for responders was 287 days (median). The longest RBC transfusion-free period for non-responders was 29 days (median). The longest RBC transfusion-free period for responders was 266 days (median).

Over 50% of responders who were transfusion-dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA patients, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 9).

Table 9 Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 patients with HCV enrolled in phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the phase III studies are presented for each dose studied in Table 10.

Table 10 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

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

Data presented as geometric mean (95% CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the film-coated tablet formulation. 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%.

Distribution

Eltrombopag is highly bound to human plasma proteins (>99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

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 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC_{50} value of 2.7 μM [1.2 μg/ml]). *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC_{50} value of 2.7 μM [1.2 μg/ml]).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in patients with mild to moderate renal impairment, and 60% lower in patients with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein-bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag have not been established in patients with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult patients with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41% higher in patients with mild hepatic impairment and 80% to 93% higher in patients with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein-bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East-Asians) and 88 patients with ITP (18 East-Asians). Based on estimates from the population pharmacokinetic analysis, East-Asian ITP patients had approximately 49% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East-Asian patients who were predominantly Caucasian (see section 4.2).

The influence of East-/Southeast-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East-Asians and 69 Southeast-Asians). Based on estimates from the population pharmacokinetic analysis, East-/Southeast-Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥75 years. Based on model estimate, elderly (≥65 years) patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between paediatric and adult patients. East-/Southeast-Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of eltrombopag in paediatric patients with ITP are shown in Table 11.

Table 11 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric patients with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**$AUC_{(0-\tau)}$ (µg.hr/ml)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates

5.3 Preclinical safety data

Safety pharmacology and repeat-dose toxicity

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥6 times the human clinical exposure in adult ITP patients at 75 mg/day and 3 times the human clinical exposure in adult HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from Days 4-32 (approximately equating to a 2-year-old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human clinical exposure in paediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in paediatric ITP patients, based on AUC. Cataracts have not been observed in adult dogs after 52 weeks of dosing at 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterised by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 or 0.8 times the human clinical exposure based on AUC in adult or paediatric ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in adult ITP patients and 3 or 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times or equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (>10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and>4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short-term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in adult or paediatric ITP patients at 75 mg/day and ≤2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28-week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times or 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Carcinogenicity and mutagenicity

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times or 8 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Reproductive toxicity

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in adult or adolescent (12-17 years old) ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioural or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

Phototoxicity

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

Juvenile animal studies

At non-tolerated doses in pre-weaning rats, ocular opacities were observed. At tolerated doses, no ocular opacities were observed (see above subsection 'Safety pharmacology and repeat-dose toxicity'). In conclusion, taking into account the exposure margins based on AUC, a risk of eltrombopag-related cataracts in paediatric patients cannot be excluded. There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Revolade 12.5 mg film-coated tablets

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose (E464)
Macrogol 400 (E1521)
Polysorbate 80 (E433)
Titanium dioxide (E171)

Revolade 25 mg film-coated tablets

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose (E464)
Macrogol 400 (E1521)
Polysorbate 80 (E433)
Titanium dioxide (E171)

Revolade 50 mg film-coated tablets

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose (E464)
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 400 (E1521)
Titanium dioxide (E171)

Revolade 75 mg film-coated tablets

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Tablet coating
Hypromellose (E464)
Iron oxide red (E172)
Iron oxide black (E172)
Macrogol 400 (E1521)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Film-coated tablets

Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Revolade 12.5 mg film-coated tablets

EU/1/10/612/010
EU/1/10/612/011
EU/1/10/612/012

Revolade 25 mg film-coated tablets

EU/1/10/612/001
EU/1/10/612/002
EU/1/10/612/003

Revolade 50 mg film-coated tablets

EU/1/10/612/004
EU/1/10/612/005
EU/1/10/612/006

Revolade 75 mg film-coated tablets

EU/1/10/612/007
EU/1/10/612/008
EU/1/10/612/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of latest renewal: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains eltrombopag olamine equivalent to 25 mg of eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

Reddish-brown to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Revolade is indicated for the treatment of paediatric 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).

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

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.

The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation (see section 5.2). When switching between the tablet and the powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Immune (primary) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥50 000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric population aged 6 to 17 years
The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Paediatric population aged 1 to 5 years
The recommended starting dose of eltrombopag is 25 mg once daily.

Monitoring and dose adjustment
After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥50 000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

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 full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50 000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

Table 1 Dose adjustments of eltrombopag in ITP patients

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.

* For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.
♦ For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

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

It is necessary to 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 decrease or increase, would be 25 mg once daily.

Discontinuation
Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 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. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50 000-75 000/µl. Platelet counts >75 000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen
Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment
The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50 000-75 000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. It is recommended to wait for 2 weeks to assess the effects of this and any subsequent dose adjustments.

A dose of 100 mg eltrombopag once daily must not be exceeded.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

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 100 mg/day.
≥50 000/µl to ≤100 000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon.
>100 000/µl to ≤150 000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
>150 000/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*.

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

♦ On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation
If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe aplastic anaemia

Initial dose regimen
Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment
Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥50 000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
<50 000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥50 000/µl to ≤150 000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
>150 000/µl to ≤250 000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>250 000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤100 000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders
For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to <30 000/µl, haemoglobin drops to <9 g/dl or absolute neutrophil count (ANC) to $<0.5 \times 10^9$/l, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation
If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate *(*see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment
No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment
Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 3 weeks should be observed before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events (TEEs), in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly
There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between patients aged at least 65 years and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East-/Southeast-Asian patients
For adult and paediatric patients of East-/Southeast-Asian ancestry, including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population
Revolade is not recommended for use in children under the age of one year with ITP due to insufficient data on safety and efficacy. The safety and efficacy of eltrombopag has not been established in children and adolescents (<18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.

Method of administration (see section 6.6)

Oral use.
The suspension should be taken at least two hours before or four hours 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) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤35 g/l or model for end stage liver disease (MELD) score ≥10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤35 g/l) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct-acting antiviral agents

Safety and efficacy have not been established in combination with direct-acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening (see section 4.8).

Serum alanine aminotransferase (ALT), aspartate aminotrasferase (AST) and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥3 times the upper limit of normal [x ULN] in patients with normal liver function, or ≥3 x baseline or >5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) 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.

Caution is required when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients a lower starting dose of eltrombopag should be used. Close monitoring is required when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤35 g/l) or with MELD score ≥10 at baseline.

Chronic HCV patients with liver cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In two controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) occurred more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤35 g/l) or with a MELD score ≥10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤35 g/l) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1 439), 38 out of 955 patients (4%) treated with eltrombopag and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus <1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤35 g/l) or MELD ≥10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for 2 weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count >200 000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical studies in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of TEEs of any aetiology.

No case of TEE was identified from a clinical study in refractory SAA, however the risk of these events cannot be excluded in this patient population due to the limited number of exposed patients. As the highest authorised dose is indicated for patients with SAA (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical studies, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin-receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome (MDS)

There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS. 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.

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 SAA 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 Revolade have not been established for the treatment of thrombocytopenia due to MDS. Revolade should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

In clinical studies with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1 439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical studies of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Paediatric population

The above warnings and precautions for ITP also apply to the paediatric population.

Interference with laboratory tests

Eltrombopag is highly coloured and so has the potential to interfere with some laboratory tests. Serum discolouration and interference with total bilirubin and creatinine testing have been reported in patients taking Revolade. If the laboratory results and clinical observations are inconsistent, re-testing using another method may help in determining the validity of the result.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% confidence interval [CI]: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilising human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20%, and decreased C_{min} by 32%. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Ciclosporin

A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor). The co-administration of 200 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 39% and 24%, respectively. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section 4.2). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1 524 mg aluminium hydroxide and 1 425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of a single 100 mg dose of eltrombopag with repeat dose lopinavir/ritonavir 400/100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{0-\infty}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with lopinavir/ritonavir takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations, whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV protease inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Food interaction

The administration of eltrombopag tablet or powder for oral suspension formulations with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [<50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent (see section 4.2).

Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 59% and mean C_{max} by 65%.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high-calcium, moderate-fat and moderate-calorie meal reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 75% and mean C_{max} by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%).

Food low in calcium (<50 mg calcium), including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain, did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

Immune thrombocytopenia in adult and paediatric patients

The safety of Revolade was assessed in adult patients (N=763) using the pooled double-blind, placebo-controlled studies TRA100773A and B, TRA102537 (RAISE) and TRA113765, in which 403 patients were exposed to Revolade and 179 to placebo, in addition to data from the completed open-label studies (N=360) TRA108057 (REPEAT), TRA105325 (EXTEND) and TRA112940 (see section 5.1). Patients received study medication for up to 8 years (in EXTEND). The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included nausea, diarrhoea, increased alanine aminotransferase and back pain.

The safety of Revolade in paediatric patients (aged 1 to 17 years) with previously treated ITP has been demonstrated in two studies (N=171) (see section 5.1). PETIT2 (TRA115450) was a two-part, double-blind and open-label, randomised, placebo-controlled study. Patients were randomised 2:1 and received Revolade (n=63) or placebo (n=29) for up to 13 weeks in the randomised period of the study. PETIT (TRA108062) was a three-part, staggered-cohort, open-label and double-blind, randomised, placebo-controlled study. Patients were randomised 2:1 and received Revolade (n=44) or placebo (n=21), for up to 7 weeks. The profile of adverse reactions was comparable to that seen in adults with some additional adverse reactions, marked ♦ in the table below. The most common adverse reactions in paediatric ITP patients 1 year and older (≥3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain, oropharyngeal pain, toothache and rhinorrhoea.

Thrombocytopenia with HCV infection in adult patients

ENABLE 1 (TPL103922 n=716, 715 treated with eltrombopag) and ENABLE 2 (TPL108390 n=805) were randomised, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of Revolade in thrombocytopenic patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies the safety population consisted of all randomised patients who received double-blind study medicinal product during Part 2 of ENABLE 1 (Revolade treatment n=450, placebo treatment n=232) and ENABLE 2 (Revolade treatment n=506, placebo treatment n=252). Patients are analysed according to the treatment received (total safety double-blind population, Revolade n=955 and placebo n=484). The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included headache, anaemia, decreased appetite, cough, nausea, diarrhoea, hyperbilirubinaemia, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and oedema.

Severe aplastic anaemia in adult patients

The safety of Revolade in severe aplastic anaemia was assessed in a single-arm, open-label study (N=43) in which 11 patients (26%) were treated for >6 months and 7 patients (16%) were treated for >1 year (see section 5.1). The most common adverse reactions occurring in at least 10% of patients included headache, dizziness, cough, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, arthralgia, pain in extremity, muscle spasms, fatigue and pyrexia.

List of adverse reactions

The adverse reactions in the adult ITP studies (N=763), paediatric ITP studies (N=171), the HCV studies (N=1,520), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA system organ class and by frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); not known (cannot be estimated from the available data).

ITP study population

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Nasopharyngitis♦, upper respiratory tract infection♦
	Common	Pharyngitis, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection, gingivitis
	Uncommon	Skin infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Rectosigmoid cancer
Blood and lymphatic system disorders	Common	Anaemia, eosinophilia, leukocytosis, thrombocytopenia, haemoglobin decreased, white blood cell count decreased
	Uncommon	Anisocytosis, haemolytic anaemia, myelocytosis, band neutrophil count increased, myelocyte present, platelet count increased, haemoglobin increased
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Hypokalaemia, decreased appetite, blood uric acid increased
	Uncommon	Anorexia, gout, hypocalcaemia
Psychiatric disorders	Common	Sleep disorder, depression
	Uncommon	Apathy, mood altered, tearfulness

Nervous system disorders	Common	Paraesthesia, hypoaesthesia, somnolence, migraine
	Uncommon	Tremor, balance disorder, dysaesthesia, hemiparesis, migraine with aura, neuropathy peripheral, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache
Eye disorders	Common	Dry eye, vision blurred, eye pain, visual acuity reduced
	Uncommon	Lenticular opacities, astigmatism, cataract cortical, lacrimation increased, retinal haemorrhage, retinal pigment epitheliopathy, visual impairment, visual acuity tests abnormal, blepharitis, keratoconjunctivitis sicca
Ear and labyrinth disorders	Common	Ear pain, vertigo
Cardiac disorders	Uncommon	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged
Vascular disorders	Common	Deep vein thrombosis, haematoma, hot flush
	Uncommon	Embolism, thrombophlebitis superficial, flushing
Respiratory, thoracic and mediastinal disorders	Very common	Cough♦
	Common	Oropharyngeal pain♦, rhinorrhoea♦
	Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, sinus disorder, sleep apnoea syndrome
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Mouth ulceration, toothache♦, vomiting, abdominal pain*, mouth haemorrhage, flatulence * Very common in paediatric ITP
	Uncommon	Dry mouth, glossodynia, abdominal tenderness, faeces discoloured, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Hepatobiliary disorders	Very common	Alanine aminotransferase increased†
	Common	Aspartate aminotransferase increased†, hyperbilirubinaemia, hepatic function abnormal
	Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Rash, alopecia, hyperhidrosis, pruritus generalised, petechiae
	Uncommon	Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Common	Myalgia, muscle spasm, musculoskeletal pain, bone pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Proteinuria, blood creatinine increased, thrombotic microangiopathy with renal failure‡
	Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, blood urea increased, urine protein/creatinine ratio increased
Reproductive system and breast disorders	Common	Menorrhagia

General disorders and administration site conditions	Common	Pyrexia*, chest pain, asthenia *Very common in paediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	Common	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	Uncommon	Sunburn

♦ Additional adverse reactions observed in paediatric studies (aged 1to 17 years).

† Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

‡ Grouped term with preferred terms acute kidney injury and renal failure

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes
	Uncommon	Gastroenteritis, pharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Hepatic neoplasm malignant
Blood and lymphatic system disorders	Very common	Anaemia
	Common	Lymphopenia
	Uncommon	Haemolytic anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hyperglycaemia, abnormal loss of weight
Psychiatric disorders	Common	Depression, anxiety, sleep disorder
	Uncommon	Confusional state, agitation
Nervous system disorders	Very common	Headache
	Common	Dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia
Eye disorders	Common	Cataract, retinal exudates, dry eye, ocular icterus, retinal haemorrhage
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitations
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough

Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastrooesophagal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal
	Uncomon	Oesophageal varices haemorrhage, gastritis, aphthous stomatitis
Hepatobiliary disorders	Common	Hyperbilirubinaemia, jaundice, drug-induced liver injury
	Uncommon	Portal vein thrombosis, hepatic failure
Skin and subcutaneous tissue disorders	Very common	Pruritus
	Common	Rash, dry skin, eczema, rash pruritic, erythema, hyperhidrosis, pruritus generalised, alopecia
	Uncommon	Skin lesion, skin discolouration, skin hyperpigmentation, night sweats
Musculoskeletal and connective tissue disorder	Very common	Myalgia
	Common	Arthralgia, muscle spasms, back pain, pain in extremity, musculoskeletal pain, bone pain
Renal and urinary disorders	Uncommon	Thrombotic microangiopathy with acute renal failure†, dysuria
General disorders and administration site conditions	Very common	Pyrexia, fatigue, influenza-like illness, asthenia, chills
	Common	Irritability, pain, malaise, injection site reaction, non-cardiac chest pain, oedema, oedema peripheral
	Uncommon	Injection site pruritus, injection site rash, chest discomfort
Investigations	Common	Blood bilirubin increased, weight decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, international normalised ratio increased, activated partial thromboplastin time prolonged, blood glucose increased, blood albumin decreased
	Uncommon	Electrocardiogram QT prolonged

† Grouped term with preferred terms oliguria, renal failure and renal impairment

SAA study population

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Neutropenia, splenic infarction
Metabolism and nutrition disorders	Common	Iron overload, decreased appetite, hypoglycaemia, increased appetite
Psychiatric disorders	Common	Anxiety, depression
Nervous system disorders	Very common	Headache, dizziness
	Common	Syncope
Eye disorders	Common	Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters
Respiratory, thoracic and mediastinal disorders	Very common	Cough, oropharyngeal pain, rhinorrhoea
	Common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, gingival bleeding, abdominal pain
	Common	Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence
Hepatobiliary disorders	Very common	Transaminases increased
	Common	Blood bilirubin increased (hyperbilirubinemia), jaundice
	Not known	Drug-induced liver injury* * Cases of drug-induced liver injury have been reported in patients with ITP and HCV
Skin and subcutaneous tissue disorders	Common	Petechiae, rash, pruritus, urticaria, skin lesion, rash macular
	Not known	Skin discolouration, skin hyperpigmentation
Musculosketal and connective tissue disorders	Very common	Arthralgia, pain in extremity, muscle spasms
	Common	Back pain, myalgia, bone pain
Renal and urinary disorders	Common	Chromaturia
General disorders and administration site conditions	Very common	Fatigue, pyrexia, chills
	Common	Asthenia, oedema peripheral, malaise
Investigations	Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies among adult ITP patients receiving eltrombopag (n=446), 17 patients experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1) (see section 4.4).

In a placebo-controlled study (n=288, Safety population), following 2 weeks' treatment in preparation for invasive procedures, 6 of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1%) patients in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count >200 000/µl.

No specific risk factors were identified in those patients who experienced a TEE with the exception of platelet counts ≥200 000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1 439), 38 out of 955 patients (4%) treated with eltrombopag experienced a TEE and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus <1% for placebo) (see section 4.4). Patients with low albumin levels (≤35 g/l) or MELD ≥10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤35 g/l) or MELD score ≥10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Hepatotoxicity

In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum ALT, AST and bilirubin were observed (see section 4.4).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo-controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥3 x ULN was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

In the single-arm phase II monotherapy refractory SAA study, concurrent ALT or AST >3 x ULN with total (indirect) bilirubin >1.5 x ULN were reported in 5% of patients. Total bilirubin >1.5 x ULN occurred in 14% of patients.

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

Haematologic malignancies

In the single-arm, open-label study in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) patient has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the patient ingested 5 000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin. The platelet counts were 672 000/µl on Day 18 after ingestion and the maximum platelet count was 929 000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Immune (primary) thrombocytopenia (ITP) studies

Two phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year. The single-arm phase II study TAPER (CETB115J2411) evaluated the safety and efficacy of eltrombopag and its ability to induce sustained response after treatment discontinuation in 105 adult ITP patients who relapsed or failed to respond to first-line corticosteroid treatment.

Double-blind placebo-controlled studies
RAISE:
197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag treated patients were maintained on ≤25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16 000/µl for both treatment groups and in the eltrombopag group were maintained above 50 000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained <30 000/µl throughout the study.

Platelet count response between 50 000-400 000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6-month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 4 Secondary efficacy results from RAISE

	Eltrombopag N=135	Placebo N=62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥50 000-400 000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥75% of assessments in the target range (50 000 to 400 000/µl), n (%)	51 (38)	4 (7)
p-value [a]	<0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
p-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
p-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
p-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
p-value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33%) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70% of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6-month treatment period.

TRA100773B:
The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥50 000/µl at Day 43 from a baseline of <30 000/µl; patients who withdrew prematurely due to a platelet count >200 000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated ITP were randomised 2:1 eltrombopag (n=76) to placebo (n=38).

Table 5 Efficacy results from TRA100773B

	Eltrombopag N=74	Placebo N=38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥50 000/µl after up to 42 days of dosing (compared to a baseline count of <30 000/µl), n (%)	43 (59)	6 (16)
p-value[a]	<0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
p-value[a]	0.029	

a Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤15 000/µl, >15 000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤15 000/µl the median platelet counts did not reach the target level (>50 000/µl), although in both studies 43% of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count ≤15 000/µl treated with eltrombopag responded at the end of the 6-month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

Open-label non-controlled studies
REPEAT (TRA108057):
This open-label, repeat-dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

EXTEND (TRA105325):
Eltrombopag was administered to 302 ITP patients in this open-label extension study, 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19 000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85 000/µl, 85 000/µl, 105 000/µl, 64 000/µl, 75 000/µl, 119 000/µl and 76 000/µl, respectively.

TAPER (CETB115J2411):
This was a single-arm phase II study including ITP patients treated with eltrombopag after first-line corticosteroid failure irrespective of time since diagnosis. A total of 105 patients were enrolled on the study and started eltrombopag treatment on 50 mg once daily (25 mg once daily for patients of East-/Southeast-Asian ancestry). The dose of eltrombopag was adjusted during the treatment period based on individual platelet counts with the goal to achieve a platelet count ≥100 000/µl.

Of the 105 patients who were enrolled in the study and who received at least one dose of eltrombopag, 69 patients (65.7%) completed treatment and 36 patients (34.3%) discontinued treatment early.

Analysis of sustained response off treatment
The primary endpoint was the proportion of patients with sustained response off treatment until Month 12. Patients who reached a platelet count of ≥100 000/µl and maintained platelet counts around 100 000/µl for 2 months (no counts below 70 000/µl) were eligible for tapering off eltrombopag and treatment discontinuation. To be considered as having achieved a sustained response off treatment, a patient had to maintain platelet counts ≥30 000/µl, in the absence of bleeding events or the use of rescue therapy, both during the treatment tapering period and following discontinuation of treatment until Month 12.

The duration of tapering was individualised depending on the starting dose and the response of the patient. The tapering schedule recommended dose reductions of 25 mg every 2 weeks if the platelet counts were stable. After the daily dose was reduced to 25 mg for 2 weeks, the dose of 25 mg was then only administered on alternate days for 2 weeks until treatment discontinuation. The tapering was done in smaller decrements of 12.5 mg every second week for patients of East-/Southeast-Asian ancestry. If a relapse (defined as platelet count <30 000/µl) occurred, patients were offered a new course of eltrombopag at the appropriate starting dose.

Eighty-nine patients (84.8%) achieved a complete response (platelet count ≥100 000/µl) (Step 1, Table 6) and 65 patients (61.9%) maintained the complete response for at least 2 months with no platelet counts below 70 000/µl (Step 2, Table 6). Forty-four patients (41.9%) were able to be tapered off eltrombopag until treatment discontinuation while maintaining platelet counts ≥30 000/µl in the absence of bleeding events or the use of rescue therapy (Step 3, Table 6).

The study met the primary objective by demonstrating that eltrombopag was able to induce sustained response off treatment, in the absence of bleeding events or the use of rescue therapy, by Month 12 in 32 of the 105 enrolled patients (30.5%; p<0.0001; 95% CI: 21.9, 40.2) (Step 4, Table 6). By Month 24, 20 of the 105 enrolled patients (19.0%; 95% CI: 12.0, 27.9) maintained sustained response off treatment in the absence of bleeding events or the use of rescue therapy (Step 5, Table 6).

The median duration of sustained response after treatment discontinuation to Month 12 was 33.3 weeks (min-max: 4-51), and the median duration of sustained response after treatment discontinuation to Month 24 was 88.6 weeks (min-max: 57-107).

After tapering off and discontinuation of eltrombopag treatment, 12 patients had a loss of response, 8 of them re-started eltrombopag and 7 had a recovery response.

During the 2-year follow-up, 6 out of 105 patients (5.7%) experienced thromboembolic events, of which 3 patients (2.9%) experienced deep vein thrombosis, 1 patient (1.0%) experienced superficial vein thrombosis, 1 patient (1.0%) experienced cavernous sinus thrombosis, 1 patient (1.0%) experienced cerebrovascular accident and 1 patient (1.0%) experienced pulmonary embolism. Of the 6 patients, 4 patients experienced thromboembolic events that were reported at or greater than Grade 3, and 4 patients experienced thromboembolic event that were reported as serious. No fatal cases were reported.

Twenty out of 105 patients (19.0%) experienced mild to severe haemorrhage events on treatment before tapering started. Five out of 65 patients (7.7%) who started tapering experienced mild to moderate haemorrhage events during tapering. No severe haemorrhage event occurred during tapering. Two out of 44 patients (4.5%) who tapered off and discontinued eltrombopag treatment experienced mild to moderate haemorrhage events after treatment discontinuation until Month 12. No severe haemorrhage event occurred during this period. None of the patients who discontinued eltrombopag and entered the second year follow-up experienced haemorrhage event during the second year. Two fatal intracranial haemorrhage events were reported during the 2-year follow-up. Both events occurred on treatment, not in the context of tapering. The events were not considered to be related to study treatment.

The overall safety analysis is consistent with previously reported data and the risk-benefit assessment remained unchanged for the use of eltrombopag in patients with ITP.

Table 6 Proportion of patients with sustained response off treatment at Month 12 and at Month 24 (full analysis set) in TAPER

	All patients N=105		Hypothesis testing	
	n (%)	95% CI	p-value	Reject H0
Step 1: Patients who reached platelet count ≥100 000/µl at least once	89 (84.8)	(76.4, 91.0)		
Step 2: Patients who maintained stable platelet count for 2 months after reaching 100 000/µl (no counts <70 000/µl)	65 (61.9)	(51.9, 71.2)		
Step 3: Patients who were able to be tapered off eltrombopag until treatment discontinuation, maintaining platelet count ≥30 000/µl in the absence of bleeding events or use of any rescue therapy	44 (41.9)	(32.3, 51.9)		
Step 4: Patients with sustained response off treatment until Month 12, with platelet count maintained ≥30 000/µl in the absence of bleeding events or use of any rescue therapy	32 (30.5)	(21.9, 40.2)	<0.0001*	Yes
Step 5: Patients with sustained response off treatment from Month 12 to Month 24, maintaining platelet count ≥30 000/µl in the absence of bleeding events or use of any rescue therapy	20 (19.0)	(12.0, 27.9)		

N: The total number of patients in the treatment group. This is the denominator for percentage (%) calculation.
n: Number of patients in the corresponding category.
The 95% CI for the frequency distribution was computed using Clopper-Pearson exact method. Clopper-Pearson test was used for testing whether the proportion of responders was >15%. CI and p-values are reported.
* Indicates statistical significance (one-sided) at the 0.05 level.

Results of response on treatment analysis by time since ITP diagnosis
An ad-hoc analysis was conducted on the n=105 patients by time since ITP diagnosis to assess the response to eltrombopag across four different ITP categories by time since diagnosis (newly diagnosed ITP <3 months, persistent ITP 3 to <6 months, persistent ITP 6 to ≤12 months, and chronic ITP >12 months). 49% of patients (n=51) had an ITP diagnosis of <3 months, 20% (n=21) of 3 to <6 months, 17% (n=18) of 6 to ≤12 months and 14% (n=15) of >12 months.

Until the cut-off date (22-Oct-2021), patients were exposed to eltrombopag for a median (Q1-Q3) duration of 6.2 months (2.3-12.0 months). The median (Q1-Q3) platelet count at baseline was 16 000/µl (7 800-28 000/µl).

Platelet count response, defined as a platelet count ≥50 000/µl at least once by Week 9 without rescue therapy, was achieved in 84% (95% CI: 71% to 93%) of newly diagnosed ITP patients, 91% (95% CI: 70% to 99%) and 94% (95% CI: 73% to 100%) of persistent ITP patients (i.e. with ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and in 87% (95% CI: 60% to 98%) of chronic ITP patients.

The rate of complete response, defined as platelet count ≥100 000/µl at least once by Week 9 without rescue therapy, was 75% (95% CI: 60% to 86%) in newly diagnosed ITP patients, 76% (95% CI: 53% to 92%) and 72% (95% CI: 47% to 90%) in persistent ITP patients (ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and 87% (95% CI: 60% to 98%) in chronic ITP patients.

The rate of durable response, defined as a platelet count ≥50 000/µl for at least 6 out of 8 consecutive assessments without rescue therapy during the first 6 months on study, was 71% (95% CI: 56% to 83%) in newly diagnosed ITP patients, 81% (95% CI: 58% to 95%) and 72% (95% CI: 47% to 90.3%) in persistent ITP patients (ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and 80% (95% CI: 52% to 96%) in chronic ITP patients.

When assessed with the WHO Bleeding Scale, the proportion of newly diagnosed and persistent ITP patients without bleeding at Week 4 ranged from 88% to 95% compared to 37% to 57% at baseline. For chronic ITP patients it was 93% compared to 73% at baseline.

The safety of eltrombopag was consistent across all ITP categories and in line with its known safety profile.

Clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)
The safety and efficacy of eltrombopag in paediatric patients have been investigated two studies.

TRA115450 (PETIT2):
The primary endpoint was a sustained response, defined as the proportion of patients receiving eltrombopag, compared to placebo, achieving platelet counts ≥50 000/µl for at least 6 out of 8 weeks (in the absence of rescue therapy), between weeks 5 to 12 during the double-blind randomised period. Patients were diagnosed with chronic ITP for at least 1 year and were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count <30 000/µl. Ninety-two patients were randomised by three age cohort strata (2:1) to eltrombopag (n=63) or placebo (n=29). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag patients (40%) compared with placebo patients (3%) achieved the primary endpoint (Odds Ratio: 18.0 [95% CI: 2.3, 140.9] p <0.001) which was similar across the three age cohorts (Table 7).

Table 7 Sustained platelet response rates by age cohort in paediatric patients with chronic ITP

	Eltrombopag n/N (%) [95% CI]	Placebo n/N (%) [95% CI]
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

Statistically fewer eltrombopag patients required rescue treatment during the randomised period compared to placebo patients (19% [12/63] vs. 24% [7/29], p=0.032).

At baseline, 71% of patients in the eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of eltrombopag patients reporting any bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo patients reported any bleeding.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of patients were able to reduce (n=1) or discontinue (n=7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT):
The primary endpoint was the proportion of patients achieving platelet counts ≥50 000/µl at least once between weeks 1 and 6 of the randomised period. Patients were diagnosed with ITP for at least 6 months and were refractory or relapsed to at least one prior ITP therapy with a platelet count <30 000/µl (n=67). During the randomised period of the study, patients were randomised by three age cohort strata (2:1) to eltrombopag (n=45) or placebo (n=22). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag patients (62%) compared with placebo patients (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p=0.011).

Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT Study.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled studies. ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of <75 000/µl were enrolled and stratified by platelet count (<50 000/µl and ≥50 000/µl to <75 000/µl), screening HCV RNA (<800 000 IU/ml and ≥800 000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64%) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59 500/µl in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts <20 000/µl, <50 000/µl and ≥50 000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label eltrombopag to increase the platelet count to ≥90 000/µl for ENABLE 1 and ≥100 000/µl for ENABLE 2. The median time to achieve the target platelet count ≥90 000/µl (ENABLE 1) or ≥100 000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 8). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (<50 000 vs. >50 000), viral load (<800 000 IU/ml vs. ≥800 000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 8 Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts and initiating antiviral therapy [c]	1 439/1 520 (95%)		680/715 (95%)		759/805 (94%)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering antiviral treatment phase	**n=956**	**n=485**	**n=450**	**n=232**	**n=506**	**n=253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤35g/l	11	8				
>35g/l	25	16				
MELD score[f]						
≥10	18	10				
<10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 µg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1 200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 µg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1 400 mg orally in 2 divided doses)

c Target platelet count was ≥90 000/µl for ENABLE 1 and ≥100 000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 patients then withdrew consent prior to receiving antiviral therapy.

d *p*-value <0.05 for eltrombopag versus placebo

e 64% patients participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following: significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p=<0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45% vs. 27%). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre open-label study in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤30 000/µl.

The majority of patients, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 patients had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anaemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ⩾50%, where excluded from participation.

At baseline the median platelet count was 20 000/µl, haemoglobin was 8.4 g/dl, ANC was 0.58 x 10^9/l and absolute reticulocyte count was 24.3 x10^9/l. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20 000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by >1.5g/dl, or a reduction in ≥4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase >0.5 x 10^9/l.

The haematological response rate was 40% (17/43 patients; 95 % CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion-free period for non-responders was 27 days (median). The longest platelet transfusion-free period for responders was 287 days (median). The longest RBC transfusion-free period for non-responders was 29 days (median). The longest RBC transfusion-free period for responders was 266 days (median).

Over 50% of responders who were transfusion-dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA patients, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 9).

Table 9 Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 patients with HCV enrolled in phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the phase III studies are presented for each dose studied in Table 10.

Table 10 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

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

Data presented as geometric mean (95% CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the film-coated tablet formulation. 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%.

Distribution

Eltrombopag is highly bound to human plasma proteins (>99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

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 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC_{50} value of 2.7 μM [1.2 μg/ml]). *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC_{50} value of 2.7 μM [1.2 μg/ml]).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in patients with mild to moderate renal impairment, and 60% lower in patients with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein-bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag have not been established in patients with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult patients with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41% higher in patients with mild hepatic impairment and 80% to 93% higher in patients with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein-bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score $\geq$5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East-Asians) and 88 patients with ITP (18 East-Asians). Based on estimates from the population pharmacokinetic analysis, East-Asian ITP patients had approximately 49% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non- East-Asian patients who were predominantly Caucasian (see section 4.2).

The influence of East-/Southeast-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East-Asians and 69 Southeast-Asians). Based on estimates from the population pharmacokinetic analysis, East-/Southeast-Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥75 years. Based on model estimate, elderly (≥65 years) patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric Population (aged 1 to 17 years)

The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between paediatric and adult patients. East-/Southeast-Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of eltrombopag in paediatric patients with ITP are shown in Table 11.

Table 11 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric patients with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**$AUC_{(0-\tau)}$ (µg.hr/ml)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95% CI). $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates

5.3 Preclinical safety data

Safety pharmacology and repeat-dose toxicity

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥6 times the human clinical exposure in adult ITP patients at 75 mg/day and 3 times the human clinical exposure in adult HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from days 4-32 (approximately equating to a 2-year-old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human clinical exposure in paediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in paediatric ITP patients, based on AUC. Cataracts have not been observed in adult dogs after 52 weeks of dosing at 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterised by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 or 0.8 times the human clinical exposure based on AUC in adult or paediatric ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in adult ITP and 3 or 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (>10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and>4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short-term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in adult or paediatric ITP patients at 75 mg/day and ≤2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28-week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times or 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Carcinogenicity and mutagenicity

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times or 8 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Reproductive toxicity

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in adult or adolescent (12-17 years) ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioural or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

Phototoxicity

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

Juvenile animal studies

At non-tolerated doses in pre-weaning rats, ocular opacities were observed. At tolerated doses, no ocular opacities were observed (see above subsection ‘Safety pharmacology and repeat-dose toxicity’). In conclusion, taking into account the exposure margins based on AUC, a risk of eltrombopag-related cataracts in paediatric patients cannot be excluded. There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sucralose
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Following reconstitution, the medicinal product should be administered immediately but may be stored for a maximum period of 30 minutes.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Heat-sealed foil laminate sachets. The laminate material is comprised of polyester (PET) / orientated polyamide (OPA) / 9 µm aluminium foil (AL) / low density polyethylene heat seal layer (LDPE). The product contact material is the polyethylene heat seal layer. The sachets are co-packaged in a kit with a 40 ml HDPE mixing bottle, and 30 single-use 20 ml oral dosing syringes (polypropylene/silicon rubber) with 1 ml graduations. In addition, a screw cap (ethylene vinyl acetate / LDPE) with syringe-port capability is provided.

Pack size of 30 sachets.

6.6 Special precautions for disposal

Instructions for use

Avoid direct contact with the medicine. Wash any exposed area immediately with soap and water.

Preparation and administration of the powder for oral suspension:

- Administer the oral suspension immediately after preparation. Discard suspension if not administered within 30 minutes after preparation.
- Prepare the suspension with water only.
- Add 20 ml of water and the contents of the prescribed number of sachets (depending on the recommended dose) to the provided mixing bottle and mix gently.
- Give the entire contents of the bottle to the patient using one of the accompanying oral syringes.
- IMPORTANT: Because some medicine will remain in the mixing bottle, complete the following steps.
- Add 10 ml of water to the mixing bottle and mix gently.
- Give the entire contents of the bottle to the patient using the same oral syringe.

Cleaning of the mixing equipment:
- Discard the used oral syringe.
- Rinse the mixing bottle and lid, under running water. (The mixing bottle may become stained from the medicine. This is normal.)
- Let all the equipment dry in the air.
- Wash your hands with soap and water.

Do not re-use the oral dosing syringe. A new single-use oral dosing syringe should be used to prepare each dose of Revolade for oral suspension.

For more details on preparation and administration of the suspension, see Instructions for Use in the package leaflet.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of latest renewal: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Revolade 12.5 mg, 25 mg, 50 mg and 75 mg film-coated tablets:

Lek d.d
Verovskova Ulica 57
Ljubljana 1526
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana 1000
Slovenia

Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Glaxo Wellcome S.A.
Avenida de Extremadura 3
09400 Aranda de Duero
Burgos
Spain

Revolade 25 mg powder for oral suspension:

Lek d.d
Verovskova Ulica 57
Ljubljana 1526
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana 1000
Slovenia

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 12.5 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/010 (14 film-coated tablets)
EU/1/10/612/011 (28 film-coated tablets)
EU/1/10/612/012 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 12.5 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 12.5 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 25 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/001 (14 film-coated tablets)
EU/1/10/612/002 (28 film-coated tablets)
EU/1/10/612/003 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 25 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 50 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/004 (14 film-coated tablets)
EU/1/10/612/005 (28 film-coated tablets)
EU/1/10/612/006 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 75 mg – 14, 28, 84 (3 PACKS of 28) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/007 (14 film-coated tablets)
EU/1/10/612/008 (28 film-coated tablets)
EU/1/10/612/009 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box –75 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 75 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of 25 mg powder for oral suspension

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg powder for oral suspension

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains eltrombopag olamine equivalent to 25 mg of eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets and 1 mixing bottle + 30 single-use oral syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/013 (30 sachets of powder for oral suspension)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg sachets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of 25 mg powder for oral suspension – without blue box – 30 sachets

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg powder for oral suspension

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains eltrombopag olamine equivalent to 25 mg of eltrombopag.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg sachets

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Revolade 25 mg powder for oral suspension

eltrombopag

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Revolade 12.5 mg film-coated tablets
Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets
eltrombopag

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:

1. What Revolade is and what it is used for
2. What you need to know before you take Revolade
3. How to take Revolade
4. Possible side effects
5. How to store Revolade
6. Contents of the pack and other information

1. What Revolade is and what it is used for

Revolade contains eltrombopag, which belongs to a group of medicines called thrombopoietin-receptor agonists. It is used to help increase the number of platelets in your blood. Platelets are blood cells that help to reduce or prevent bleeding.

- Revolade is used to treat a bleeding disorder called immune (primary) thrombocytopenia (ITP) in patients aged 1 year and above who have already taken other medicines (corticosteroids or immunoglobulins), which have not worked.

  ITP is caused by a low blood platelet count (thrombocytopenia). People with ITP have an increased risk of bleeding. Symptoms patients with ITP may notice include petechiae (pinpoint-sized flat round red spots under the skin), bruising, nosebleeds, bleeding gums and not being able to control bleeding if they are cut or injured.

- Revolade can also be used to treat low platelet count (thrombocytopenia) in adults with hepatitis C virus (HCV) infections, if they have had problems with side effects while on interferon treatment. Many people with hepatitis C have low platelet counts, not only as a result of the disease, but also due to some of the antiviral medicines that are used to treat it. Taking Revolade may make it easier for you to complete a full course of antiviral medicine (peginterferon and ribavirin).

- Revolade may also be used to treat adult patients with low blood counts caused by severe aplastic anaemia (SAA). SAA is a disease in which the bone marrow is damaged, causing a deficiency of the red blood cells (anaemia), white blood cells (leukopenia) and platelets (thrombocytopenia).

2. What you need to know before you take Revolade

Do not take Revolade

- **if you are allergic** to eltrombopag or any of the other ingredients of this medicine (listed in section 6 under '***What Revolade contains***').
  ➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions

Talk to your doctor before taking Revolade:

- if you have **liver problems**. People who have low platelet counts as well as advanced chronic (long-term) liver disease are more at risk of side effects, including life-threatening liver damage and blood clots. If your doctor considers that the benefits of taking Revolade outweigh the risks, you will be closely monitored during treatment.
- if you are at risk of **blood clots** in your veins or arteries, or you know that blood clots are common in your family.
  You may be at **higher risk of blood clots**:
  - as you get older
  - if you have had to stay in bed for a long time
  - if you have cancer
  - if you are taking the contraceptive birth control pill or hormone replacement therapy
  - if you have recently had surgery or received a physical injury
  - if you are very overweight (obese)
  - if you are a smoker
  - if you have advanced chronic liver disease

  ➔ If any of these apply to you, **tell your doctor** before starting treatment. You should not take Revolade unless your doctor considers that the expected benefits outweigh the risk of blood clots.
- if you have **cataracts** (the lens of the eye getting cloudy)
- if you have another **blood condition**, such as myelodysplastic syndrome (MDS). Your doctor will carry out tests to check that you do not have this blood condition before you start Revolade. If you have MDS and take Revolade, your MDS may get worse.
  ➔ Tell your doctor if any of these apply to you.

Eye examinations

Your doctor will recommend that you are checked for cataracts. If you do not have routine eye-tests your doctor should arrange regular testing. You may also be checked for the occurrence of any bleeding in or around your retina (the light-sensitive layer of cells at the back of the eye).

You will need regular tests

Before you start taking Revolade, your doctor will carry out blood tests to check your blood cells, including platelets. These tests will be repeated at intervals while you are taking it.

Blood tests for liver function

Revolade can cause blood test results that may be signs of liver damage - an increase of some liver enzymes, especially bilirubin and alanine / aspartate transaminases. If you are taking interferon-based treatments together with Revolade to treat low platelet count due to hepatitis C, some liver problems can get worse.

You will have blood tests to check your liver function before you start taking Revolade and at intervals while you are taking it. You may need to stop taking Revolade if the amount of these substances increases too much, or if you get other signs of liver damage.

➔ **Read the information '*Liver problems*' in section 4 of this leaflet.**

Blood tests for platelet count

If you stop taking Revolade, your blood platelet count is likely to become low again within several days. The platelet count will be monitored, and your doctor will discuss appropriate precautions with you.

A very high blood platelet count may increase the risk of blood clotting. However blood clots can also form with normal or even low platelet counts. Your doctor will adjust your dose of Revolade to ensure that your platelet count does not become too high.

 **Get medical help immediately** if you have any of these signs of a **blood clot**:
- **swelling**, **pain** or tenderness in **one leg**
- **sudden shortness of breath** especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools

Tests to check your bone marrow
In people who have problems with their bone marrow, medicines like Revolade could make the problems worse. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with Revolade.

Checks for digestive bleeding
If you are taking interferon-based treatments together with Revolade you will be monitored for any signs of bleeding in your stomach or intestine after you stop taking Revolade.

Heart monitoring
Your doctor may consider it necessary to monitor your heart during treatment with Revolade and carry out an electrocardiogram (ECG) test.

Older people (65 years and above)
There are limited data on the use of Revolade in patients aged 65 years and older. Care should be taken when using Revolade if you are aged 65 years or above.

Children and adolescents
Revolade is not recommended for children aged under 1 year who have ITP. It is also not recommended for people under 18 years with low platelet counts due to hepatitis C or severe aplastic anaemia.

Other medicines and Revolade
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without prescription and vitamins.

Some everyday medicines interact with Revolade – including prescription and non-prescription medicines and minerals. These include:
- antacid medicines to treat **indigestion**, **heartburn** or **stomach ulcers** (see also '***When to take it***' in section 3)
- medicines called statins, to **lower cholesterol**
- some medicines to treat **HIV infection**, such as lopinavir and/or ritonavir
- ciclosporin used in the context of **transplantations** or **immune diseases**
- minerals such as iron, calcium, magnesium, aluminium, selenium and zinc which may be found in **vitamin and mineral supplements** (see also '***When to take it***' in section 3)
- medicines such as methotrexate and topotecan, to treat **cancer**

➔ **Talk to your doctor** if you take any of these. Some of them are not to be taken with Revolade, or the dose may need adjusting, or you may need to alter the timing of when you take them. Your doctor will review the medicines you are taking, and suggest suitable replacements if necessary.

If you are also taking medicines to prevent blood clots there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking **corticosteroids, danazol,** and/or **azathioprine** you may need to take a lower dose or to stop taking them while you are taking Revolade.

Revolade with food and drink
Do not take Revolade with dairy foods or drinks as the calcium in dairy products affects the absorption of the medicine. For more information, see '***When to take it***' in section 3.

Pregnancy and breast-feeding
Don't use Revolade if you are pregnant unless your doctor specifically recommends it. The effect of Revolade during pregnancy is not known.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby.
- **Use a reliable method of contraception** while you're taking Revolade, to prevent pregnancy
- **If you do become pregnant during treatment** with Revolade, tell your doctor.

Don't breast-feed while you are taking Revolade. It is not known whether Revolade passes into breast-milk.

➔ **If you are breast-feeding** or planning to breast-feed, tell your doctor.

Driving and using machines
Revolade can make you dizzy and have other side effects that make you less alert.

➔ **Don't drive or use machines** unless you are sure you're not affected.

Revolade contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Revolade

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Do not change the dose or schedule for taking Revolade unless your doctor or pharmacist advises you to. While you are taking Revolade, you will be under the care of a doctor with specialist experience in treating your condition.

How much to take
For ITP
Adults and **children** (6 to 17 years) – the usual starting dose for ITP is **one 50 mg tablet** of Revolade a day. If you are of East-/Southeast-Asian origin you may need to start at a **lower dose of 25 mg.**

Children (1 to 5 years) — the usual starting dose for ITP is **one 25 mg tablet** of Revolade a day.

For hepatitis C
Adults - the usual starting dose for hepatitis C is **one 25 mg tablet** of Revolade a day. If you are of East-/Southeast-Asian origin you will start on the **same 25 mg dose.**

For SAA
Adults - the usual starting dose for SAA is **one 50 mg tablet** of Revolade a day. If you are of East-/Southeast-Asian origin you may need to start at a **lower dose of 25 mg.**

Revolade may take 1 to 2 weeks to work. Based on your response to Revolade your doctor may recommend that your daily dose is changed.

How to take the tablets
Swallow the tablet whole, with some water.

When to take it

Make sure that –
- in the **4 hours before** you take Revolade
- and the **2 hours after** you take Revolade

you don't consume any of the following:
- **dairy foods** such as cheese, butter, yoghurt or ice cream
- **milk or milk shakes,** drinks containing milk, yoghurt or cream
- **antacids,** a type of medicine for **indigestion and heartburn**
- some **mineral and vitamin supplements** including iron, calcium, magnesium, aluminium, selenium and zinc

If you do, the medicine will not be properly absorbed into your body.



For more advice about suitable foods and drinks, talk to your doctor.

If you take more Revolade than you should
Contact a doctor or pharmacist immediately. If possible show them the pack, or this leaflet. You will be monitored for any signs or symptoms of side effects and given appropriate treatment immediately.

If you forget to take Revolade
Take the next dose at the usual time. Do not take more than one dose of Revolade in one day.

If you stop taking Revolade
Don't stop taking Revolade without talking to your doctor. If your doctor advises you to stop treatment, your platelet count will then be checked each week for four weeks. See also '***Bleeding or bruising after you stop treatment***' in section 4.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Symptoms needing attention: see a doctor
People taking Revolade for either ITP or low blood platelet counts due to hepatitis C could develop signs of potentially serious side effects. **It is important to tell a doctor if you develop these symptoms**.

Higher risk of blood clots
Certain people may have a higher risk of blood clots, and medicines like Revolade could make this problem worse. The sudden blocking of a blood vessel by a blood clot is an uncommon side effect and may affect up to 1 in 100 people.

**Get medical help immediately if you develop signs and symptoms of a blood clot, such as**:
- **swelling, pain, heat, redness,** or tenderness in **one leg**
- **sudden shortness of breath**, especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools.

Liver problems
Revolade can cause changes that show up in blood tests, and may be signs of liver damage. Liver problems (increased enzymes showing up in blood tests) are common and may affect up to 1 in 10 people. Other liver problems are uncommon and may affect up to 1 in 100 people.

If you have either of these signs of liver problems:
- **yellowing** of the skin or the whites of the eyes (jaundice)
- unusually **dark-coloured urine**

➔ **tell your doctor immediately**.

Bleeding or bruising after you stop treatment
Within two weeks of stopping Revolade, your blood platelet count will usually drop back down to what it was before starting Revolade. The lower platelet count may increase the risk of bleeding or bruising. Your doctor will check your platelet count for at least 4 weeks after you stop taking Revolade.

➔ **Tell your doctor** if you have any bleeding or bruising after stopping Revolade.

Some people have **bleeding in the digestive system** after they stop taking peginterferon, ribavirin, and Revolade. Symptoms include:
- black tarry stools (discoloured bowel movements are a uncommon side effect that may affect up to 1 in 100 people)
- blood in your stools
- vomiting blood or something that looks like coffee grounds

➔ **Tell your doctor** immediately if you have any of these symptoms.

The following side effects have been reported to be associated with treatment with Revolade in adult patients with ITP:

Very common side effects
These may affect **more than 1 in 10** people:
- common cold
- feeling sick (nausea)
- diarrhoea
- cough
- infection in the nose, sinuses, throat and upper airways (upper respiratory tract infection)
- back pain

Very common side effects that may show up in blood tests:
- increased of liver enzymes (alanine aminotransferase (ALT))

Common side effects
These may affect **up to 1 in 10** people:

- muscle pain, muscle spasm, muscle weakness
- bone pain
- heavy menstrual period
- sore throat and discomfort when swallowing
- eye problems including abnormal eye test, dry eye, eye pain and blurred vision
- vomiting
- flu (influenza)
- cold sore
- pneumonia
- irritation and inflammation (swelling) of the sinuses
- inflammation (swelling) and infection of the tonsils,
- infection of the lungs, sinuses, nose and throat
- inflammation of the gum tissue
- loss of appetite
- feeling of tingling, prickling or numbness, commonly called “pins and needles”
- decreased skin sensations
- feeling drowsy
- ear pain
- pain, swelling and tenderness in one of your legs (usually the calf) with warm skin in the affected area (signs of a blood clot in a deep vein)
- localised swelling filled with blood from a break in a blood vessel (haematoma)
- hot flushes
- mouth problems including dry mouth, sore mouth, sensitive tongue, bleeding gums, mouth ulcers
- runny nose
- toothache
- abdominal pain
- abnormal liver function
- skin changes including excessive sweating, itching bumpy rash, red spots, changes in appearance of the skin
- hair loss
- foamy, frothy or bubbly-looking urine (signs of protein in urine)
- high temperature, feeling hot
- chest pain
- feeling weak
- problems sleeping, depression
- migraine
- decreased vision
- spinning sensation (vertigo)
- digestive wind/gas

Common side effects that may show up in blood test:

- decreased number of red blood cells (anaemia)
- decreased number of platelets (thrombocytopenia)
- decreased number of white blood cells
- decreased haemoglobin level
- increased number of eosinophils
- increased number of white blood cells (leukocytosis)
- increased levels of uric acid
- decreased levels of potassium
- increased levels of creatinine
- increased levels of alkaline phosphatase
- increase of liver enzymes (aspartate aminotransferase (AST))
- increase in blood bilirubin (a substance produced by the liver)
- increased levels of some proteins

Uncommon side effects

These may affect **up to 1 in 100** people:

- allergic reaction
- interruption of blood supply to part of the heart
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing, which could be signs of a blood clot in the lungs (see '***Higher risk of blood clots***' earlier in section 4)
- the loss of function of part of the lung caused by a blockage in the lung artery
- possible pain, swelling, and/or redness around a vein which could be signs of blood clot in a vein
- yellowing of the skin and/or abdominal pain which could be signs of a blockage in the bile tract, lesion on liver, liver damage due to inflammation (see '***Liver problems***' earlier in section 4)
- liver injury due to medication
- heart beating faster, irregular heartbeat, bluish discolouration of the skin, disturbances of heart rhythm (QT prolongation) which could be signs of a disorder related to the heart and the blood vessels
- blood clot
- flushing
- painful swollen joints caused by uric acid (gout)
- lack of interest, mood changes, crying that is difficult to stop, or occurs at unexpected times
- problems with balance, speech and nerve function, shaking
- painful or abnormal skin sensations
- paralysis on one side of the body
- migraine with aura
- nerve damage
- dilation or swelling of blood vessels that cause headache
- eye problems including increased production of tears, cloudy lens in the eye (cataract), bleeding of the retina, dry eyes
- problems with the nose, throat and sinuses, breathing problems when sleeping
- mouth and throat blisters/sores
- loss of appetite
- digestive system problems including frequent bowel movements, food poisoning, blood in stool, vomiting of blood
- rectal bleeding, change in stool colour, abdominal bloating, constipation
- mouth problems, including dry or sore mouth, tongue pain, bleeding gums, discomfort in mouth
- sunburn
- feeling hot, feeling anxious

- redness or swelling around a wound
- bleeding around a catheter (if present) into the skin
- sensation of a foreign body
- kidney problems including inflammation of the kidney, excessive urination at night, kidney failure, white cells in urine
- cold sweat
- generally feeling unwell
- infection of the skin
- skin changes including skin discolouration, peeling, redness, itching and sweating
- muscular weakness
- cancer of rectum and colon

Uncommon side effects that may show up in laboratory tests:
- changes in the shape of red blood cells
- presence of developing white blood cells which may be indicative of certain diseases
- increased number of platelets
- decreased levels of calcium
- decreased number of red blood cells (anaemia) caused by excessive destruction of red blood cells (haemolytic anaemia)
- increased number of myelocytes
- increased band neutrophils
- increased blood urea
- increased levels of protein in urine
- increased levels of blood albumin
- increased levels of total protein
- decreased levels of blood albumin
- increased pH of urine
- increased level of haemoglobin

The following additional side effects have been reported to be associated with treatment with Revolade in children (aged 1 to 17 years) with ITP:
If these side effects become severe, please tell your doctor, pharmacist or nurse.

Very common side effects
These may affect **more than 1 in 10** children:
- infection in the nose, sinuses, throat and upper airways, common cold (upper respiratory tract infection)
- diarrhoea
- abdominal pain
- cough
- high temperature
- feeling sick (nausea)

Common side effects
These may affect **up to 1 in 10** children:
- difficulty in sleeping (insomnia)
- toothache
- pain in the nose and throat
- itchy, runny or blocked nose
- sore throat, runny nose, nasal congestion and sneezing
- mouth problems including dry mouth, sore mouth, sensitive tongue, bleeding gums, mouth ulcers

The following side effects have been reported to be associated with treatment with Revolade in combination with peginterferon and ribavirin in patients with HCV:

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- loss of appetite
- cough
- feeling sick (nausea), diarrhoea
- muscle pain, muscle weakness
- itching
- feeling tired
- fever
- unusual hair loss
- feeling weak
- flu-like illness
- swelling in the hands or feet
- chills

Very common side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia)

Common side effects
These may affect **up to 1 in 10** people:
- infection of the urinary system
- inflammation of the nasal passages, throat and mouth, flu-like symptoms, dry mouth, sore or inflamed mouth, toothache
- weight loss
- sleep disorders, abnormal drowsiness, depression, anxiety
- dizziness, problems with attention and memory, change in mood
- decreased brain function further to liver injury
- tingling or numbness of the hands or feet
- fever, headache
- eye problems, including cloudy lens in the eye (cataract), dry eye, small yellow deposits in the retina, yellowing of the whites of the eye
- bleeding of the retina
- spinning sensation (vertigo)
- fast or irregular heartbeat (palpitations), shortness of breath
- cough bringing up phlegm, runny nose, flu (influenza), cold sore, sore throat and discomfort when swallowing
- digestive system problems, including vomiting, stomach pain, indigestion, constipation, swollen stomach, taste disturbances, piles (haemorrhoids), stomach pain/discomfort, swollen blood vessels and bleeding in the gullet (oesophagus)
- toothache
- liver problems, including tumour in the liver, yellowing of the whites of the eyes or skin (jaundice), liver injury due to medication (see ***'Liver problems'*** earlier in section 4)
- skin changes, including rash, dry skin, eczema, redness of the skin, itching, excessive sweating, unusual skin growths, hair loss
- joint pain, back pain, bone pain, pain in extremities (arms, legs, hands or feet), muscle spasms
- irritability, generally feeling unwell, skin reaction such as redness or swelling and pain at the site of injection, chest pain and discomfort, build-up of fluid in the body or extremities causing swelling
- infection in the nose, sinuses, throat and upper airways, common cold (upper respiratory tract infection), inflammation of mucous membrane lining the bronchi
- depression, anxiety, sleep problems, nervousness

Common side effects that may show up in blood tests:
- increased blood sugar (glucose)
- decreased number of white blood cells
- decreased number of neutrophils
- decreased level of blood albumin
- decreased level of haemoglobin
- increased levels of blood bilirubin (a substance produced by the liver)
- changes in the enzymes that control blood clotting

Uncommon side effects
These may affect **up to 1 in 100** people:
- painful urination
- disturbances of heart rhythm (QT prolongation)
- stomach flu (gastroenteritis), sore throat
- mouth blisters/sores, inflammation of the stomach
- skin changes including change in colour, peeling, redness, itching, lesion and night sweats
- blood clots in a vein to the liver (possible liver and/or digestive system damage)
- abnormal blood clotting in small blood vessels with kidney failure
- rash, bruising at the injection site, chest discomfort
- decreased number of red blood cells (anaemia) caused by excessive destruction of red blood cells (haemolytic anaemia)
- confusion, agitation
- liver failure

The following side effects have been reported to be associated with treatment with Revolade in patients with severe aplastic anaemia (SAA):
If these side effects become severe, please tell your doctor, pharmacist or nurse.

Very common side effects
These may affect **more than 1 in 10** people.
- cough
- headache
- mouth and throat pain
- diarrhoea
- feeling sick (nausea)
- joint pain (arthralgia)
- pain in extremities (arms, legs, hands and feet)
- dizziness
- feeling very tired
- fever
- chills
- itchy eyes
- blisters in the mouth
- bleeding of the gums
- abdominal pain
- muscle spasms

Very common side effects that may show up in the blood tests
- abnormal changes to the cells in your bone marrow
- increased levels of liver enzymes (aspartate aminotransferase (AST))

Common side effects
These may affect up to **1 in 10** people.
- anxiety
- depression
- feeling cold
- generally feeling unwell
- eye problems including vision problems, blurred vision, cloudy lens in the eye (cataract), spots or deposits in eye (vitreous floaters), dry eye, itchy eye, yellowing of the whites of the eyes or skin
- nose bleed
- digestive system problems including difficulty swallowing, mouth pain, swollen tongue, vomiting, loss of appetite, stomach pain/discomfort, swollen stomach, digestive wind/gas, constipation, intestinal motility disorder which can cause contipation, bloating, diarrhea and/or above mentioned symptoms, change in stool colour
- fainting
- skin problems including small red or purple spots caused by bleeding into the skin (petechiae) rash, itching, hives, skin lesion
- back pain
- muscle pain
- bone pain
- weakness (asthenia)
- swelling of the lower limbs due to the accumulation of fluids
- abnormal colored urine
- interruption in blood supply to spleen (splenic infarction)
- runny nose

C**ommon side effects that may show up in the blood tests**
- increase in enzymes due to muscle breakdown *(*creatine phosphokinase*)*
- accumulation of iron in the body (iron overload)
- decrease in blood sugar levels (hypoglycaemia)
- increased levels of blood bilirubin (a substance produced by the liver)
- decreased levels of white blood cells

Side effects with frequency not known
Frequency cannot be estimated from the available data
- skin discolouration
- darkening of the skin
- liver injury due to medication

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Revolade

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Revolade contains
The active substance in Revolade is eltrombopag.

12.5 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.

25 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

50 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

75 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

The other ingredients are: hypromellose, macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, titanium dioxide (E171).

Revolade 12.5 mg and 25 mg film-coated tablets also contain polysorbate 80 (E433).

Revolade 50 mg film-coated tablets also contain iron oxide red (E172) and iron oxide yellow (E172).

Revolade 75 mg film-coated tablets also contain iron oxide red (E172) and iron oxide black (E172).

What Revolade looks like and contents of the pack
Revolade 12.5 mg film-coated tablets are round, biconvex, white, debossed with ‘GS MZ1’ and ‘12.5’ on one side.

Revolade 25 mg film-coated tablets are round, biconvex, white, debossed with ‘GS NX3’ and ‘25’ on one side.

Revolade 50 mg film-coated tablets are round, biconvex, brown, debossed with ‘GS UFU’ and ‘50’ on one side.

Revolade 75 mg film-coated tablets are round, biconvex, pink, debossed with ‘GS FFS’ and ‘75’ on one side.

They are supplied in aluminum blisters in a carton containing 14 or 28 film-coated tablets and multipacks containg 84 (3 packs of 28) film-coated tablets).

Not all pack sizes may be available in your country.

Marketing authorisation holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Lek d.d
Verovskova Ulica 57
Ljubljana 1526
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana 1000
Slovenia

Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Glaxo Wellcome S.A.
Avenida de Extremadura 3
09400 Aranda de Duero
Burgos
Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 555

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698370

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package Leaflet: Information for the patient

Revolade 25 mg powder for oral suspension
eltrombopag

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:

1. What Revolade is and what it is used for
2. What you need to know before you take Revolade
3. How to take Revolade
4. Possible side effects
5. How to store Revolade
6. Contents of the pack and other information
   Instructions for use

1. What Revolade is and what it is used for

Revolade contains eltrombopag, which belongs to a group of medicines called thrombopoietin-receptor agonists. It is used to help increase the number of platelets in your blood. Platelets are blood cells that help to reduce or prevent bleeding.

- Revolade is used to treat a bleeding disorder called immune (primary) thrombocytopenia (ITP) in patients aged 1 year and above who have already taken other medicines (corticosteroids or immunoglobulins), which have not worked.

  ITP is caused by a low blood platelet count (thrombocytopenia). People with ITP have an increased risk of bleeding. Symptoms patients with ITP may notice include petechiae (pinpoint-sized flat round red spots under the skin), bruising, nosebleeds, bleeding gums and not being able to control bleeding if they are cut or injured.

- Revolade can also be used to treat low platelet count (thrombocytopenia) in adults with hepatitis C virus (HCV) infections, if they have had problems with side effects while on interferon treatment. Many people with hepatitis C have low platelet counts, not only as a result of the disease, but also due to some of the antiviral medicines that are used to treat it. Taking Revolade may make it easier for you to complete a full course of antiviral medicine (peginterferon and ribavirin).

- Revolade may also be used to treat adult patients with low blood counts caused by severe aplastic anaemia (SAA). SAA is a disease in which the bone marrow is damaged, causing a deficiency of the red blood cells (anaemia), white blood cells (leukopenia) and platelets (thrombocytopenia).

2. What you need to know before you take Revolade

Do not take Revolade

- if you are **allergic** to eltrombopag or any of the other ingredients of this medicine (listed in section 6 under '***What Revolade contains***').
  ➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions

Talk to your doctor before taking Revolade:

- if you have **liver problems**. People who have low platelet counts as well as advanced chronic (long-term) liver disease are more at risk of side effects, including life-threatening liver damage and blood clots. If your doctor considers that the benefits of taking Revolade outweigh the risks, you will be closely monitored during treatment.
- if you are at risk of **blood clots** in your veins or arteries, or you know that blood clots are common in your family.
  You may be at **higher risk of blood clots**:
  - as you get older
  - if you have had to stay in bed for a long time
  - if you have cancer
  - if you are taking the contraceptive birth control pill or hormone replacement therapy
  - if you have recently had surgery or received a physical injury
  - if you are very overweight (obese)
  - if you are a smoker
  - if you have advanced chronic liver disease

  ➔ If any of these apply to you **tell your doctor** before starting treatment. You should not take Revolade unless your doctor considers that the expected benefits outweigh the risk of blood clots.
- if you have **cataracts** (the lens of the eye getting cloudy)
- if you have another **blood condition**, such as myelodysplastic syndrome (MDS). Your doctor will carry out tests to check that you do not have this blood condition before you start Revolade. If you have MDS and take Revolade, your MDS may get worse.
  ➔ Tell your doctor if any of these apply to you.

Eye examinations

Your doctor will recommend that you are checked for cataracts. If you do not have routine eye-tests, your doctor should arrange regular testing. You may also be checked for the occurrence of any bleeding in or around your retina (the light-sensitive layer of cells at the back of the eye).

You will need regular tests

Before you start taking Revolade, your doctor will carry out blood tests to check your blood cells, including platelets. These tests will be repeated at intervals while you are taking it.

Blood tests for liver function

Revolade can cause blood test results that may be signs of liver damage - an increase of some liver enzymes, especially bilirubin and alanine / aspartate transaminases. If you are taking interferon-based treatments together with Revolade to treat low platelet count due to hepatitis C, some liver problems can get worse.

You will have blood tests to check your liver function before you start taking Revolade and at intervals while you are taking it. You may need to stop taking Revolade if the amount of these substances increases too much, or if you get other signs of liver damage.

➔ **Read the information '*Liver problems*' in section 4 of this leaflet.**

Blood tests for platelet count
If you stop taking Revolade, your blood platelet count is likely to become low again within several days. The platelet count will be monitored, and your doctor will discuss appropriate precautions with you.

A very high blood platelet count may increase the risk of blood clotting. However blood clots can also form with normal or even low platelet counts. Your doctor will adjust your dose of Revolade to ensure that your platelet count does not become too high.

 **Get medical help immediately** if you have any of these signs of a **blood clot**:
- **swelling, pain** or tenderness in **one leg**
- **sudden shortness of breath** especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools

Tests to check your bone marrow
In people who have problems with their bone marrow, medicines like Revolade could make the problems worse. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with Revolade.

Checks for digestive bleeding
If you are taking interferon-based treatments together with Revolade you will be monitored for any signs of bleeding in your stomach or intestine after you stop taking Revolade.

Heart monitoring
Your doctor may consider it necessary to monitor your heart during treatment with Revolade and carry out an electrocardiogram (ECG) test.

Older people (65 years and above)
There are limited data on the use of Revolade in patients aged 65 years and older. Care should be taken when using Revolade if you are aged 65 years or above.

Children and adolescents
Revolade is not recommended for children aged under 1 year who have ITP. It is also not recommended for people under 18 years with low platelet counts due to hepatitis C or severe aplastic anaemia.

Other medicines and Revolade
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without prescription and vitamins.

Some everyday medicines interact with Revolade – including prescription and non-prescription medicines and minerals. These include:
- antacid medicines to treat **indigestion, heartburn** or **stomach ulcers** (see also '***When to take it***' in section 3)
- medicines called statins, to **lower cholesterol**
- some medicines to treat **HIV infection**, such as lopinavir and/or ritonavir
- ciclosporin used in the context of **transplantations** or **immune diseases**
- minerals such as iron, calcium, magnesium, aluminium, selenium and zinc which may be found in **vitamin and mineral supplements** (see also '***When to take it***' in section 3)
- medicines such as methotrexate and topotecan, to treat **cancer**

➔ **Talk to your doctor** if you take any of these. Some of them are not to be taken with Revolade, or the dose may need adjusting, or you may need to alter the timing of when you take them. Your doctor will review the medicines you are taking, and suggest suitable replacements if necessary.

If you are also taking medicines to prevent blood clots, there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking **corticosteroids, danazol,** and/or **azathioprine** you may need to take a lower dose or to stop taking them while you are taking Revolade.

Revolade with food and drink
Do not take Revolade with dairy foods or drinks as the calcium in dairy products affects the absorption of the medicine. For more information, see '***When to take it***' in section 3.

Pregnancy and breast-feeding
Don't use Revolade if you are pregnant unless your doctor specifically recommends it. The effect of Revolade during pregnancy is not known.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby.
- **Use a reliable method of contraception** while you're taking Revolade, to prevent pregnancy
- **If you do become pregnant during treatment** with Revolade, tell your doctor.

Don't breast-feed while you are taking Revolade. It is not known whether Revolade passes into breast-milk.

➔ **If you are breast-feeding** or planning to breast-feed, tell your doctor.

Driving and using machines
Revolade can make you dizzy and have other side effects that make you less alert.

➔ **Don't drive or use machines** unless you are sure you're not affected.

3. How to take Revolade

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Do not change the dose or schedule for taking Revolade unless your doctor or pharmacist advises you to. While you are taking Revolade, you will be under the care of a doctor with specialist experience in treating your condition.

How much to take
For ITP
Adults and **children** (6 to 17 years) **-** the usual starting dose for ITP is **two 25 mg sachets** of Revolade a day. If you are of East-/Southeast-Asian origin you may need to start at a **lower dose of 25 mg.**

Children (1 to 5 years) — the usual starting dose for ITP is **one 25 mg sachet** of Revolade a day.

For hepatitis C
Adults - the usual starting dose for hepatitis C is **one 25 mg sachet** of Revolade a day. If you are of East-/Southeast-Asian origin you will start on the **same 25 mg dose.**

For SAA
Adults - the usual starting dose for SAA is **two 25 mg sachets** of Revolade a day. If you are of East-/Southeast-Asian origin you may need to start at a **lower dose of 25 mg.**

Revolade may take 1 to 2 weeks to work. Based on your response to Revolade your doctor may recommend that your daily dose is changed.

How to give a dose of medicine
The powder for oral suspension is in sachets, the contents of which will need to mixed before you can take the medicine. After section 6 of this leaflet there are **Instructions For Use** on how to mix and administer the medicine. If you have questions or do not understand the Instructions For Use, talk to your doctor, nurse or pharmacist.

IMPORTANT — Use the medicine immediately after you have mixed the powder with water. If you do not use it **within 30 minutes** of mixing it, you will need to mix a new dose. Do not re-use the oral dosing syringe. A new single-use oral dosing syringe should be used to prepare each dose of Revolade for oral suspension.

When to take it

Make sure –
- in the **4 hours before** you take Revolade
- and the **2 hours after** you take Revolade

you don't consume any of the following:
- **dairy foods** such as cheese, butter, yoghurt or ice cream
- **milk or milk shakes,** drinks containing milk, yoghurt or cream
- **antacids,** a type of medicine for **indigestion and heartburn**
- some **mineral and vitamin supplements** including iron, calcium, magnesium, aluminium, selenium and zinc

If you do, the medicine will not be properly absorbed into your body.



For more advice about suitable foods and drinks, talk to your doctor.

If you take more Revolade than you should
Contact a doctor or pharmacist immediately. If possible show them the pack, or this leaflet. You will be monitored for any signs or symptoms of side effects and given appropriate treatment immediately.

If you forget to take Revolade
Take your next dose at the usual time. Do not take more than one dose of Revolade in one day.

If you stop taking Revolade
Don't stop taking Revolade without talking to your doctor. If your doctor advises you to stop treatment, your platelet count will then be checked each week for four weeks. See also '***Bleeding or bruising after you stop treatment***' in section 4.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Symptoms needing attention: see a doctor
People taking Revolade for either ITP or low blood platelet counts due to hepatitis C could develop signs of potentially serious side effects. **It is important to tell a doctor if you develop these symptoms**.

Higher risk of blood clots
Certain people may have a higher risk of blood clots, and medicines like Revolade could make this problem worse. The sudden blocking of a blood vessel by a blood clot is an uncommon side effect and may affect up to 1 in 100 people.

 **Get medical help immediately if you develop signs and symptoms of a blood clot, such as**:
- **swelling, pain, heat, redness** or tenderness in **one leg**
- **sudden shortness of breath**, especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools.

Liver problems
Revolade can cause changes that show up in blood tests, and may be signs of liver damage. Liver problems (increased enzymes showing up in blood tests) are common and may affect up to 1 in 10 people. Other liver problems are uncommon and may affect up to 1 in 100 people.

If you have either of these signs of liver problems:
- **yellowing** of the skin or the whites of the eyes (jaundice)
- unusually **dark-coloured urine**

➔ **tell your doctor immediately**.

Bleeding or bruising after you stop treatment
Within two weeks of stopping Revolade, your blood platelet count will usually drop back down to what it was before starting Revolade. The lower platelet count may increase the risk of bleeding or bruising. Your doctor will check your platelet count for at least 4 weeks after you stop taking Revolade.

➔ **Tell your doctor** if you have any bleeding or bruising after stopping Revolade.

Some people have **bleeding in the digestive system** after they stop taking peginterferon, ribavirin, and Revolade. Symptoms include:
- black tarry stools (discoloured bowel movements are a uncommon side effect that may affect up to 1 in 100 people)
- blood in your stools
- vomiting blood or something that looks like coffee grounds

➔ **Tell your doctor** immediately if you have any of these symptoms.

The following side effects have been reported to be associated with treatment with Revolade in adult patients with ITP:

Very common side effects
These may affect **more than 1 in 10** people:
- common cold
- feeling sick (nausea)
- diarrhoea
- cough
- infection in the nose, sinuses, throat and upper airways (upper respiratory tract infection)
- back pain

Very common side effects that may show up in blood tests:
- increased of liver enzymes (alanine aminotransferase (ALT))

Common side effects
These may affect **up to 1 in 10** people:
- muscle pain, muscle spasm, muscle weakness
- bone pain
- heavy menstrual period
- sore throat and discomfort when swallowing
- eye problems including abnormal eye test, dry eye, eye pain and blurred vision
- vomiting
- flu (influenza)
- cold sore
- pneumonia
- irritation and inflammation (swelling) of the sinuses
- inflammation (swelling) and infection of the tonsils
- infection of the lungs, sinuses, nose and throat
- inflammation of the gum tissue
- loss of appetite
- feeling of tingling, prickling or numbness, commonly called “pins and needles”
- decreased skin sensations
- feeling drowsy
- ear pain
- pain, swelling and tenderness in one of your legs (usually the calf) with warm skin in the affected area (signs of a blood clot in a deep vein)
- localised swelling filled with blood from a break in a blood vessel (haematoma)
- hot flushes
- mouth problems including dry mouth, sore mouth, sensitive tongue, bleeding gums, mouth ulcers
- runny nose
- toothache
- abdominal pain
- abnormal liver function
- skin changes including excessive sweating, itching bumpy rash, red spots, changes in appearance of the skin
- hair loss
- foamy, frothy or bubbly-looking urine (signs of protein in urine)
- high temperature, feeling hot
- chest pain
- feeling weak
- problems sleeping, depression
- migraine
- decreased vision
- spinning sensation (vertigo)
- digestive wind/gas

Common side effects that may show up in blood test:

- decreased number of red blood cells (anaemia)
- decreased number of platelets (thrombocytopenia)
- decreased number of white blood cells
- decreased haemoglobin level
- increased number of eosinophils
- increased number of white blood cells (leukocytosis)
- increased levels of uric acid
- decreased levels of potassium
- increased levels of creatinine
- increased levels of alkaline phosphatase
- increase of liver enzymes (aspartate aminotransferase (AST))
- increase in blood bilirubin (a substance produced by the liver)
- increased levels of some proteins

Uncommon side effects

These may affect **up to 1 in 100** people:

- allergic reaction
- interruption of blood supply to part of the heart
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing, which could be signs of a blood clot in the lungs (see '***Higher risk of blood clots***' earlier in section 4)
- the loss of function of part of the lung caused by a blockage in the lung artery
- possible pain, swelling, and/or redness around a vein which could be signs of blood clot in a vein
- yellowing of the skin and/or abdominal pain which could be signs of a blockage in the bile tract, lesion on liver, liver damage due to inflammation (see '***Liver problems***' earlier in section 4)
- liver injury due to medication
- heart beating faster, irregular heartbeat, bluish discolouration of the skin, disturbances of heart rhythm (QT prolongation) which could be signs of a disorder related to the heart and the blood vessels
- blood clot
- flushing
- painful swollen joints caused by uric acid (gout)
- lack of interest, mood changes, crying that is difficult to stop, or occurs at unexpected times
- problems with balance, speech and nerve function, shaking
- painful or abnormal skin sensations
- paralysis on one side of the body
- migraine with aura
- nerve damage
- dilation or swelling of blood vessels that cause headache
- eye problems including increased production of tears, cloudy lens in the eye (cataract), bleeding of the retina, dry eyes
- problems with the nose, throat and sinuses, breathing problems when sleeping
- mouth and throat blisters/sores
- loss of appetite
- digestive system problems including frequent bowel movements, food poisoning, blood in stool, vomiting of blood
- rectal bleeding, change in stool colour, abdominal bloating, constipation
- mouth problems, including dry or sore mouth, tongue pain, bleeding gums, discomfort in mouth
- sunburn
- feeling hot, feeling anxious

- redness or swelling around a wound
- bleeding around a catheter (if present) into the skin
- sensation of a foreign body
- kidney problems including inflammation of the kidney, excessive urination at night, kidney failure, white cells in urine
- cold sweat
- generally feeling unwell
- infection of the skin
- skin changes including skin discolouration, peeling, redness, itching and sweating
- muscular weakness
- cancer of rectum and colon

Uncommon side effects that may show up in laboratory tests:
- changes in the shape of red blood cells
- presence of developing white blood cells which may be indicative of certain diseases
- increased number of platelets
- decreased levels of calcium
- decreased number of red blood cells (anaemia) caused by excessive destruction of red blood cells (haemolytic anaemia)
- increased number of myelocytes
- increased band neutrophils
- increased blood urea
- increased levels of protein in urine
- increased levels of blood albumin
- increased levels of total protein
- decreased levels of blood albumin
- increased pH of urine
- increased level of haemoglobin

The following additional side effects have been reported to be associated with treatment with Revolade in children (aged 1 to 17 years) with ITP:
If these side effects become severe, please tell your doctor, pharmacist or nurse.

Very common side effects
These may affect **more than 1 in 10** children:
- infection in the nose, sinuses, throat and upper airways, common cold (upper respiratory tract infection)
- diarrhoea
- abdominal pain
- cough
- high temperature
- feeling sick (nausea)

Common side effects
These may affect **up to 1 in 10** children:
- difficulty in sleeping (insomnia)
- toothache
- pain in the nose and throat
- itchy, runny or blocked nose
- sore throat, runny nose, nasal congestion and sneezing
- mouth problems including dry mouth, sore mouth, sensitive tongue, bleeding gums, mouth ulcers

The following side effects have been reported to be associated with treatment with Revolade in combination with peginterferon and ribavirin in patients with HCV:

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- loss of appetite
- cough
- feeling sick (nausea), diarrhoea
- muscle pain, muscle weakness
- itching
- feeling tired
- fever
- unusual hair loss
- feeling weak
- flu-like illness
- swelling in the hands or feet
- chills

Very common side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia)

Common side effects
These may affect **up to 1 in 10** people:
- infection of the urinary system
- inflammation of the nasal passages, throat and mouth, flu-like symptoms, dry mouth, sore or inflamed mouth, toothache
- weight loss
- sleep disorders, abnormal drowsiness, depression, anxiety
- dizziness, problems with attention and memory, change in mood
- decreased brain function further to liver injury
- tingling or numbness of the hands or feet
- fever, headache
- eye problems, including cloudy lens in the eye (cataract), dry eye, small yellow deposits in the retina, yellowing of the whites of the eye
- bleeding of the retina
- spinning sensation (vertigo)
- fast or irregular heartbeat (palpitations), shortness of breath
- cough bringing up phlegm, runny nose, flu (influenza), cold sore, sore throat and discomfort when swallowing
- digestive system problems, including vomiting, stomach pain, indigestion, constipation, swollen stomach, taste disturbances, piles (haemorrhoids), stomach pain/discomfort, swollen blood vessels and bleeding in the gullet (oesophagus)
- toothache
- liver problems, including tumour in the liver, yellowing of the whites of the eyes or skin (jaundice), liver injury due to medication (see ***'Liver problems'*** earlier in section 4)
- skin changes, including rash, dry skin, eczema, redness of the skin, itching, excessive sweating, unusual skin growths, hair loss
- joint pain, back pain, bone pain, pain in extremities (arms, legs, hands or feet), muscle spasms
- irritability, generally feeling unwell, skin reaction such as redness or swelling and pain at the site of injection, chest pain and discomfort, build-up of fluid in the body or extremities causing swelling
- infection in the nose, sinuses, throat and upper airways, common cold (upper respiratory tract infection), inflammation of mucous membrane lining the bronchi
- depression, anxiety, sleep problems, nervousness

Common side effects that may show up in blood tests:
- increased blood sugar (glucose)
- decreased number of white blood cells
- decreased number of neutrophils
- decreased level of blood albumin
- decreased level of haemoglobin
- increased levels of blood bilirubin (a substance produced by the liver)
- changes in the enzymes that control blood clotting

Uncommon side effects
These may affect **up to 1 in 100** people:
- painful urination
- disturbances of heart rhythm (QT prolongation)
- stomach flu (gastroenteritis), sore throat
- mouth blisters/sores, inflammation of the stomach
- skin changes including change in colour, peeling, redness, itching, lesion and night sweats
- blood clots in a vein to the liver (possible liver and/or digestive system damage)
- abnormal blood clotting in small blood vessels with kidney failure
- rash, bruising at the injection site, chest discomfort
- decreased number of red blood cells (anaemia) caused by excessive destruction of red blood cells (haemolytic anaemia)
- confusion, agitation
- liver failure

The following side effects have been reported to be associated with treatment with Revolade in patients with severe aplastic anaemia (SAA):
If these side effects become severe, please tell your doctor, pharmacist or nurse.

Very common side effects
These may affect **more than 1 in 10** people.
- cough
- headache
- mouth and throat pain
- diarrhoea
- feeling sick (nausea)
- joint pain (arthralgia)
- pain in extremities (arms, legs, hands and feet)
- dizziness
- feeling very tired
- fever
- chills
- itchy eyes
- blisters in the mouth
- bleeding of the gums
- abdominal pain
- muscle spasms

Very common side effects that may show up in the blood tests
- abnormal changes to the cells in your bone marrow
- increased levels of liver enzymes (aspartate aminotransferase (AST))

Common side effects
These may affect up to **1 in 10** people.
- anxiety
- depression
- feeling cold
- generally feeling unwell
- eye problems including vision problems, blurred vision, cloudy lens in the eye (cataract), spots or deposits in eye (vitreous floaters), dry eye, itchy eye, yellowing of the whites of the eyes or skin
- nose bleed
- digestive system problems including difficulty swallowing, mouth pain, swollen tongue, vomiting, loss of appetite, stomach pain/discomfort, swollen stomach, digestive wind/gas, constipation, intestinal motility disorder which can cause contipation, bloating, diarrhea and/or above mentioned symptoms, change in stool colour
- fainting
- skin problems including small red or purple spots caused by bleeding into the skin (petechiae) rash, itching, hives, skin lesion
- back pain
- muscle pain
- bone pain
- weakness (asthenia)
- swelling of the lower limbs due to the accumulation of fluids
- abnormal colored urine
- interruption in blood supply to spleen (splenic infarction)
- runny nose

C**ommon side effects that may show up in the blood tests**
- increase in enzymes due to muscle breakdown *(*creatine phosphokinase*)*
- accumulation of iron in the body (iron overload)
- decrease in blood sugar levels (hypoglycaemia)
- increased levels of blood bilirubin (a substance produced by the liver)
- decreased levels of white blood cells

Side effects with frequency not known
Frequency cannot be estimated from the available data
- skin discolouration
- darkening of the skin
- liver injury due to medication

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Revolade

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the sachet.

This medicine does not require any special storage conditions.

Do not open the foil sachets until ready for use. After mixing, Revolade oral suspension should be administered immediately, but may be stored for no more than 30 minutes at room temperature.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Revolade contains
25 mg powder for oral suspension
The active substance in Revolade is eltrombopag. Each sachet contains a powder for reconstitution that delivers 32 mg eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid.

The other ingredients are: mannitol, sucralose and xanthan gum.

What Revolade looks like and contents of the pack
Revolade 25 mg powder for oral suspension is available in kits containing 30 sachets; each sachet contains a reddish-brown to yellow powder. Each pack contains 30 sachets, one 40 ml reusable mixing bottle with lid and cap, and 30 single-use oral dosing syringes.

Marketing authorisation holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Lek d.d
Verovskova Ulica 57
Ljubljana 1526
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana 1000
Slovenia

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 555

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698370

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

INSTRUCTIONS FOR USE

Revolade 25 mg powder for oral suspension

(eltrombopag)

Read and follow these instructions to prepare a dose of Revolade and give it to the patient. If you have any questions, or if you damage or lose any of the supplies in your kit, ask your doctor, nurse or pharmacist for advice

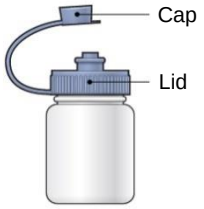
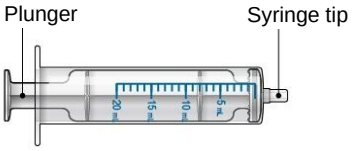
Before you start
Read these messages first

- Revolade powder must be mixed only with **water** at room temperature.

Give the medicine to the patient immediately after you have mixed the powder with water. If you don't use the medicine **within 30 minutes** of mixing it, you will need to mix a new dose. Dispose of the unused mixture in your household waste; **don't pour it down the drain**.

- Try not to let the medicine touch your skin. If this happens, wash the area immediately with soap and water. If you get a skin reaction, or if you have any questions, contact the doctor.
- If you spill any powder or liquid, clean it up with a damp cloth (see step 14 of the instructions).
- **Take care that** children do not play with the bottle, cap, lid or syringes — there is a risk of choking if children put them in their mouth.

What you need
Each Revolade powder for oral suspension kit contains:

30 sachets of powder	
1 reusable mixing bottle with lid and cap (*note — the mixing bottle may become stained*)	
30 single-use oral dosing syringes	

To prepare and give a dose of Revolade, you need:

- The correct number of sachets your doctor has prescribed (supplied in the kit)
- 1 reusable mixing bottle with lid and cap (supplied in the kit)
- 1 single-use oral dosing syringe (supplied in the kit)
- 1 clean glass or cup filled with drinking water (not supplied)
- scissors to cut sachet (not supplied)

Make sure that the bottle, cap and lid are dry before you use them.
To prepare the dose

1. Make sure the lid is not on the mixing bottle.

2. Fill the syringe with 20 ml drinking water from the glass or cup. A new single-use oral dosing syringe should be used to prepare each dose of Revolade for oral suspension.

- Start with the plunger pushed all the way into the syringe.
- Put the tip of the syringe all the way into the water
- Pull back on the plunger to the 20 ml mark on the syringe.



3. Empty water into open mixing bottle

- Slowly pushing the plunger all the way into the syringe.



4. Take only the prescribed number of sachets for one dose out of the kit.

- **25 mg dose — 1 sachet**
- **50 mg dose — 2 sachets**
- **75 mg dose — 3 sachets**

5. Add the powder from the prescribed number of sachets to the bottle.

- Tap the top of each sachet to make sure the contents fall to the bottom
- Cut off the top of each sachet with scissors
- Empty all contents of each sachet into the mixing bottle
- Make sure not to spill the powder outside the mixing bottle.



6. Screw the lid onto the mixing bottle. Make sure the cap is firmly pushed onto the lid, so it is closed.

7. Gently and slowly shake the mixing bottle backwards and forwards for **at least 20 seconds** to mix the water with the powder.

- **Don't shake** the bottle **hard** — that could make the medicine foam.



To give a dose to a patient

8. Make sure the plunger is pushed all the way into the syringe.

- **Pull cap off** the lid of the mixing bottle
- **Insert the syringe tip** into the hole in the bottle lid.

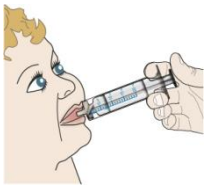
9. Fill the syringe with the medicine.

- Turn the mixing bottle upside-down together with the syringe.
- Pull back the plunger until all the medicine is in the syringe.
- The medicine is a dark brown liquid.
- Remove the syringe from the bottle.



10. Give the medicine to the patient. Do this straight away when you have mixed the dose.

- Place the tip of the syringe into the inside of the patient's cheek.
- **Slowly push the plunger all the way down** so the medicine goes into the patient's mouth.
  Make sure the patient has time to swallow.



IMPORTANT:
You have now given the patient nearly all of their dose of medicine. But there will still be some left in the bottle, even though you may not be able to see it.
Now **you need to complete steps 11 to 13** to make sure the patient receives all of the medicine.

11. Again **fill the syringe,** this time with 10 ml of drinking water.

- Start with the plunger pushed all the way down into the syringe.
- Put the tip of the syringe all the way into the water
- Pull back on the plunger to the 10 ml mark on the syringe.



12. Empty the water into the mixing bottle.

- Insert the tip of the syringe into the hole in the lid of the mixing bottle.
- Slowly push the plunger all the way into the syringe.
- Push the cap firmly back on to the lid of the mixing bottle.



13. Repeat steps 7 to 10 – gently shake the bottle to mix the rest of the medicine, then give all the rest of the liquid to the patient.

To clean up

14. If you have spilt any powder or mixed medicine, **clean it up with a damp disposable cloth**. You may choose to wear disposable gloves so your skin doesn't get stained.

- Dispose of the cloth and gloves used to clean up the spillage in your household waste.

15. Clean the mixing equipment.

- Throw away the used oral dosing syringe. A new oral dosing syringe should be used to prepare each dose of Revolade for oral suspension.
- **Rinse** the mixing bottle and lid under running water. (The mixing bottle may become stained from the medicine. This is normal.)
- Let all the equipment **dry** in the air.
- **Wash your hands** with soap and water.

After you have used all 30 sachets in the kit, **dispose of the bottle.** Always start with a complete new kit for each 30 sachets.

Keep Revolade powder for oral suspension, including the dosing kit, and all medicines out of the reach of children.

販売名	レボレード錠 12.5 mg／25 mg	[アトガム点滴静注液 250 mg]	[ロミプレート皮下注 250 μg 調製用]	[サイモグロブリン点滴静注用 25 mg]
一般的名称	エルトロンボパグ　オラミン	抗ヒト胸腺細胞ウマ免疫グロブリン	ロミプロスチム（遺伝子組換え）	抗ヒト胸腺細胞ウサギ免疫グロブリン
会社名	ノバルティスファーマ株式会社	ファイザー株式会社	協和キリン株式会社	サノフィ株式会社
効能又は効果	○慢性特発性血小板減少性紫斑病 ○再生不良性貧血	中等症以上の再生不良性貧血	○慢性特発性血小板減少性紫斑病 ○再生不良性貧血	○中等症以上の再生不良性貧血 ○造血幹細胞移植の前治療 ○造血幹細胞移植後の急性移植片対宿主病 ○下記の臓器移植後の急性拒絶反応の治療 腎移植，肝移植，心移植，肺移植，膵移植，小腸移植
添付文書改訂月	―	2023 年 3 月	2023 年 9 月	2023 年 4 月

販売名	[ネオーラル内用液 10%，ネオーラル 10 mg カプセル／25 mg カプセル／50 mg カプセル]
一般的名称	シクロスポリン
会社名	ノバルティスファーマ株式会社
効能又は効果	〈ネオーラル 10mg カプセル〉 〈ネオーラル 25mg カプセル〉 〈ネオーラル 50mg カプセル〉 ○下記の臓器移植における拒絶反応の抑制 腎移植，肝移植，心移植，肺移植，膵移植，小腸移植 ○骨髄移植における拒絶反応及び移植片対宿主病の抑制 ○ベーチェット病（眼症状のある場合），及びその他の非感染性ぶどう膜炎（既存治療で効果不十分であり，視力低下のおそれのある活動性の中間部又は後部の非感染性ぶどう膜炎に限る） ○尋常性乾癬（皮疹が全身の 30%以上に及ぶものあるいは難治性の場合），膿疱性乾癬，乾癬性紅皮症，関節症性乾癬 ○再生不良性貧血，赤芽球癆 ○ネフローゼ症候群（頻回再発型あるいはステロイドに抵抗性を示す場合） ○全身型重症筋無力症（胸腺摘出後の治療において，ステロイド剤の投与が効果不十分，又は副作用により困難な場合） ○アトピー性皮膚炎（既存治療で十分な効果が得られない患者） ○細胞移植に伴う免疫反応の抑制 〈ネオーラル内用液 10%〉 ○下記の臓器移植における拒絶反応の抑制 腎移植，肝移植，心移植，肺移植，膵移植，小腸移植 ○骨髄移植における拒絶反応及び移植片対宿主病の抑制 ○ベーチェット病（眼症状のある場合），及びその他の非感染性ぶどう膜炎（既存治療で効果不十分であり，視力低下のおそれのある活動性の中間部又は後部の非感染性ぶどう膜炎に限る） ○尋常性乾癬（皮疹が全身の 30%以上に及ぶものあるいは難治性の場合），膿疱性乾癬，乾癬性紅皮症，関節症性乾癬 ○再生不良性貧血，赤芽球癆 ○ネフローゼ症候群（頻回再発型あるいはステロイドに抵抗性を示す場合）

販売名	[ネオーラル内用液 10%，ネオーラル 10 mg カプセル／25 mg カプセル／50 mg カプセル]
	○全身型重症筋無力症（胸腺摘出後の治療において，ステロイド剤の投与が効果不十分，又は副作用により困難な場合） ○アトピー性皮膚炎（既存治療で十分な効果が得られない患者） ○川崎病の急性期（重症であり，冠動脈障害の発生の危険がある場合） ○細胞移植に伴う免疫反応の抑制
添付文書改訂月	2022 年 2 月

日本標準商品分類番号
876399

2023年3月作成（第1版）

貯　　法：2～8℃で保存
有効期間：18ヶ月
生物由来製品、劇薬、処方箋医薬品注)

免疫抑制剤
抗ヒト胸腺細胞ウマ免疫グロブリン点滴静注液

アトガム®点滴静注液250mg

ATGAM® Intravenous Infusion 250mg

承認番号	30500AMX00124
販売開始	—

注）注意-医師等の処方箋により使用すること

1. 警告

本剤は、緊急時に十分対応できる医療施設において、再生不良性貧血に関する十分な知識・経験を持つ医師のもとで、本剤が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に過敏症の既往歴がある患者［7.2、8.1、9.1.1参照］
2.2 他のウマ免疫グロブリン製剤に過敏症の既往歴がある患者［7.2、9.1.1参照］
2.3 重症感染症を合併している患者［感染症が増悪し致命的となるおそれがある］［8.2、9.1.2、10.2、11.1.2参照］
2.4 生ワクチンを接種しないこと［10.1参照］

3. 組成・性状

3.1 組成

販売名	アトガム点滴静注液250mg	
容量	1アンプル中5mL	
有効成分	抗ヒト胸腺細胞ウマ免疫グロブリンa)	250mg
添加剤	グリシン	112.6mg
	その他、pH調整剤を含有する	

a）本剤は、製造工程でヒト胸腺細胞、ヘパリン（ブタ腸由来）、ウマ血漿、ヒト赤血球及びヒト血漿を使用している。

3.2 製剤の性状

販売名	アトガム点滴静注液250mg
性状	無色～微赤色又は褐色の、澄明若しくはわずかに乳白色を呈する液
pH	6.4～7.2
浸透圧比	約1.2（生理食塩液に対する比）

4. 効能又は効果

中等症以上の再生不良性貧血

5. 効能又は効果に関連する注意

診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に使用すること。［17.1.1参照］

6. 用法及び用量

通常、1日1回体重1kgあたり抗ヒト胸腺細胞ウマ免疫グロブリンとして40mgを緩徐に点滴静注する。投与期間は4日間とする。

7. 用法及び用量に関連する注意

7.1 血清病、ショック、アナフィラキシー、サイトカイン放出症候群等のInfusion reactionがあらわれることがあるため、以下のとおり対応すること。［8.1、11.1.1参照］
・本剤の投与前に副腎皮質ホルモン剤や抗ヒスタミン剤等を投与すること。
・本剤の初回投与時には、投与前の皮膚試験の実施や投与開始後1時間は極めて緩徐に投与する等により忍容性を確認の上で特に注意して投与すること。
・本剤は4時間以上かけて投与すること。12～18時間かけて投与することが望ましい。

7.2 本剤又は他のウマ血清製剤の投与歴のある患者には、他種由来の抗ヒト胸腺細胞免疫グロブリン製剤の投与も考慮した上で、やむを得ず本剤を投与する際には、投与に先立って、救急処置対策等の必要な処置を講じ、医師の十分な観察のもと慎重に投与すること。［2.1、2.2、9.1.1参照］

8. 重要な基本的注意

8.1 本剤の初回投与前に皮膚試験を実施する場合には、以下のとおり対応すること。
・未希釈の本剤を用いてプリック試験を実施する。穿刺から10分後に膨疹が認められた場合、プリック試験陽性と判断する。
・プリック試験において膨疹が認められない場合には、続いて皮内試験を実施する。皮内試験は、生理食塩水で1000倍希釈した本剤0.02mL、及び対照として同量の生理食塩水を皮内に投与する。皮内投与10分後に、本剤投与部位に生理食塩水の投与部位と比較して直径が3mm以上大きい膨疹が認められた場合、皮内試験陽性と判断する。［2.1、7.1、11.1.1参照］
8.2 感染症（日和見感染症を含む）の発現若しくは悪化、又は肝炎ウイルスの再活性化や増悪による肝炎があらわれることがあるので、本剤投与に先立って肝炎ウイルス等の感染の有無を確認し、本剤投与前に適切な処置を行うこと。［2.3、9.1.2、10.2、11.1.2参照］
8.3 骨髄抑制、出血、腎機能障害及び肝機能障害があらわれることがあるので、本剤投与中及び投与終了後の一定期間は定期的に血液学的検査を行う等、患者の状態を十分に観察すること。［11.1.3-11.1.6参照］

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 本剤又は他のウマ血清製剤の投与歴のある患者

ショックを起こすおそれがある。［2.1、2.2、7.2参照］

9.1.2 感染症を合併している患者

本剤の免疫抑制作用により病態を悪化させるおそれがある。［2.3、8.2、10.2、11.1.2参照］

9.1.3 肝炎ウイルスの感染又は既往を有する患者

本剤投与中及び投与終了後の一定期間は、継続して肝機能検査や肝炎ウイルスマーカーのモニタリングを行うなど、肝炎ウイルスの再活性化や肝炎の増悪の徴候や症状の発現に注意すること。［11.1.2参照］

9.5 妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はIgGであり胎盤を通過する可能性があるため、胎児及び出生児に免疫抑制作用が引き起こされる可能性がある。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒト乳汁中への分泌は不明である。

9.7 小児等

2歳未満の小児等を対象とした臨床試験は実施していない。

10. 相互作用

10.1 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
生ワクチン ［2.4参照］	投与されたウイルスの体内での増殖が抑制され、発症するおそれがある。	本剤の免疫抑制作用による。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
不活化ワクチン	抗体反応が低下するおそれがある。	本剤の免疫抑制作用による。
他の免疫抑制剤 シクロスポリン等 [2.3、8.2、9.1.2、11.1.2参照]	感染及びウイルスの再活性化のおそれがある。	相加的に免疫抑制作用が増強される可能性がある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 Infusion reaction

血清病（33.3%、1/3例）、ショック（頻度不明）、アナフィラキシー（頻度不明）、サイトカイン放出症候群（頻度不明）等があらわれることがある。[7.1、8.1参照]

11.1.2 感染症

ウイルスの再活性化（サイトメガロウイルス（66.7%、2/3例）、エプスタイン・バーウイルス（頻度不明）、単純ヘルペスウイルス（頻度不明）、B型肝炎（頻度不明）、BKウイルス腎症（頻度不明） 等）、日和見感染（細菌性及び真菌性）（頻度不明）、敗血症（頻度不明）等があらわれることがある。[2.3、8.2、9.1.2、9.1.3、10.2参照]

11.1.3 骨髄抑制

リンパ球減少症（33.3%、1/3例）、白血球減少症（33.3%、1/3例）、発熱性好中球減少症（頻度不明）、好中球減少症（頻度不明）、血小板減少症（頻度不明）、汎血球減少症（頻度不明）、顆粒球減少症（頻度不明）等の骨髄抑制があらわれることがある。[8.3参照]

11.1.4 出血

胃腸出血（頻度不明）、鼻出血（頻度不明）等の出血があらわれることがある。[8.3参照]

11.1.5 腎機能障害

血中クレアチニン増加（33.3%、1/3例）、急性腎障害（頻度不明）、蛋白尿（頻度不明）等の腎機能障害があらわれることがある。[8.3参照]

11.1.6 肝機能障害

AST増加（頻度不明）、ALT増加（頻度不明）等の肝機能障害があらわれることがある。[8.3参照]

11.1.7 間質性肺炎（頻度不明）

11.2 その他の副作用

	33.3% (1/3例)	頻度不明
胃腸障害	腹痛	下痢、上腹部痛、嘔吐、口内炎、悪心、消化管穿孔、口腔内痛
一般・全身障害及び投与部位の状態	異常感、注入部位血管外漏出、浮腫	発熱、胸痛、倦怠感、注入部位紅斑、注入部位腫脹、注入部位疼痛、無力症、疼痛、悪寒
眼障害		眼窩周囲浮腫
感染症及び寄生虫症		感染、限局性感染、ウイルス性肝炎
筋骨格系及び結合組織障害		関節痛、筋肉痛、背部痛、筋固縮、側腹部痛、四肢痛
血液及びリンパ系障害		溶血、リンパ節症、溶血性貧血、貧血、好酸球増加症
血管障害		高血圧、低血圧、血栓性静脈炎、血管炎、腸骨静脈閉塞、深部静脈血栓症
呼吸器、胸郭及び縦隔障害		胸水、呼吸困難、咳嗽、咽頭痙攣、肺水腫、無呼吸、口腔咽頭痛、しゃっくり
障害、中毒及び処置合併症		腎臓破裂、動静脈瘻血栓症、創離開
腎及び尿路障害		腎動脈血栓症、腎腫大
神経系障害		頭痛、痙攣、失神、錯感覚、浮動性めまい、脳炎、ジスキネジア、振戦
心臓障害		徐脈、頻脈、うっ血性心不全
精神障害		激越、錯乱状態、失見当識
先天性、家族性及び遺伝性障害		形成不全
代謝及び栄養障害		高血糖
皮膚及び皮下組織障害		発疹、そう痒症、蕁麻疹、アレルギー性皮膚炎、寝汗、多汗症

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 希釈前後に拘らず、本剤を振らないこと。

14.1.2 本剤は、0.9%塩化ナトリウム注射液で1mg/mLとなるように希釈して使用すること。

14.1.3 本剤を希釈する際は、泡を立てないよう転倒混和し、円を描くように緩やかに回して希釈すること。

14.1.4 希釈後は速やかに使用すること。

14.2 薬剤投与時の注意

14.2.1 点滴静注する際には、点滴セットにインラインフィルター（ポアサイズ0.2～1.0ミクロン）を使用すること。

16. 薬物動態

16.1 血中濃度

日本人再生不良性貧血患者3例ずつに本剤10mg/kg/日又は20mg/kg/日を8日間[注)] 点滴静脈内投与（4時間以上）した。8日目投与終了後1時間の平均血清中濃度はそれぞれ1180μg/mL及び2060μg/mLであった。また、本剤点滴静脈内投与後の消失半減期は1.3日～6日の範囲であった[1)]。

注）本剤の承認された用法及び用量は、40mg/kg/日を4日間投与である。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内第Ⅲ相試験

中等症（stage 2b）[2)] 以上の再生不良性貧血患者3例（小児1例を含む）を対象に、本剤40mg/kgを4日間連続で静脈内投与した際の有効性及び安全性の評価を目的とした、多施設共同、非盲検、単群試験を実施した。

主要評価項目である投与後12週時点の血液学的反応[注)] は、3例中2例（小児1例を含む）で「有効」であった。

本剤40mg/kgが投与された3例全例に副作用が認められ、サイトメガロウイルス感染が2例、腹痛、異常感、注入部位血管外漏出、浮腫、血清病、血中クレアチニン増加、リンパ球減少、白血球数減少が各1例に認められた[3)]。[5.参照]

注）以下の2項目以上を満たした場合に「有効」とする。造血因子もしくは輸血に依存的な改善については、「有効」とみなさない。
- 好中球絶対数500/μL以上
- 血小板数20,000/μL以上
- 網赤血球数60,000/μL以上

18. 薬効薬理

18.1 作用機序

本剤はリンパ球表面の多様なタンパク質に結合する様々な抗体で構成され[4~7)]、顆粒球、血小板及び骨髄細胞に結合する[8)]。本剤の主な作用機序として、循環血中のTリンパ球に最も強く作用し、リンパ球を減少させることが示唆されている[9,10)]。

18.2 免疫抑制作用

18.2.1 *In vitro* T細胞表面抗原への結合阻害試験

本剤は健康被験者由来のT細胞における表面抗原CD2、CD3、CD4、CD8、CD25及びCD28に対する結合能を示した[5,7)]。

18.2.2 *In vitro*補体依存性細胞障害試験

本剤と健康被験者由来の末梢血単核細胞をインキュベートしたところ、濃度依存的な細胞溶解が認められた[4)]。

18.2.3 *In vitro*アポトーシス誘導試験

本剤と健康被験者由来の末梢血単核細胞をインキュベートしたところ、アポトーシス誘導がみられた[11)]。

19. 有効成分に関する理化学的知見

一般的名称：抗ヒト胸腺細胞ウマ免疫グロブリン
Anti-human Thymocyte Immunoglobulin, Equine

分子量：約150,000

本質：ヒト由来の胸腺細胞で免疫したウマの血漿から分離精製した免疫グロブリンG

20. 取扱い上の注意

光を避けて外箱に入れて、凍結を避けて保管すること。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

5アンプル

23. 主要文献

1) 日本人再生不良性貧血患者における薬物動態（2023年3月27日承認、CTD2.7.2.2.1）
2) 再生不良性貧血の診断基準と診療の参照ガイド改訂版作成のためのワーキンググループ.再生不良性貧血診療の参照ガイド令和1年改訂版.
3) 国内第Ⅲ相試験（B5411003 試験）（2023年3月27日承認、CTD2.7.6.6）
4) Fisher RI, Silver BA, Vanhaelen CP, et al. : Cancer Res. 1982 ; 42 (6) : 2465-9
5) Raefsky EL, Gascon P, Gratwohl A, et al. : Blood 1986 ; 68 (3) : 712-9
6) Bourdage JS, Hamlin DM. : Transplantation 1995 ; 59 (8) : 1194-200
7) Merion RM, Howell T, Bromberg JS. : Transplantation 1998 ; 65 (11) : 1481-9
8) Greco B, Bielory L, Stephany D, et al. : Blood 1983 ; 62 (5) : 1047-54
9) Scheinberg P, Nunez O, Weinstein B, et al. : New Engl J Med. 2011 ; 365 (5) : 430-8
10) Abouna GM, al-Abdullah IH, Kelly-Sullivan D, et al. : Transplantation 1995 ; 59 (11) : 1564-8
11) Feng X, Kajigaya S, Solomou EE, et al. : Blood 2008 ; 111 (11) : 3675-83

24. 文献請求先及び問い合わせ先

ファイザー株式会社　製品情報センター
〒151-8589　東京都渋谷区代々木3-22-7
学術情報ダイヤル　0120-664-467
FAX　03-3379-3053

26. 製造販売業者等

26.1 製造販売元

ファイザー株式会社
東京都渋谷区代々木3-22-7

Ⓡ登録商標

＊＊2023年9月改訂（第4版、効能変更、用法・用量変更）
＊2023年1月改訂（第3版）
貯法：2～8℃に保存
有効期間：36箇月

CI

日本標準商品分類番号
873999

処方箋医薬品注）

造血刺激因子製剤／トロンボポエチン受容体作動薬
ロミプロスチム（遺伝子組換え）製剤

ロミプレート®皮下注250μg調製用

Romiplate® for s.c. injection

注）注意－医師等の処方箋により使用すること

承認番号	22300AMX00437
販売開始	2011年4月

2．禁忌（次の患者には投与しないこと）
本剤の成分に対し過敏症の既往歴のある患者

3．組成・性状
3.1 組成

販売名	ロミプレート皮下注250μg調製用	
有効成分	ロミプロスチム（遺伝子組換え）375μg注） ただし、本剤の調製方法に基づき、1バイアルあたり0.72mLの注射用水に溶解した溶液0.5mL中に含まれるロミプロスチム（遺伝子組換え）は250μgである。	
添加剤	D-マンニトール	30mg
	精製白糖	15mg
	L-ヒスチジン	1.2mg
	ポリソルベート20	0.03mg
	希塩酸	適量

注）本剤は、注射器への吸引時及び投与時の損失を考慮し、1バイアルから250μgを注射可能な量を確保するために過量充填されている。

3.2 製剤の性状

販売名	ロミプレート皮下注250μg調製用
色・性状	白色の塊（凍結乾燥製剤）
pH	5.0
浸透圧	約1（500μg/mL）

＊＊4．効能又は効果
○慢性特発性血小板減少性紫斑病
○再生不良性貧血

5．効能又は効果に関連する注意
〈慢性特発性血小板減少性紫斑病〉
5.1 他の治療にて十分な効果が得られない場合、又は忍容性に問題があると考えられる場合に使用すること。
5.2 血小板数、臨床症状からみて出血リスクが高いと考えられる場合に使用すること。
〈再生不良性貧血〉
＊＊5.3「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、最新の再生不良性貧血診療の参照ガイドを参考に、本剤の投与が適切と判断される患者に投与すること[1]。[17.1.4-17.1.6参照]

＊＊6．用法及び用量
〈慢性特発性血小板減少性紫斑病〉
通常、成人には、ロミプロスチム（遺伝子組換え）として初回投与量1μg/kgを皮下投与する。投与開始後、血小板数、症状に応じて投与量を適宜増減し、週1回皮下投与する。また、最高投与量は週1回10μg/kgとする。
〈再生不良性貧血〉
通常、成人には、ロミプロスチム（遺伝子組換え）として初回投与量10μg/kgを皮下投与する。投与開始後、患者の状態に応じて投与量を適宜増減し、週1回皮下投与する。また、最高投与量は週1回20μg/kgとする。

7．用法及び用量に関連する注意
〈慢性特発性血小板減少性紫斑病〉
7.1 本剤は下表を参照の上、治療上必要最小限の用量で使用すること。

血小板数	調節方法
50,000/μL未満	1μg/kg増量する。
50,000/μL～200,000/μL	出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮する。
200,000/μL～400,000/μL	1μg/kg減量する。
400,000/μL超	休薬する。休薬後、血小板数が200,000/μLまで減少した場合には原則として休薬前の投与量より1μg/kg減量し、投与を再開する。

7.2 本剤投与中は、血小板数が安定するまで（少なくとも4週間にわたり用量調整せずに血小板数が50,000/μL以上）、血小板数を毎週測定すること。血小板数が安定した場合でも4週に1回を目安に血小板数を測定すること。
7.3 本剤は出血のリスクが高い場合に使用し、血小板数を正常化する目的で使用しないこと。
7.4 最高投与量として週1回10μg/kgを4週間連続投与しても、臨床上重大な出血リスクを回避できるレベルに血小板数が増加しなかった場合は、本剤の投与を中止するなど、適切な処置を行うこと。
〈再生不良性貧血〉
＊＊7.5 シクロスポリン又は抗胸腺細胞免疫グロブリンで未治療の場合は、原則として両剤と併用すること。シクロスポリンのみとの併用は、抗胸腺細胞免疫グロブリンが適用できない場合に考慮すること。また、併用薬の電子添文を確認すること。[17.1.5、17.1.6参照]
7.6 本剤投与開始時並びに用量調節時には、週1回を目安に血球数を測定すること。用量が維持されている場合でも、4週に1回を目安に血球数を測定すること。
7.7 本剤の投与量を調節する場合には、通常、1回5μg/kgずつ調節すること。
7.8 同一用量を4週間連続投与しても血小板数の増加（目安として、輸血非依存下で、血小板数が本剤投与開始前から20,000/μL以上増加、又は血小板数が10,000/μL以上で本剤投与開始から100%以上増加）が認められない場合には、増量を考慮すること。

®登録商標

7.9 本剤は下表を参照の上、治療上必要最小限の用量で使用すること。

血小板数	調節方法
200,000/μL～400,000/μL	減量する。
400,000/μL超	休薬する。休薬後、血小板数が200,000/μLまで減少した場合には原則として休薬前の投与量より減量し投与を再開する。なお、休薬前の投与量が5μg/kg以下のときは、血小板数が50,000/μLまで減少した場合に休薬前と同じ投与量で投与を再開してもよい。

＊＊7.10 以下の表を目安とし、3血球系統が改善し、輸血をせずに4～8週間以上持続した場合には、減量すること。1回投与量の減量に代わり、同一用量で投与間隔を2週に1回に延長してもよい。

3血球系統の改善の目安

血小板数	100,000/μL超 (既存治療で効果不十分な場合は50,000/μL超)
ヘモグロビン濃度	10g/dL超
好中球数	1,000/μL超

減量後も4週間3血球系統の改善を維持した場合には、4週ごとに更に投与量の減量を考慮すること(投与量が5μg/kg以下の場合には休薬を考慮すること)。減量後に3血球系統のいずれかに悪化が認められた場合には、増量を考慮すること(休薬中であった場合には、休薬前の投与量で再開してもよい)。2週に1回投与中に増量する場合には、1回の投与量は変えず、投与間隔を週1回投与に戻すこと。

＊＊7.11 以下の時点まで本剤を投与しても、3血球系統のいずれの改善も認められない場合は､本剤の投与を中止するなど、適切な処置を行うこと。

・シクロスポリン又は抗胸腺細胞免疫グロブリンで未治療の場合：本剤投与開始後26週時点
・既存治療で効果不十分な場合：最高投与量として週1回20μg/kgを8週間連続投与した時点

8. 重要な基本的注意

〈効能共通〉

8.1 本剤は、血液疾患の治療に十分な経験を持つ医師のもとで使用すること。

8.2 本剤の投与中止により血小板減少を認めることがあるため、本剤の中止後4週間程度は頻回に全血算(赤血球、白血球及び血小板)の検査を実施すること。[9.1.2､11.1.3参照]

8.3 本剤を含むトロンボポエチン受容体作動薬には、骨髄のレチクリン線維の形成及び線維化を進行させる可能性があるので、本剤の投与開始前には、末梢血液像(末梢血塗抹標本)、全血算(赤血球、白血球及び血小板)及び網状赤血球数の検査を行い、全ての血球系の形態異常の有無を十分観察すること。また、本剤投与中は、末梢血液像(末梢血塗抹標本)、全血算(赤血球、白血球及び血小板)及び網状赤血球数の検査を4週に1回を目安に実施し、全ての血球系の形態異常及び血球減少の存否を観察すること。[11.1.2参照]

8.4 血小板数が正常範囲を超えると、血栓症又は血栓塞栓症のリスクが増加する可能性がある。また、血小板数が正常範囲以下であっても血栓塞栓症が認められているため、血小板数にかかわらず血栓症又は血栓塞栓症の発現に注意すること。本剤投与後は、定期的に血小板数を測定し、血小板数が治療の目標とするレベルを超えた場合には、本剤の減量又は休薬を考慮するなど注意すること。[9.1.1、11.1.1参照]

8.5 本剤に対する反応性の低下が認められた場合、又は血小板数の維持が困難になった場合は、原因(本剤に対する中和抗体の産生、又は骨髄線維症等の可能性)の究明に努めること。

8.6 トロンボポエチン受容体作動薬には、既存の骨髄異形成症候群等の造血器腫瘍を進行させる可能性がある。

〈再生不良性貧血〉

＊＊8.7 再生不良性貧血患者の一部では経過観察中に骨髄異形成症候群や急性骨髄性白血病に移行することが知られており、再生不良性貧血患者を対象とした海外臨床試験及び国際共同臨床試験においても、本剤との因果関係は明らかでないものの、本剤投与後に染色体異常が認められた例が報告されている。本剤投与中は、定期的に白血球分画を含む全血算及び末梢血塗抹標本検査を行い、幼若細胞や形態学的異常の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、骨髄検査(染色体異常の評価を含む)の実施を考慮し、本剤の投与継続の可否を判断すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 脳梗塞、心筋梗塞、肺塞栓等の患者又はそれらの既往歴を有する患者

血栓症又は血栓塞栓症を起こすおそれがある。[8.4参照]

9.1.2 抗凝固剤又は抗血小板剤を使用中の患者

本剤の投与を中止した場合、血小板減少症の増悪により患者の出血リスクが上昇するおそれがある。[8.2､11.1.3参照]

9.2 腎機能障害患者

有効性及び安全性を指標とした臨床試験は実施していない。

9.3 肝機能障害患者

有効性及び安全性を指標とした臨床試験は実施していない。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。動物実験(ラット)で胎児における血小板数増加及び新生児死亡率の増加並びに動物実験(マウス)で胎児における着床後胚損失率の増加及び母動物における体重増加抑制が報告されている。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

9.7 小児等

低出生体重児、新生児、乳児、幼児又は小児(18歳未満)を対象とした有効性及び安全性を指標とした国内臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら、慎重に投与を行うこと。一般に生理機能(肝機能、腎機能、心機能等)が低下していることが多く、また、合併症を併発又は他の薬剤を使用している可能性が高い。

11. 副作用

次の副作用があらわれることがあるので､観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

＊＊11.1.1 血栓症・血栓塞栓症[注)]

肺塞栓症(0.8%)､深部静脈血栓症(0.8%)､心筋梗塞(0.6%)､血栓性静脈炎(0.5%)等があらわれることがある。[8.4参照]

注)発現頻度は、慢性特発性血小板減少性紫斑病の承認時までの臨床試験に基づく。

＊＊11.1.2 骨髄レチクリン増生(1.6%)

骨髄レチクリン増生が認められることがあり、骨髄線維化があらわれる可能性がある。血球系の形態異常又は血球減少を認めた場合は、本剤の投与を中止すること。また、線維化状態の確認のため骨髄生検・特殊染色等の実施を考慮すること。[8.3参照]

11.1.3 出血(頻度不明)

本剤の投与中止後に出血を生じることがある。[8.2、9.1.2参照]

11.2 その他の副作用

	10%以上	1～10%未満	1%未満
血液およびリンパ系障害		血小板血症、血小板減少症	貧血
精神障害		不眠症	うつ病
神経系障害	頭痛	浮動性めまい、錯感覚(ピリピリ感等)	感覚鈍麻、嗜眠、片頭痛、末梢性ニューロパチー、味覚異常
血管障害			ほてり、潮紅、高血圧
呼吸器、胸郭および縦隔障害			呼吸困難､咳嗽､鼻出血

	10%以上	1～10%未満	1%未満
胃腸障害		悪心、下痢、腹痛	嘔吐、上腹部痛、腹部不快感、消化不良、便秘
皮膚および皮下組織障害		発疹、そう痒症	脱毛症、斑状出血、そう痒性皮疹、点状出血、多汗症
筋骨格系および結合組織障害		関節痛、筋肉痛、四肢痛、筋痙縮、筋骨格痛、背部痛	骨痛、筋骨格系胸痛、筋力低下、筋骨格硬直
＊＊全身障害および投与局所様態		疲労、注射部位反応(疼痛、血腫、刺激感、腫脹、紅斑、出血、発疹を含む)、浮腫(末梢性浮腫、全身性浮腫、顔面浮腫、顔面腫脹を含む)、発熱、倦怠感、疼痛、感冒様症状、悪寒、無力症	胸痛
その他		食欲不振、挫傷、回転性めまい	鼻咽頭炎、血小板数増加、インフルエンザ、体重減少、膣出血、動悸、フィブリンDダイマー増加

13. 過量投与

13.1 症状

血小板数が過剰に増加し、血栓症又は血栓塞栓症の合併症を生じるおそれがある。

13.2 処置

本剤の投与を中止し、血小板数をモニターすること。血小板数が回復した後は、「7.用法及び用量に関連する注意」に従い、本剤の治療を再開すること。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 本剤は、1回使い切りのバイアルであり、注射用水0.72mLにより溶解し、正確に測りとるために0.01mL又は0.1mL目盛り注射器等を用いる。注射用水以外のもので溶解しないこと。本剤の含有量は以下のとおりとなるが、1バイアルあたり投与できる最大液量は0.5mLである。

本剤の含有量

1バイアル中の含量	注射用水0.72mLで溶解した溶液0.5mL中に含まれる量	最終濃度
375μg	250μg/0.5mL	500μg/mL

14.1.2 バイアルは静かに混和し、過度又は急激な攪拌は避けること。振とうしないこと。通常、本剤は2分以内に溶解する。溶解後溶液は無色澄明である。変色の有無、及びバイアル内に微粒子が含まれていないか溶解後溶液を目視検査すること。微粒子、又は変色が認められた溶液は使用しないこと。

14.1.3 溶解後溶液は、室温(25℃)又は冷蔵保存(2～8℃)し、24時間以内に投与を開始すること。溶解後溶液は遮光下で保存すること。

14.1.4 1バイアルから2回以上の薬液採取は行わないこと。

14.2 薬剤投与時の注意

14.2.1 本剤の投与に際して必要量(mL)を計算するために、まず個々の患者の1回投与量(μg)を「6.用法及び用量」に従い算出する。例えば、体重55kgの患者が初回投与量1μg/kgで投与を開始する場合、必要な患者の1回投与量は55μgである。これを溶解後溶液の最終濃度(500μg/mL)で割ると、患者に投与すべき必要量(mL)が算出される。この場合は、必要量は55(μg)/500(μg/mL)=0.11mLとなる。

14.2.2 1回当たり0.5mLを超える場合には、複数のバイアルから必要量(mL)を確保すること。

15. その他の注意

15.1 臨床使用に基づく情報

＊＊15.1.1 慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、291例中2例(0.7%)に、本剤に対する中和抗体が認められたが、その後の追跡調査ではいずれの症例も中和抗体は認められていない。なお、国内臨床試験において、本剤に対する中和抗体は認められていない。再生不良性貧血患者を対象とした海外臨床試験及び国際共同臨床試験において、本剤に対する中和抗体は認められていない。

15.1.2 慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において、造血器腫瘍の発現が認められた。骨髄異形成症候群患者[注)]では、疾患の進行に伴い急性骨髄性白血病へ移行することが知られている。骨髄異形成症候群患者を対象とした海外臨床試験において、一過性の芽球の増加と、急性骨髄性白血病への移行が認められたとの報告がある[2)]。

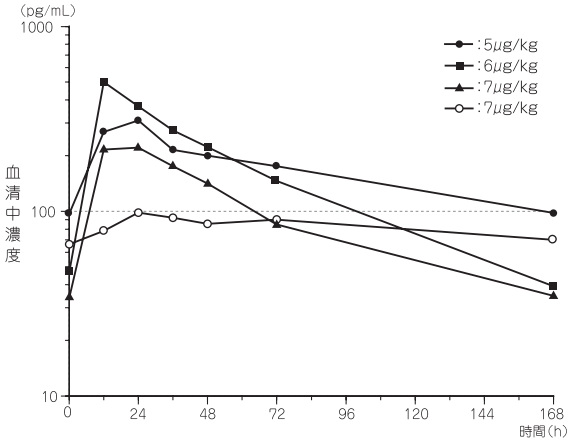
注)骨髄異形成症候群患者への投与は、国内外において承認外である。

16. 薬物動態

16.1 血中濃度

〈慢性特発性血小板減少性紫斑病〉

慢性特発性血小板減少性紫斑病患者(4例)に本剤5～7μg/kgを週1回反復皮下投与したときのロミプロスチムの血清中濃度推移及び血清中薬物動態パラメータは以下のとおりであった[3)]。



慢性特発性血小板減少性紫斑病患者に反復皮下投与したときの被験者ごとのロミプロスチムの血清中濃度推移

慢性特発性血小板減少性紫斑病患者に反復皮下投与したときの被験者ごとのロミプロスチムの血清中薬物動態パラメータ

投与量(μg/kg)	t_{max}(h)	C_{max}(pg/mL)	AUC_{0-168}(pg・h/mL)	$t_{1/2}$(h)
5	24	310	28500	116
6	12	501	27400	47.6
7	24	98.4	13900	−
7	24	221	16400	58.8

〈再生不良性貧血〉

日本人の既存治療で効果不十分な再生不良性貧血患者(8例)に本剤10μg/kgを週1回4週間反復皮下投与したときの血清中薬物動態パラメータは以下のとおりであった[4)]。

日本人の既存治療で効果不十分な再生不良性貧血患者に反復皮下投与したときの投与4週目のロミプロスチムの血清中薬物動態パラメータ

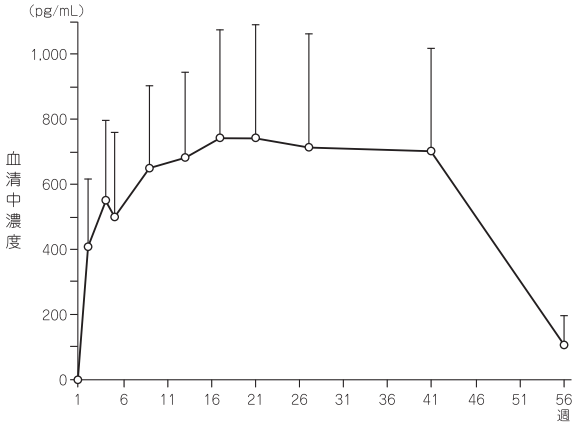
投与量(μg/kg)	例数	t_{max}(h)	C_{max}(pg/mL)	AUC_{0-168}(pg・h/mL)	$t_{1/2}$(h)
10	8	16.4 ±12.7	5810 ±3310	305000 ±175000	108.5 ±32.6

平均値±標準偏差

日本人の既存治療で効果不十分な再生不良性貧血患者に対し、投与開始1～4週目に本剤10μg/kgを週1回皮下投与し、投与開始5～52週目に血小板反応及び血球数に応じて本剤5～20μg/kgを週1回皮下投与したときのロミプロスチムの血清中濃度推移は以下のとおりであった[4)]。

本剤の投与量推移(μg/kg)

週	1～4	5	9	13	17	21	24	27	31	35	41
平均投与量	10.0	14.2	16.5	16.9	16.8	16.8	16.4	16.2	16.0	16.0	15.5



週	1	2	4	5	9	13	17	21	27	41	56[a)]
例数	23	8	24	8	22	23	22	22	21	20	24

a)投与中止例は、本剤最終投与から4週間経過時の血清中濃度を用いた。

日本人の既存治療で効果不十分な再生不良性貧血患者におけるロミプロスチムの血清中濃度推移(平均値＋標準偏差)

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈慢性特発性血小板減少性紫斑病〉

17.1.1 国内第Ⅲ相試験

過去に1種類以上の慢性特発性血小板減少性紫斑病治療歴を有し、脾臓摘出歴の有無を問わない血小板数が30,000/μL未満の血小板減少を呈する成人慢性特発性血小板減少性紫斑病患者(本剤群22例、プラセボ群12例)を対象として、本剤を3μg/kgから投与開始した[注1)]。12週間の投与期間において、有効性に関する主要評価項目である血小板反応(投与第2～13週目の各週の規定日に測定した血小板数が50,000/μL以上に増加すること)が認められた週数は、本剤群で9.5±3.3週(平均値±標準偏差)、プラセボ群で0.2±0.4週であり、本剤群で有意(P＜0.0001)に高値であった[5)]。

副作用発現頻度は、本剤群で40.9%(9/22例)であった。主な副作用は、頭痛22.7%(5/22例)、疲労及び四肢痛 各9.1%(2/22例)であった。

17.1.2 海外第Ⅲ相試験(脾臓摘出歴を有する患者)

過去に1種類以上の慢性特発性血小板減少性紫斑病治療歴を有し、血小板数が30,000/μL未満の成人慢性特発性血小板減少性紫斑病患者63例(本剤群42例、プラセボ群21例)を対象として、本剤を1μg/kgから投与開始した。24週間の投与期間において、持続血小板反応(治療期間の最後の8週間のうち6週間以上で血小板数が50,000/μL以上であること)が認められた患者の割合は、本剤群で38.1%(16/42例)、プラセボ群で0%(0/21例)であり、本剤群で有意(P＜0.0013)に高値であった[6)]。

副作用発現頻度は、本剤群で54.8%(23/42例)であった。主な副作用は、頭痛26.2%(11/42例)、筋痛16.7%(7/42例)、浮動性めまい及び疲労 各9.5%(4/42例)であった。

17.1.3 海外第Ⅲ相試験(脾臓摘出歴を有さない患者)

過去に1種類以上の慢性特発性血小板減少性紫斑病治療歴を有し、血小板数が30,000/μL未満の成人慢性特発性血小板減少性紫斑病患者62例(本剤群41例、プラセボ群21例)を対象として、本剤を1μg/kgから投与開始した。24週間の投与期間において、持続血小板反応が認められた患者の割合は、本剤群で61.0%(25/41例)、プラセボ群で4.8%(1/21例)であり、本剤群で有意(P＜0.0001)に高値であった[6)]。

副作用発現頻度は、本剤群で26.2%(11/42例)であった。主な副作用は、頭痛11.9%(5/42例)、関節痛7.1%(3/42例)及び注射部位内出血4.8%(2/42例)であった。

注1)本剤の慢性特発性血小板減少性紫斑病に対する承認された初回投与量は1μg/kgである。

〈再生不良性貧血〉

17.1.4 国際共同第Ⅱ/Ⅲ相試験(既存治療で効果不十分な患者)

抗胸腺細胞免疫グロブリンを含む免疫抑制療法で効果不十分、又はシクロスポリンで効果不十分かつ抗胸腺細胞免疫グロブリンが適用とならない成人再生不良性貧血患者31例(日本人24例、韓国人7例)を対象として、本剤を10μg/kgで週1回投与を開始し、血球数等に応じて用量を5～20μg/kgの間で適宜調整した。投与27週時における血液学的反応率[95%信頼区間]は、83.9[66.3, 94.5]%であった。なお、血液学的反応率は1系統以上の血球に改善[注2)]を認めた患者の割合と定義した[7)]。

副作用発現頻度は、54.8%(17/31例)であった。主な副作用は、日本人では、頭痛及び筋痙縮 各16.7%(4/24例)、アラニンアミノトランスフェラーゼ増加、フィブリンDダイマー増加、倦怠感及び四肢痛 各8.3%(2/24例)であった。なお、韓国人では、血小板数増加14.3%(1/7例)のみであった。[5.3参照]

注2)血液学的反応の効果判定基準

血小板数	20,000/μL以上増加したとき、又は血小板数が10,000/μL以上でありベースラインから100%以上増加したとき、又は8週間連続して血小板輸血非依存。
ヘモグロビン濃度	9g/dL未満の被験者のヘモグロビン濃度が赤血球輸血なしで1.5g/dL以上増加したとき、又は、赤血球輸血量の減少(8週間連続した期間に累積で輸血量が800mL以上減少)。
好中球数	500/μL未満の被験者の好中球数が100%以上増加したとき、又は、好中球数が1,000/μL未満の被験者の好中球数が500/μL以上増加したとき。

＊＊17.1.5 国際共同第Ⅱ/Ⅲ相3剤併用試験(シクロスポリン又は抗胸腺細胞免疫グロブリンで未治療の患者)

輸血を要する非重症又は重症若しくは最重症であり、シクロスポリン又は抗胸腺細胞免疫グロブリンで未治療の成人再生不良性貧血患者17例(日本人9例、韓国人7例、台湾人1例)に抗胸腺細胞免疫グロブリン及びシクロスポリンと本剤を併用投与した。本剤は10μg/kgで週1回投与を開始し、血球数等に応じて用量を5～20μg/kgの間で適宜調整した。投与27週時点の奏効率[注3)][95%信頼区間]は76.5[50.10, 93.19]%であった[8)]。

副作用発現頻度は、29.4%(5/17例)であった。認められた副作用は、γ-グルタミルトランスフェラーゼ増加11.8%(2/17例)、上咽頭炎、アラニンアミノトランスフェラーゼ増加、アスパラギン酸アミノトランスフェラーゼ増加、血中ビリルビン増加、腫瘍マーカー上昇、レチクリン増加及び関節痛 各5.9%(1/17例)であった。[5.3、7.5参照]

＊＊17.1.6 国際共同第Ⅱ/Ⅲ相2剤併用試験(シクロスポリン又は抗胸腺細胞免疫グロブリンで未治療の患者)

輸血を要する非重症又は重症若しくは最重症であり、シクロスポリン又は抗胸腺細胞免疫グロブリンで未治療の成人再生不良性貧血患者24例(日本人9例、韓国人15例)にシクロスポリンと本剤を併用投与した。本剤は10μg/kgで週1回投与を開始し、血球数等に応じて用量を5～20μg/kgの間で適宜調整した。投与27週時点の奏効率[注3)][95%信頼区間]は41.7[22.11, 63.36]%であった[9)]。

副作用発現頻度は、12.5%(3/24例)であった。認められた副作用は、悪心、肝機能検査異常、凝固検査異常及び浮動性めまい 各4.2%(1/24例)であった。[5.3、7.5参照]

注3)奏効率の定義

以下の基準で部分奏効以上の被験者割合

完全奏効	以下のすべての基準を満たす ヘモグロビン濃度　10g/dL以上 好中球数　1,000/μL以上 血小板数　100,000/μL以上
部分奏効	重症又は最重症の場合： 血小板輸血及び赤血球輸血非依存であり、かつ、以下の基準のうち2つ以上を満たす 好中球数　500/μL以上 血小板数　20,000/μL以上 網赤血球数　20,000/μL以上 輸血を要する非重症の場合：血小板輸血及び赤血球輸血非依存
反応なし	上記の基準を満たさない

18. 薬効薬理

18.1 作用機序

本剤は、巨核球系前駆細胞に直接作用し、血小板造血作用を発揮する。また、本剤は、トロンボポエチン受容体に結合し、活性化させることで、巨核球系前駆細胞の増殖及び分化を促進する。

さらに、骨髄造血幹細胞及び造血前駆細胞に作用し、これらの細胞の増殖及び分化を促進する。

18.2 造血作用

本剤は、正常マウス、ラット、アカゲザル及びカニクイザルに静脈内又は皮下投与した際に、血小板造血作用(血小板数の増加)を示し、脾臓摘出マウスへの皮下投与においても同様な作用を示した。また、血小板に対する自己抗体の産生により、血小板破壊が起こり血小板減少を呈するW/BF1系マウスへの皮下投与により、血小板数減少に対して改善作用を示した[10)]。さらに、化学療法剤／放射線により多系統の骨髄不全を惹起した骨髄抑制マウスへの皮下投与により、血小板数及び赤血球数の減少に対して改善作用を示した[11)]。

19．有効成分に関する理化学的知見

一般名

ロミプロスチム(遺伝子組換え)
(Romiplostim(Genetical Recombination))

分子量

59,085

本質

ロミプロスチム(遺伝子組換え)は、遺伝子組換えFc-ペプチド融合タンパク質であり、2～228番目はヒトIgG1のFc領域、また229～269番目はヒトトロンボポエチン受容体結合配列を含むペプチドからなる。ロミプロスチムは、269個のアミノ酸残基からなるサブユニット2分子から構成されるタンパク質である。

20．取扱い上の注意

外箱開封後は遮光して保存すること。

＊21．承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈既存治療で効果不十分な再生不良性貧血〉

21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22．包装

1バイアル

23．主要文献

1) 再生不良性貧血診療の参照ガイド(厚生労働科学研究費補助金 難治性疾患政策研究事業 特発性造血障害に関する調査研究班)
2) 米国添付文書
3) 社内資料：日本人成人慢性免疫性(特発性)血小板減少性紫斑病患者を対象とした本剤の長期投与の効果(2011年1月21日承認、CTD2.7.6.13)
4) 社内資料：既存治療で効果不十分な再生不良性貧血患者における血清中濃度及び薬物動態パラメータ
5) Shirasugi Y, et al.：Int J Hematol. 2011; 94: 71-80
6) Kuter DJ, et al.：Lancet. 2008; 371: 395-403
7) 社内資料：既存治療で効果不十分な再生不良性貧血患者を対象とした国際共同臨床試験(2019年6月18日承認、CTD2.7.6.2)
＊＊8) 社内資料：免疫抑制療法未治療の再生不良性貧血患者を対象とした国際共同臨床試験(3剤併用)(2023年9月25日承認、CTD2.7.6.1)
＊＊9) 社内資料：免疫抑制療法未治療の再生不良性貧血患者を対象とした国際共同臨床試験(2剤併用)(2023年9月25日承認、CTD2.7.6.2)
10) 社内資料：薬理試験(効力を裏付ける試験)(2011年1月21日承認、CTD2.6.2.2)
11) McElroy PL, et al.：Exp Hematol. 2015; 43: 479-487

24．文献請求先及び問い合わせ先

協和キリン株式会社　くすり相談窓口
〒100-0004　東京都千代田区大手町1-9-2
電話　0120-850-150
受付時間　9:00～17:30(土・日・祝日及び弊社休日を除く)

26．製造販売業者等

26.1 製造販売元

協和キリン株式会社
東京都千代田区大手町1-9-2

＊2023年４月改訂（第２版）
2022年６月改訂（第１版、再審査結果）

貯　　法：凍結を避け、２～８℃で保存
有効期間：36ヵ月

日本標準商品分類番号
876399

承認番号	22000AMY00004000
販売開始	2008年11月

THYIeL01

免疫抑制剤
抗ヒト胸腺細胞ウサギ免疫グロブリン製剤
生物由来製品、劇薬、処方箋医薬品：注意－医師等の処方箋により使用すること

サイモグロブリン® 点滴静注用 25mg
Thymoglobuline® I.V. Infusion

sanofi

1. 警告

本剤は、緊急時に十分対応できる医療施設において、再生不良性貧血、造血幹細胞移植又は臓器移植に関する十分な知識・経験を持つ医師のもとで、本剤が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の試験投与でショック状態等の過敏症が認められた患者［7.1 参照］
2.2 重症感染症（肺炎、敗血症等）を合併している患者［感染症が増悪し致命的となることがある。］
2.3 妊婦［9.5 参照］
2.4 弱毒生ワクチンを投与中の患者［10.1 参照］

3. 組成・性状

3.1 組成

成　　分		1バイアル中の分量	備　考
有効成分	抗ヒト胸腺細胞ウサギ免疫グロブリン	25mg	ウサギ血液由来
添加剤	グリシン	50mg	－
	D-マンニトール	50mg	－
	ポリソルベート80	2.5mg	－
	塩化ナトリウム	10mg	－
	pH調節剤２成分		

本剤は製造工程でヒトの胸腺細胞及び赤血球を使用している。

3.2 製剤の性状

性　　状	白色ないし乳白色の凍結乾燥製剤である。本剤を日局注射用水で溶解したとき、無色ないし淡黄色の澄明又はわずかに混濁した液となる。
pH[注)]	6.5～7.2
浸透圧比[注)]	約0.9（生理食塩液に対する比）

注）日局注射用水５mLで溶解後

4. 効能又は効果

○中等症以上の再生不良性貧血
○造血幹細胞移植の前治療
○造血幹細胞移植後の急性移植片対宿主病
○下記の臓器移植後の急性拒絶反応の治療
腎移植、肝移植、心移植、肺移植、膵移植、小腸移植

5. 効能又は効果に関連する注意

〈中等症以上の再生不良性貧血〉

5.1 本剤は下記の重症度基準による中等症以上の再生不良性貧血患者に使用すること。

再生不良性貧血の重症度基準
（厚生労働省特定疾患特発性造血障害調査研究班基準（平成16年度修正））[1)]

最重症	好中球200/μL未満に加えて、以下の１項目以上を満たす 網赤血球　20,000/μL未満 血小板　20,000/μL未満
重症	以下の２項目以上を満たす 網赤血球　20,000/μL未満 好中球　500/μL未満 血小板　20,000/μL未満
やや重症	以下の２項目以上を満たし、定期的な赤血球輸血を必要とする 網赤血球　60,000/μL未満 好中球　1,000/μL未満 血小板　50,000/μL未満
中等症	以下の２項目以上を満たす 網赤血球　60,000/μL未満 好中球　1,000/μL未満 血小板　50,000/μL未満
軽症	それ以外のもの

注）定期的な赤血球輸血とは毎月２単位以上の輸血が必要なときを指す。

〈造血幹細胞移植後の急性移植片対宿主病〉

5.2 ステロイド療法によっても十分な効果が得られない場合にのみ適用を考慮すること。

〈臓器移植後の急性拒絶反応の治療〉

5.3 本剤は、原則としてステロイド療法で十分な治療効果が得られない場合に使用すること。
5.4 原則として、急性拒絶反応の確定診断後に本剤を投与すること。

6. 用法及び用量

〈中等症以上の再生不良性貧血〉

通常、１日１回体重１kgあたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして2.5～3.75mgを、生理食塩液又は５%ブドウ糖注射液500mLで希釈して、６時間以上かけ緩徐に点滴静注する。投与期間は５日間とする。

〈造血幹細胞移植の前治療〉

通常、１日１回体重１kgあたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして2.5mgを、生理食塩液又は５%ブドウ糖注射液500mLで希釈して、６時間以上かけ緩徐に点滴静注する。投与期間は造血幹細胞移植５日前より４日間とする。

〈造血幹細胞移植後の急性移植片対宿主病〉

通常、１日１回体重１kgあたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして2.5～3.75mgを、生理食塩液又は５%ブドウ糖注射液500mLで希釈して、６時間以上かけ緩徐に点滴静注する。投与期間は５日間とする。

〈臓器移植後の急性拒絶反応の治療〉

腎移植の場合
通常、１日１回体重１kgあたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして1.5mgを、１バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして25mg）あたり、生理食塩液又は５%ブドウ糖注射液50mLで希釈して、６時間以上かけ緩徐

に点滴静注する。投与期間は7～14日間とする。
肝移植、肺移植、膵移植及び小腸移植の場合
通常、1日1回体重1kgあたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして1.5mgを、1バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして25mg）あたり、生理食塩液又は5%ブドウ糖注射液50mLで希釈して、6時間以上かけ緩徐に点滴静注する。投与期間は最大14日間とする。
心移植の場合
通常、1日1回体重1kgあたり抗ヒト胸腺細胞ウサギ免疫グロブリンとして1.5～2.5mgを、1バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして25mg）あたり、生理食塩液又は5%ブドウ糖注射液50mLで希釈して、6時間以上かけ緩徐に点滴静注する。投与期間は最大14日間とする。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 アナフィラキシー等の過敏症状を起こすことがあるので、使用に際しては、十分な問診を行うとともに、あらかじめ本剤の試験投与を行うこと。
試験投与は通常、本剤1バイアルを日局注射用水5mLにて溶解後、その0.5mL（抗ヒト胸腺細胞ウサギ免疫グロブリンとして2.5mg）を100mLの生理食塩液で希釈して、1時間以上かけて点滴静注する。試験投与中は医師が患者の状態を十分に観察し、安全性を確認すること。[2.1 参照]

＊**7.2** 本剤又は他のウサギ血清製剤の投与歴のある患者には、他種由来の抗ヒト胸腺細胞免疫グロブリン製剤の投与も考慮した上で、本剤をやむを得ず再投与する際には、投与に先立って、本剤に対する抗体の有無の確認や救急処置対策等、必要な処置を講じた上で、医師の十分な観察のもと慎重に投与すること。[8.6 参照]

〈臓器移植後の急性拒絶反応の治療〉

7.3 本剤を投与する際には、血小板を含む全血算値に十分注意し、以下に示す減量基準等を参考に、適切な処置を行うこと。
(1) 血小板数が50,000～75,000/mm^{3}又は白血球数が2,000～3,000/mm^{3}の場合、本剤の減量を考慮すること。
(2) 持続的で重度の血小板減少症（<50,000/mm^3）又は白血球減少症（<2,000/mm^3）が認められた場合、本剤の投与中止を考慮すること。

7.4 心移植後の急性拒絶反応の治療において、1.5mg/kgよりも高用量を投与する期間は、過度の免疫抑制状態の持続を避けるため、5日間までを目安にすること。

8. 重要な基本的注意

〈効能共通〉

8.1 ショック等重篤な副作用を起こすことがあるので、投与前にショック症状発現時の救急処置対策を考慮しておくこと。投与中は注意して使用し、医師が経過を十分に観察すること。[11.1.1 参照]

8.2 本剤の投与前に感染症が認められた場合、感染症の治療を優先し、患者の状態が安定した後、本剤を投与すること。また、投与中並びに投与後に重篤な感染症（ウイルス感染症、細菌感染症、真菌感染症等）が発症する場合がある。[11.1.3-11.1.6 参照]

8.3 間質性肺炎を起こすことがあるので、咳嗽、呼吸困難、低酸素症等の呼吸器症状に注意すること。[11.1.7 参照]

8.4 本剤投与の初期に発熱、悪寒、呼吸困難、悪心、嘔吐、下痢、頻脈、低血圧、高血圧、倦怠感、発疹、頭痛等があらわれることがあるので、その旨を患者にあらかじめ説明しておくこと。また、重度のinfusion reaction（サイトカイン放出症候群を含む）があらわれ、重篤な心障害や肺障害（心筋梗塞、急性呼吸窮迫症候群、肺水腫）に至ることがあるので、投与中は患者を厳密に観察すること。これらの症状を軽減させるため、あらかじめ副腎皮質ホルモン剤等を投与することが望ましい。また、解熱剤、抗ヒスタミン剤の併用も本剤の投与初期に頻発するこれらの症状を軽減する。[11.1.2 参照]

8.5 本剤投与時に交差反応性抗体に起因する血小板減少があらわれ、出血傾向が増悪するおそれがあるので、定期的に血小板数を測定し、患者の状態を十分に観察すること。[11.1.8、11.1.9 参照]

8.6 本剤投与に先立って、本剤又は他のウサギ血清製剤の治療歴の有無を必ず確認すること。また、本剤の投与後には、患者にウサギ血清製剤を投与した旨を十分認識させるために、本剤の医薬品名を記載した用紙に、使用量、使用期間、病院名、担当医師名を記入し、治療終了後に治療歴として保管するとともに同様の記録を患者に渡すこと。[7.2 参照]

8.7 AST、ALTの上昇等を伴う重篤な肝障害、血小板減少、白血球減少があらわれることがあるので、定期的に血液検査を行うこと。[9.3、11.1.8、11.1.10 参照]

8.8 急性腎障害があらわれることがあるので、投与に先立って患者が脱水状態にないことを確認すること。[11.1.12 参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 本剤又は他のウサギ血清製剤の投与歴のある患者
ショックを起こすおそれがある。

9.1.2 ウイルス感染症の患者
本剤の免疫抑制作用により病態を悪化させるおそれがある。

9.1.3 細菌感染症の患者
本剤の免疫抑制作用により病態を悪化させるおそれがある。

9.1.4 真菌感染症の患者
本剤の免疫抑制作用により病態を悪化させるおそれがある。

9.1.5 薬物過敏症の既往歴のある患者

9.1.6 アレルギー素因のある患者

9.1.7 心疾患のある患者
心機能を悪化させるおそれがある。

9.1.8 免疫抑制剤を投与された肝炎ウイルスキャリアの患者
免疫抑制剤を投与されたB型肝炎ウイルスキャリアの患者において、B型肝炎ウイルスの再活性化による肝炎があらわれることがある。また、HBs抗原陰性の患者において、免疫抑制剤の投与開始後にB型肝炎ウイルスの再活性化による肝炎を発症した症例が報告されている。また、C型肝炎ウイルスキャリアの患者において、免疫抑制剤の投与開始後にC型肝炎の悪化がみられることがある。肝炎ウイルスキャリアの患者に本剤を投与する場合は、肝機能検査値や肝炎ウイルスマーカーのモニタリングを行うなど、B型肝炎ウイルスの再活性化やC型肝炎の悪化の徴候や症状の発現に注意すること。[11.1.3 参照]

9.1.9 急性腎障害の危険性の高い患者
投与量及び投与速度を出来るだけ低くすることが望ましい。[11.1.12 参照]

9.2 腎機能障害患者
腎機能を悪化させるおそれがある。[11.1.12 参照]

9.3 肝機能障害患者
肝機能を悪化させるおそれがある。[8.7、11.1.10 参照]

9.5 妊婦
妊婦又は妊娠している可能性のある女性には、投与しないこと。[2.3 参照]

9.6 授乳婦
治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

9.7 小児等
慎重に投与すること。小児等を対象とした臨床試験は実施していない。

9.8 高齢者
患者の状態を観察しながら慎重に投与すること。一般に生理機能（腎機能、肝機能、免疫機能等）が低下している。

10. 相互作用

10.1 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
弱毒生ワクチン おたふくかぜ、麻疹、風疹及びこれらの混合ワクチン等 ［2.4 参照］	本剤投与後、弱毒生ワクチンを接種する場合には、発病するおそれがある。	本剤の免疫抑制作用による。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
他の免疫抑制剤 シクロスポリン等	過度の免疫抑制による感染症あるいはリンパ増殖性疾患を惹起する危険性があるので、併用する場合には慎重に投与すること。	相加的に免疫抑制作用が増強される可能性がある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 ショック（頻度不明）、**アナフィラキシー**（0.4%）

呼吸困難、血圧低下、頻脈等の異常が認められた場合には投与を中止し、適切な処置を行うこと。［8.1 参照］

11.1.2 重度のinfusion reaction（サイトカイン放出症候群を含む）（頻度不明）

重篤な心障害や肺障害（心筋梗塞、急性呼吸窮迫症候群、肺水腫）に至ることがあるので、発熱、悪寒、呼吸困難、悪心、嘔吐、下痢、頻脈、低血圧、高血圧、倦怠感、発疹、頭痛等の異常が認められた場合には投与を中止し、適切な処置を行うこと。［8.4 参照］

11.1.3 感染症（肺炎、敗血症等）（11.2%）

ウイルス（アデノウイルス、サイトメガロウイルス、ヘルペス等）、細菌、真菌（アスペルギルス等）等による重篤な感染症があらわれることがある。また、免疫抑制剤を投与されたB型又はC型肝炎ウイルスキャリアの患者において、B型肝炎ウイルスの再活性化による肝炎やC型肝炎の悪化があらわれることがある。［8.2、9.1.8 参照］

11.1.4 発熱性好中球減少症（頻度不明）

［8.2 参照］

11.1.5 進行性多巣性白質脳症（PML）（頻度不明）

本剤の治療期間中及び治療終了後は患者の状態を十分に観察し、意識障害、認知障害、麻痺症状（片麻痺、四肢麻痺）、言語障害等の症状があらわれた場合は、MRIによる画像診断及び脳脊髄液検査を行うとともに、投与を中止し、適切な処置を行うこと。［8.2 参照］

11.1.6 BKウイルス腎症（頻度不明）

減量又は投与を中止し、適切な処置を行うこと。［8.2 参照］

11.1.7 間質性肺炎（2.1%）

発熱、咳嗽、呼吸困難、胸部X線検査異常等が認められた場合には、投与を中止し、適切な処置を行うこと。［8.3 参照］

11.1.8 血小板減少（31.0%）、**白血球減少**（頻度不明）

［8.5、8.7、13.1 参照］

11.1.9 出血傾向

脳出血（1.7%）、下血、胃腸出血（いずれも1.2%）、くも膜下出血、肺出血、肺胞出血（いずれも0.4%）等の出血があらわれることがある。［8.5 参照］

11.1.10 重篤な肝障害（6.2%）

［8.7、9.3 参照］

11.1.11 リンパ増殖性疾患（1.2%）

発熱、リンパ節腫大等が認められた場合には、適切な処置を行うこと。

11.1.12 急性腎障害（頻度不明）

腎機能検査値（BUN、血清クレアチニン等）の悪化、尿量減少が認められた場合には投与を中止し、適切な処置を行うこと。［8.8、9.1.9、9.2 参照］

11.2 その他の副作用

	40%以上	10～40%未満	10%未満
過敏症[注1)]		発疹、そう痒症	筋痛、紅斑、血清病[注3)]
発熱及びインフルエンザ様症状[注2)]	発熱、熱感	頭痛、関節痛、悪寒	胸痛
血液		好中球減少、リンパ球減少、血清総蛋白減少、赤血球減少、ヘマトクリット減少、ヘモグロビン減少、高カリウム血症	
精神神経系			感覚減退、筋硬直、めまい
消化器		悪心、嘔吐、下痢、腹痛	
肝臓		AST増加、ALT増加、LDH増加	Al-P増加、ビリルビン増加
循環器		動悸、血圧上昇	血圧低下、頻脈
血管			静脈炎
その他	CRP増加	脱力、疼痛、末梢性浮腫	耳鳴、呼吸困難、無力症、倦怠感、投与部位反応（疼痛、腫脹、紅斑）

注1）副腎皮質ホルモン剤等の併用で軽減される。
注2）副腎皮質ホルモン剤、解熱剤及び抗ヒスタミン剤等の併用で軽減される。
注3）発熱、発疹、関節痛、筋肉痛などの症状を伴う。なお、これらの症状は自然に消退する場合があるが、副腎皮質ホルモン剤の投与で速やかに軽減される。

12. 臨床検査結果に及ぼす影響

本剤はウサギ抗体を用いたイムノアッセイなどの検査結果に影響を及ぼす可能性がある。

13. 過量投与

13.1 症状

本剤の過量投与により、白血球減少、血小板減少が発現することがあるので、用法及び用量に定められている投与量を超えて投与しないこと。［11.1.8 参照］

13.2 処置

本剤の過量投与が疑われた場合は、輸血、血液造血因子、抗感染症薬の投与等の支持療法を行うこと。また、必要に応じ無菌管理を考慮し、血液学的検査を頻回に行い、患者の状態を十分に観察すること。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 溶解

(1) 本剤に日局注射用水５mLを加える。粉末が完全に溶解するまで、できるだけ泡を立てないよう静かに円を描くように回して溶解する。急激な振盪溶解を避けること。

(2) 本剤は蛋白製剤であるため、その溶液はわずかに混濁することがあるが、本剤の薬効には影響を及ぼさない。なお、これ以外の外観上の異常を認めた場合には使用しないこと。

(3) 本剤には防腐剤が含まれていないので、溶解後は速やかに使用すること。

14.1.2 希釈

〈効能共通〉

(1) 生理食塩液又は５%ブドウ糖注射液以外の製剤との配合は避けること。

〈中等症以上の再生不良性貧血、造血幹細胞移植の前治療、造血幹細胞移植後の急性移植片対宿主病〉

(2) 生理食塩液又は5％ブドウ糖注射液500mLで希釈すること。

〈臓器移植後の急性拒絶反応の治療〉

(3) 1バイアル（抗ヒト胸腺細胞ウサギ免疫グロブリンとして25mg）あたり、生理食塩液又は5％ブドウ糖注射液50mLで希釈すること。

14.2 薬剤投与時の注意

14.2.1 1回の投与は6時間以上かけて注入するよう流速を設定すること。

14.2.2 点滴静注する際には、点滴セットにインラインフィルター（ポアサイズ0.2ミクロン）を使用すること。

14.2.3 注入後に残った残液は廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

海外市販後の自発報告において本剤投与後の核酸増幅検査でB型肝炎ウイルスが陽性であった症例が1例報告されている。

15.2 非臨床試験に基づく情報

2週間反復静脈内投与試験（サル）において赤血球パラメータ（赤血球数、ヘマトクリット、ヘモグロビン）の減少がみられた。

16. 薬物動態

16.1 血中濃度

中等症以上の再生不良性貧血患者を対象とした国内第Ⅱ相臨床試験において、サイモグロブリン2.5mg/kg/日及び3.75mg/kg/日を、5日間、12時間以上かけて点滴静注したときの薬物動態を検討した結果は以下のとおりであった。各投与量におけるCmaxは、投与量の増加に伴った上昇が認められた。血中サイモグロブリン濃度は、投与期間中徐々に上昇し、最終投与終了後から緩やかに消失した。また、サイモグロブリン投与後、両投与群の11症例において14日目以降から抗体の出現が認められた[2]。

再生不良性貧血患者における薬物動態学的パラメータ

投与群		Cmax（μg/mL）	$T_{1/2}$（day）
2.5mg/kg/日群（n=6）	平均	119.0	8.1[注]
	最小-最大	46.7-234.0	3.9-14.3[注]
3.75mg/kg/日群（n=9）	平均	173.5	7.8
	最小-最大	52.0-500.0	2.0-16.0

注）n=4

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈中等症以上の再生不良性貧血、造血幹細胞移植の前治療、造血幹細胞移植後の急性移植片対宿主病〉

17.1.1 国内第Ⅱ相試験

〈中等症以上の再生不良性貧血〉

中等症以上の再生不良性貧血患者を対象とした国内第Ⅱ相臨床試験（登録症例数：41例）における有効性解析対象は28例であり、6ヵ月目の有効率（「著効」+「有効」/症例数）は、2.5mg/kg/日群が13.3%（2/15例）、3.75mg/kg/日群が23.1%（3/13例）であり、全体では17.9%（5/28例）であった。

〈造血幹細胞移植の前治療〉

骨髄移植患者を対象とした国内第Ⅱ相臨床試験（登録症例数：再登録2例を含む107例）における急性GVHD抑制の有効性解析対象は71例、生着の有効性解析対象は70例であった。急性GVHDの抑制効果は、グレードⅡ以上の急性GVHD発症率は2.5mg/kg/日投与で18.3%（13/71例）であった。グレードⅢ以上の急性GVHD発症率は2.5mg/kg/日投与で9.9%（7/71例）であった。生着率は2.5mg/kg/日投与で81.4%（57/70例）であった。

〈造血幹細胞移植後の急性移植片対宿主病〉

骨髄移植後の移植片対宿主病（GVHD）患者を対象とした国内第Ⅱ相臨床試験（登録症例数：40例）における有効性解析対象は既存療法無効例と考えられた急性GVHD患者24例であり、有効率（「著効」+「有効」/症例数）は2.5mg/kg/日群が61.5%（8/13例）、3.75mg/kg/日群が72.7%（8/11例）であり、全体では66.7%（16/24例）であった。

国内における再生不良性貧血、造血幹細胞移植の前治療及び造血幹細胞移植後の急性移植片対宿主病に対する臨床試験での安全性評価対象症例160例中159例（99.4%）に3,443件の副作用（臨床検査値異常を含む）が認められた。主な副作用は、発熱145例（90.6%）、熱感120例（75.0%）、白血球減少120例（75.0%）、CRP増加113例（70.6%）、好中球減少87例（54.4%）等であった。

〈臓器移植後の急性拒絶反応の治療〉

17.1.2 海外臨床試験

外国における腎移植後の急性拒絶反応の治療を目的とした二重盲検比較試験において、腎移植後に急性拒絶反応が発生した患者に、免疫抑制剤併用下、本剤1.5mg/kgを1日1回静脈内投与した結果、血清クレアチニン値を指標とした寛解率は87.8%（72/82例）であった。なお、本剤の投与日数（中央値［最小値、最大値］）は10日［3日、14日］であった[3]。

安全性評価対象症例のうち本剤が投与された82例中82例（100%）に940件の副作用（関連性がunlikelyのものを含む）が認められた。主な副作用は、悪寒40例（48.8%）、疼痛38例（46.3%）、白血球減少32例（39.0%）、腹痛31例（37.8%）、高血圧30例（36.6%）、末梢性浮腫28例（34.1%）、無力症、血小板減少症、高カリウム血症各22例（26.8%）、発熱20例（24.4%）、貧血19例（23.2%）等であった。

17.1.3 国内臨床研究

腎移植後にステロイド抵抗性の急性拒絶反応が発現した患者に、免疫抑制剤併用下、本剤1.5mg/kgを1日1回静脈内投与した結果、投与終了14日後の血清クレアチニン値が投与前値よりも低い患者の割合は85.7%（6/7例）であった。なお、本剤の投与日数（中央値［最小値、最大値］）は7日［5日、10日］であった。

17.1.4 肝移植、心移植、肺移植、膵移植、小腸移植後の急性拒絶反応の治療における副作用発現頻度が明確となる臨床試験は実施していない。

18. 薬効薬理

18.1 作用機序

本剤は、T細胞表面抗原（CD2、CD3、CD4、CD5、CD7、CD8、CD25、TCR$\alpha\beta$）並びに白血球表面抗原（CD11a）に対し親和性を示した[4,5]。また、ヒトリンパ球細胞傷害性試験において補体存在下リンパ球を溶解させた[6]。以上のことから、本剤は、ヒトT細胞表面抗原に結合し、補体依存性の細胞傷害を惹起させることにより、再生不良性貧血並びにGVHDに関与しているT細胞を減少させ、その結果これらの疾患に対して効果を示すと考えられる。

18.2 免疫抑制作用

18.2.1 ヒトリンパ球細胞傷害性試験（*in vitro*）

ヒトリンパ球に対する補体依存性の細胞傷害性を検討した結果、本剤約20μg/mLは陰性対照と比較してリンパ球の溶解を25%増加させた[6]。

18.2.2 E-ロゼット形成阻止作用（*in vitro*）

ヒトリンパ球を用いたE-ロゼット形成阻止作用を検討した結果、本剤約15μg/mLは陰性対照と比較してE-ロゼット形成を50%抑制した[6]。

18.2.3 サルにおける皮膚移植片生着延長試験（*in vivo*）

本剤（25mg/匹）は、サルにおける皮膚移植片が拒絶されるまでの日数を延長させ、*in vivo*での拒絶反応を抑制した[6]。

19. 有効成分に関する理化学的知見

一般的名称：抗ヒト胸腺細胞ウサギ免疫グロブリン
（Anti-human Thymocyte Immunoglobulin, Rabbit）

分　子　量：約160,000

本　　質：ヒトの胸腺細胞を抗原とし、ウサギを免疫して得られた抗血清から分離精製されたポリクローナル抗体で、免疫グロブリンGに属するたん白質

20. 取扱い上の注意

外箱開封後は遮光して保存すること。

22. 包装

1バイアル

23. 主要文献

1）中尾眞二　他：臨床血液.2006；47（1）：27-46

2）社内資料：再生不良性貧血患者での薬物動態（2008年7月16日承認、申請資料概要へ.（2）1））

3）Gaber A O, et al.：Transplantation. 1998;66:29-37

4）社内資料：ヒトT細胞表面抗原親和性（2008年7月16日承認、申請資料概要ホ.（1）2））

5）Tsuge I, et al.：Current Therapeutic Research. 1995;56（7）:671-7

6）社内資料：効力薬理試験（2008年7月16日承認、申請資料概要ホ.（1）1））

24. 文献請求先及び問い合わせ先

サノフィ株式会社

コールセンター　くすり相談室

〒163-1488　東京都新宿区西新宿三丁目20番2号

フリーダイヤル 0120-109-905

26. 製造販売業者等

26.1 製造販売元

サノフィ株式会社

〒163-1488　東京都新宿区西新宿三丁目20番2号

＊＊2022年2月改訂（第2版、効能変更、用法及び用量変更）
＊2020年2月改訂（第1版、効能変更、用法及び用量変更）

貯法：室温保存

有効期間：3年

日本標準商品分類番号
873999

免疫抑制剤
（カルシニューリンインヒビター）
シクロスポリン製剤

ネオーラル®内用液10%
ネオーラル®10mgカプセル
ネオーラル®25mgカプセル
ネオーラル®50mgカプセル
Neoral®

	内用液10%	10mgカプセル	25mgカプセル	50mgカプセル
承認番号	22100AMX01780000	21200AMY00062000	21200AMY00063000	21200AMY00064000
販売開始	2000年5月			

劇薬、処方箋医薬品
（注意－医師等の処方箋により使用すること）

NOVARTIS

1. 警告

1.1 臓器移植における本剤の投与は、免疫抑制療法及び移植患者の管理に精通している医師又はその指導のもとで行うこと。

1.2 アトピー性皮膚炎における本剤の投与は、アトピー性皮膚炎の治療に精通している医師のもとで、患者又はその家族に有効性及び危険性を予め十分説明し、理解したことを確認した上で投与を開始すること。［9.7.1参照］

1.3 本剤はサンディミュン（内用液又はカプセル）と生物学的に同等ではなく、バイオアベイラビリティが向上しているので、サンディミュンから本剤に切り換える際には、シクロスポリンの血中濃度（AUC、Cmax）の上昇による副作用の発現に注意すること。特に、高用量での切り換え時には、サンディミュンの投与量を上回らないようにするなど、注意すること。十分なサンディミュン使用経験を持つ専門医のもとで行うこと。
一方、本剤からサンディミュンへの切り換えについては、シクロスポリンの血中濃度が低下することがあるので、原則として切り換えを行わないこと。特に移植患者では、用量不足によって拒絶反応が発現するおそれがある。［7.1、8.2、16.1.1、16.1.2参照］

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者

2.2 タクロリムス（外用剤を除く）、ピタバスタチン、ロスバスタチン、ボセンタン、アリスキレン、アスナプレビル、バニプレビル、グラゾプレビル、ペマフィブラートを投与中の患者［10.1参照］

2.3 肝臓又は腎臓に障害のある患者で、コルヒチンを服用中の患者［9.2、9.3、10.2参照］

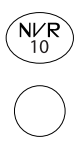
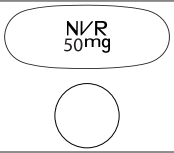
2.4 生ワクチンを接種しないこと［10.1参照］

3. 組成・性状

3.1 組成

販売名	ネオーラル内用液10%	ネオーラル10mgカプセル	ネオーラル25mgカプセル	ネオーラル50mgカプセル
有効成分	1瓶（50mL）中シクロスポリン（日局）5.0g［内用液1mLはシクロスポリン100mgに相当する］	1カプセル中シクロスポリン（日局）10mg	1カプセル中シクロスポリン（日局）25mg	1カプセル中シクロスポリン（日局）50mg
添加剤	グリセリン脂肪酸エステル、プロピレングリコール、エタノール、ポリオキシエチレン硬化ヒマシ油、トコフェロール	グリセリン脂肪酸エステル、プロピレングリコール、エタノール、ポリオキシエチレン硬化ヒマシ油、トコフェロールカプセル本体にゼラチン、グリセリン、プロピレングリコール、酸化チタン、中鎖脂肪酸トリグリセリド、大豆レシチン含有	グリセリン脂肪酸エステル、プロピレングリコール、エタノール、ポリオキシエチレン硬化ヒマシ油、トコフェロールカプセル本体にゼラチン、グリセリン、プロピレングリコール、酸化チタン、三二酸化鉄、中鎖脂肪酸トリグリセリド、大豆レシチン含有	グリセリン脂肪酸エステル、プロピレングリコール、エタノール、ポリオキシエチレン硬化ヒマシ油、トコフェロールカプセル本体にゼラチン、グリセリン、プロピレングリコール、酸化チタン、中鎖脂肪酸トリグリセリド、大豆レシチン含有

3.2 製剤の性状

販売名	ネオーラル内用液10%	ネオーラル10mgカプセル	ネオーラル25mgカプセル	ネオーラル50mgカプセル
性状	微黄色～微黄褐色澄明の油状の液で、粘性があり特異なにおいがある。	帯黄白色の光沢のある軟カプセルで特異なにおいがある。	淡黄色の光沢のある軟カプセルで特異なにおいがある。	帯黄白色の光沢のある軟カプセルで特異なにおいがある。
内容物	－	微黄色～微黄褐色澄明の油状の液で、粘性がある。		
外形	－			
識別コード	－	NVR10	NVR25mg	NVR50mg
大きさ（約）	－	長径：8.9mm 短径：6.7mm 質量：0.2g	長径：14mm 短径：8.2mm 質量：0.4g	長径：21.9mm 短径：8.5mm 質量：0.8g

4. 効能又は効果

〈ネオーラル10mgカプセル〉
〈ネオーラル25mgカプセル〉
〈ネオーラル50mgカプセル〉

○下記の臓器移植における拒絶反応の抑制
腎移植、肝移植、心移植、肺移植、膵移植、小腸移植
○骨髄移植における拒絶反応及び移植片対宿主病の抑制
○ベーチェット病（眼症状のある場合）、及びその他の非感染性ぶどう膜炎（既存治療で効果不十分であり、視力低下のおそれのある活動性の中間部又は後部の非感染性ぶどう膜炎に限る）
○尋常性乾癬（皮疹が全身の30%以上に及ぶものあるいは難治性の場合）、膿疱性乾癬、乾癬性紅皮症、関節症性乾癬
○再生不良性貧血、赤芽球癆
○ネフローゼ症候群（頻回再発型あるいはステロイドに抵抗性を示す場合）

®登録商標

○全身型重症筋無力症（胸腺摘出後の治療において、ステロイド剤の投与が効果不十分、又は副作用により困難な場合）
○アトピー性皮膚炎（既存治療で十分な効果が得られない患者）
＊＊○細胞移植に伴う免疫反応の抑制

〈ネオーラル内用液10%〉
○下記の臓器移植における拒絶反応の抑制
腎移植、肝移植、心移植、肺移植、膵移植、小腸移植
○骨髄移植における拒絶反応及び移植片対宿主病の抑制
○ベーチェット病（眼症状のある場合）、及びその他の非感染性ぶどう膜炎（既存治療で効果不十分であり、視力低下のおそれのある活動性の中間部又は後部の非感染性ぶどう膜炎に限る）
○尋常性乾癬（皮疹が全身の30%以上に及ぶものあるいは難治性の場合）、膿疱性乾癬、乾癬性紅皮症、関節症性乾癬
○再生不良性貧血、赤芽球癆
○ネフローゼ症候群（頻回再発型あるいはステロイドに抵抗性を示す場合）
○全身型重症筋無力症（胸腺摘出後の治療において、ステロイド剤の投与が効果不十分、又は副作用により困難な場合）
○アトピー性皮膚炎（既存治療で十分な効果が得られない患者）
＊○川崎病の急性期（重症であり、冠動脈障害の発生の危険がある場合）
＊＊○細胞移植に伴う免疫反応の抑制

5．効能又は効果に関連する注意
〈再生不良性貧血〉
5.1 診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に投与すること。また、寛解例で本剤投与中止後に再燃したため再投与する場合の有効性及び安全性については、十分な評価が確立していないので、患者の状態をみながら治療上の有益性が優先すると判断される場合にのみ投与すること。
〈ネフローゼ症候群〉
5.2 副腎皮質ホルモン剤に反応はするものの頻回に再発を繰り返す患者、又は副腎皮質ホルモン剤治療に抵抗性を示す患者に限ること。
〈全身型重症筋無力症〉
5.3 本剤を単独で投与した際の有効性については使用経験がなく明らかでない。
〈アトピー性皮膚炎〉
5.4 ステロイド外用剤やタクロリムス外用剤等の既存治療で十分な効果が得られず、強い炎症を伴う皮疹が体表面積の30%以上に及ぶ患者を対象にすること。
〈川崎病の急性期〉
＊5.5 静注用免疫グロブリン不応例又は静注用免疫グロブリン不応予測例に投与すること。
＊5.6 発病後7日以内に投与を開始することが望ましい。

6．用法及び用量
〈腎移植〉
通常、移植1日前からシクロスポリンとして1日量9～12mg/kgを1日2回に分けて経口投与し、以後1日2mg/kgずつ減量する。維持量は1日量4～6mg/kgを標準とするが、症状により適宜増減する。
〈肝移植〉
通常、移植1日前からシクロスポリンとして1日量14～16mg/kgを1日2回に分けて経口投与する。以後徐々に減量し、維持量は1日量5～10mg/kgを標準とするが、症状により適宜増減する。
〈心移植、肺移植、膵移植〉
通常、移植1日前からシクロスポリンとして1日量10～15mg/kgを1日2回に分けて経口投与する。以後徐々に減量し、維持量は1日量2～6mg/kgを標準とするが、症状により適宜増減する。
〈小腸移植〉
通常、シクロスポリンとして1日量14～16mg/kgを1日2回に分けて経口投与する。以後徐々に減量し、維持量は1日量5～10mg/kgを標準とするが、症状により適宜増減する。ただし、通常移植1日前からシクロスポリン注射剤で投与を開始し、内服可能となった後はできるだけ速やかに経口投与に切り換える。
〈骨髄移植〉
通常、移植1日前からシクロスポリンとして1日量6～12mg/kgを1日2回に分けて経口投与し、3～6ヵ月間継続し、その後徐々に減量し中止する。
〈ベーチェット病及びその他の非感染性ぶどう膜炎〉
通常、シクロスポリンとして1日量5mg/kgを1日2回に分けて経口投与を開始し、以後1ヵ月毎に1日1～2mg/kgずつ減量又は増量する。維持量は1日量3～5mg/kgを標準とするが、症状により適宜増減する。
〈乾癬〉
通常、1日量5mg/kgを2回に分けて経口投与する。効果がみられた場合は1ヵ月毎に1日1mg/kgずつ減量し、維持量は1日量3mg/kgを標準とする。なお、症状により適宜増減する。
〈再生不良性貧血〉
通常、シクロスポリンとして1日量6mg/kgを1日2回に分けて経口投与する。なお、患者の状態により適宜増減する。
〈ネフローゼ症候群〉
通常、シクロスポリンとして下記の用量を1日2回に分けて経口投与する。なお、症状により適宜増減する。
(1) 頻回再発型の症例
成人には1日量1.5mg/kgを投与する。また、小児の場合には1日量2.5mg/kgを投与する。
(2) ステロイドに抵抗性を示す症例
成人には1日量3mg/kgを投与する。また、小児の場合には1日量5mg/kgを投与する。
〈全身型重症筋無力症〉
通常、シクロスポリンとして1日量5mg/kgを1日2回に分けて経口投与する。効果がみられた場合は徐々に減量し、維持量は3mg/kgを標準とする。なお、症状により適宜増減する。
〈アトピー性皮膚炎〉
通常、成人にはシクロスポリンとして1日量3mg/kgを1日2回に分けて経口投与する。なお、症状により適宜増減するが1日量5mg/kgを超えないこと。
＊〈川崎病の急性期〉
通常、シクロスポリンとして1日量5mg/kgを1日2回に分けて原則5日間経口投与する。
＊＊〈細胞移植に伴う免疫反応の抑制〉
再生医療等製品の用法及び用量又は使用方法に基づき使用する。

7．用法及び用量に関連する注意
〈効能共通〉
7.1 サンディミュン（内用液又はカプセル）から本剤に切り換えて投与する場合は、原則として1：1の比（mg/kg/日）で切り換えて投与するが、シクロスポリンの血中濃度（AUC、Cmax）が上昇して副作用を発現するおそれがあるので、切り換え前後で血中濃度の測定及び臨床検査（血清クレアチニン、血圧等）を頻回に行うとともに患者の状態を十分観察し、必要に応じて投与量を調節すること。ただし、通常の開始用量（初めてサンディミュンを服用する時の投与量）より高い用量を服用している患者で、一時的に免疫抑制作用が不十分となっても病状が悪化して危険な状態に陥る可能性のない患者では、切り換え時の投与量は多くても通常の開始用量とし、血中濃度及び患者の状態に応じて投与量を調節すること。[1.3、16.1.1、16.1.2参照]
7.2 本剤の投与にあたっては血中トラフ値（trough level）を測定し、投与量を調節すること。[8.1参照]
7.2.1 臓器移植患者に投与する際には、過量投与による副作用の発現及び低用量投与による拒絶反応の発現等を防ぐため、血中濃度の測定を移植直後は頻回に行い、その後は1ヵ月に1回を目安に測定し、投与量を調節すること。

7.2.2 ベーチェット病及びその他の非感染性ぶどう膜炎、乾癬、再生不良性貧血、ネフローゼ症候群、全身型重症筋無力症、アトピー性皮膚炎患者に投与する際には、副作用の発現を防ぐため、1ヵ月に1回を目安に血中濃度を測定し、投与量を調節することが望ましい。

＊**7.2.3** 急性期の川崎病患者に投与する際には、原則として投与3日目に血中濃度を測定し、投与量を調節することが望ましい。[17.1.18参照]

〈臓器移植〉

7.3 3剤あるいは4剤の免疫抑制剤を組み合わせた多剤免疫抑制療法を行う場合には、本剤の初期投与量を低く設定することが可能な場合もあるが、移植患者の状態及び併用される他の免疫抑制剤の種類・投与量等を考慮して投与量を調節すること。

〈再生不良性貧血〉

7.4 本剤の投与量及び投与期間について、診療ガイドライン等の最新の情報を参考とし、効果がみられない場合は他の適切な治療法を考慮すること。

〈ネフローゼ症候群〉

7.5 本剤の効果は、通常、1～3ヵ月であらわれるが、3ヵ月以上継続投与しても効果があらわれない場合には投与を中止することが望ましい。また、効果がみられた場合には、その効果が維持できる用量まで減量することが望ましい。

7.6 本剤の使用前に副腎皮質ホルモン剤が維持投与されている場合は、その維持量に本剤を上乗せすること。症状により、副腎皮質ホルモン剤は適宜減量するが、増量を行う場合には本剤の使用は一旦中止すること。

〈アトピー性皮膚炎〉

7.7 投与期間はできる限り短期間にとどめること。本剤の投与中は有効性及び安全性の評価を定期的に行うこと。8週間の投与でも改善がみられない場合には投与を中止すること。なお、1回の治療期間は12週間以内を目安とする。

〈川崎病の急性期〉

＊**7.8** 本剤を5日間を超えて投与する場合には、CRP、体温及び患者の状態に応じてその必要性を慎重に判断すること。本剤を5日間投与しても効果が認められない場合は漫然と投与を継続せず、他の適切な治療を検討すること。

8. 重要な基本的注意

〈効能共通〉

8.1 本剤投与時のシクロスポリンの吸収は患者により個人差があるので、血中濃度の高い場合の副作用並びに血中濃度の低い場合の拒絶反応の発現等を防ぐため、患者の状況に応じて血中濃度を測定すること。[7.2参照]

8.2 本剤からサンディミュンへの切り換えは、本剤とサンディミュン（内用液又はカプセル）が生物学的に同等ではないことからシクロスポリンの血中濃度が低下するおそれがあるため、このような切り換えは原則として行わないこと。やむを得ず切り換える場合は、血中濃度の測定を頻回に行うとともに患者の状態を十分観察し、必要に応じて投与量を調節すること。[1.3、16.1.1、16.1.2参照]

8.3 本剤はサンディミュン（内用液又はカプセル）と生物学的に同等ではなく、バイオアベイラビリティが向上しており、シクロスポリン含有量が同じでも血中濃度に差があるため、本剤とサンディミュンを同時に用いることは避けること。[16.1.1、16.1.2参照]

8.4 腎・肝・膵機能障害等の副作用が起こることがあるので、頻回に臨床検査（血球数算定、クレアチニン、BUN、ビリルビン、AST、ALT、アミラーゼ、尿検査等）を行うなど、患者の状態を十分に観察すること。[11.1.1、11.1.2、11.1.7参照]

8.5 感染症の発現又は増悪に十分注意すること。[11.1.4参照]

8.6 他の免疫抑制剤と併用する場合は、過度の免疫抑制により感染に対する感受性の上昇、悪性リンパ腫発生の可能性があるので、十分注意すること。[10.2、11.1.11参照]

8.7 本剤の投与により副腎皮質ホルモン剤維持量の減量が可能であるが、副腎皮質ホルモン剤の副作用の発現についても引き続き観察を十分に行うこと。

8.8 血圧上昇があらわれることがあり、可逆性後白質脳症症候群、高血圧性脳症に至ることがあるので、定期的に血圧測定を行い、血圧上昇があらわれた場合には、降圧剤治療を行うなど適切な処置を行うこと。[11.1.3参照]

8.9 低マグネシウム血症により中枢神経系障害があらわれることがあるので、特に移植直後は血清マグネシウム値に注意し、マグネシウム低下がみられた場合にはマグネシウムを補給するなど、適切な処置を行うこと。

〈ベーチェット病〉

8.10 神経ベーチェット病症状（頭痛、発熱、情動失禁、運動失調、錐体外路症状、意識障害、髄液細胞増多等）の誘発又は悪化が報告されているので注意して使用し、経過を十分観察すること。[9.1.7、11.1.12参照]

〈ネフローゼ症候群〉

8.11 特に腎機能検査値（クレアチニン、BUN等）の変動に注意すること。

〈アトピー性皮膚炎〉

8.12 リンパ節腫脹を合併することがあるが、通常は自然に消失するか疾患の改善により消失する。患者の状態を定期的に観察し、本剤によってアトピー性皮膚炎が改善された後にリンパ節腫脹が持続している場合は、悪性リンパ腫の除外診断のため生検を実施することが望ましい。

8.13 活動性単純ヘルペス感染は、本剤投与前に治療しておくことが望ましい。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 膵機能障害のある患者

膵機能が悪化するおそれがある。

9.1.2 高血圧症の患者

血圧の上昇及び症状の悪化が報告されている。

9.1.3 感染症のある患者

免疫抑制により感染症が悪化するおそれがある。

9.1.4 悪性腫瘍又はその既往歴のある患者

免疫抑制により進行又は再発するおそれがある。

9.1.5 PUVA療法を含む紫外線療法中の患者

[10.2参照]

9.1.6 肝炎ウイルスキャリアの患者

肝機能検査値や肝炎ウイルスマーカーのモニタリングを行うなど、B型肝炎ウイルスの再活性化やC型肝炎の悪化の徴候や症状の発現に注意すること。免疫抑制剤を投与されたB型肝炎ウイルスキャリアの患者において、B型肝炎ウイルスの再活性化による肝炎があらわれることがある。また、HBs抗原陰性の患者において、免疫抑制剤の投与開始後にB型肝炎ウイルスの再活性化による肝炎を発症した症例が報告されている。また、C型肝炎ウイルスキャリアの患者において、免疫抑制剤の投与開始後にC型肝炎の悪化がみられることがある。

9.1.7 神経ベーチェット病の患者

治療上やむを得ないと判断される場合を除き、投与しないこと。[8.10参照]

9.2 腎機能障害患者

腎機能が悪化するおそれがあるため、慎重に投与すること。また、コルヒチンを服用中の患者には投与しないこと。[2.3、10.2参照]

9.3 肝機能障害患者

肝機能が悪化し、本剤の代謝あるいは胆汁中への排泄が遅延するおそれがあるため、慎重に投与すること。また、コルヒチンを服用中の患者には投与しないこと。[2.3、10.2参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。動物実験（ラット）で催奇形作用、また、難産及び周産期死亡が報告されている。ヒトで胎盤を通過することが報告されている[1～4]。妊娠中に本剤を投与された女性において、早産及び児への影響（低出生体重、先天奇形）の報告がある[5]。

9.6 授乳婦

授乳しないことが望ましい。母乳中へ移行するとの報告がある。

9.7 小児等

＊**9.7.1** アトピー性皮膚炎患者へは本剤投与による治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。小児等に対する本剤の臨床試験は実施されていない。[1.2参照]

川崎病の急性期患者のうち低出生体重児、新生児又は4ヵ月未満の乳児へは本剤投与による治療上の有益性が危険性を上回ると判断される場合にのみ、患者の状態を十分に観察しながら投与すること。低出生体重児、新生児又は4ヵ月未満の乳児に対する臨床試験は実施していない。

なお、他の適応疾患については、適応患者の選択を慎重に行い、投与する際には患者の状態を十分に観察すること。低出生体重児、新生児又は乳児に対する臨床試験は実施していない。

9.7.2 一般に小児での多毛の発現率（10～18%）は成人（2～6%）に比べ高い傾向がある。

9.7.3 小児のネフローゼ症候群に投与する際には、副作用の発現に十分注意すること。一般に小児と成人の副作用の発現率は同程度（35%前後）であるが、ネフローゼ症候群に対する臨床試験の結果（サンディミュン内用液及びカプセルでの成績）では成人（18～32%）に比べ小児（26～41%）で発現率が高い傾向がみられ、特に小児での多毛（10～18%）、ALP上昇（7%前後）の発現が成人（多毛：2～3%、ALP上昇：1%前後）に比べ高かった。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能（腎機能、肝機能、免疫機能等）が低下している。

10. 相互作用

多くの薬剤との相互作用が報告されているが、可能性のあるすべての組み合わせについて検討されているわけではないので、他剤と併用したり、本剤又は併用薬を休薬する場合には注意すること。本剤は代謝酵素チトクロームP450 3A4（CYP3A4）で代謝され、また、CYP3A4及びP糖蛋白の阻害作用を有するため、これらの酵素、輸送蛋白質に影響する医薬品・食品と併用する場合には、可能な限り薬物血中濃度を測定するなど用量に留意して慎重に投与すること。

10.1 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
生ワクチン （乾燥弱毒生麻しんワクチン、乾燥弱毒生風しんワクチン、経口生ポリオワクチン、乾燥BCG等） [2.4参照]	免疫抑制下で生ワクチンを接種すると発症するおそれがあるので併用しないこと。	免疫抑制下で生ワクチンを接種すると増殖し、病原性をあらわす可能性がある。
タクロリムス（外用剤を除く） （プログラフ） [2.2参照]	本剤の血中濃度が上昇することがある。また、腎障害等の副作用があらわれやすくなるので併用しないこと。	本剤の代謝が阻害されること及び副作用が相互に増強されると考えられる。
ピタバスタチン （リバロ） ロスバスタチン （クレストール） [2.2参照]	これらの薬剤の血中濃度が上昇（ピタバスタチン：Cmax6.6倍、AUC4.6倍、ロスバスタチン：Cmax10.6倍、AUC7.1倍）し、副作用の発現頻度が増加するおそれがある。また、横紋筋融解症等の重篤な副作用が発現するおそれがある。	本剤により、これらの薬剤の血漿中の濃度が上昇する。
ボセンタン （トラクリア） [2.2参照]	ボセンタンの血中濃度が急激に上昇したとの報告があり、副作用が発現するおそれがある。また、本剤の血中濃度が約50%低下したとの報告がある。	本剤が、ボセンタンのCYP3A4による代謝を阻害すること及び輸送蛋白質を阻害し肝細胞への取り込みを阻害することにより、ボセンタンの血中濃度が上昇すると考えられる。また、ボセンタンはCYP3A4を誘導するため、本剤の代謝が促進され、血中濃度が低下すると考えられる。
アリスキレン （ラジレス） [2.2参照]	アリスキレンの血中濃度が上昇するおそれがある。空腹時の併用投与によりアリスキレンのCmaxが約2.5倍、AUCが約5倍に上昇した。	本剤のP糖蛋白阻害によりアリスキレンのP糖蛋白を介した排出が抑制されると考えられる。
アスナプレビル （スンベプラ） [2.2参照]	アスナプレビルの治療効果が減少するおそれがある。	本剤の有機アニオントランスポーター阻害により、これらの薬剤の肝取込みが抑制されると考えられる。
バニプレビル （バニヘップ） グラゾプレビル （グラジナ） [2.2参照]	これらの薬剤の血中濃度が上昇するおそれがある。	
ペマフィブラート （パルモディア） [2.2参照]	ペマフィブラートの血中濃度が上昇したとの報告がある。	本剤の有機アニオントランスポーター及びCYP3A阻害により、ペマフィブラートの血中濃度が上昇すると考えられる。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
PUVA療法を含む紫外線療法 [9.1.5参照]	PUVA療法を含む紫外線療法との併用は皮膚癌発現のリスクを高める危険性があるため、やむを得ず併用する場合は定期的に皮膚癌又は前癌病変の有無を観察すること。	PUVA療法により皮膚癌が発生したとの報告があり、本剤併用による免疫抑制下では皮膚癌の発現を促進する可能性がある。
免疫抑制剤 ムロモナブCD3（OKT3） 抗胸腺細胞免疫グロブリン（ATG）製剤等 [8.6参照]	過度の免疫抑制が起こることがある。	共に免疫抑制作用を有するため。
ホスカルネット アムホテリシンB アミノ糖系抗生物質 ゲンタマイシン トブラマイシン等 スルファメトキサゾール・トリメトプリム シプロフロキサシン バンコマイシン ガンシクロビル フィブラート系薬剤 ベザフィブラート フェノフィブラート等	腎障害があらわれやすくなるので、頻回に腎機能検査（クレアチニン、BUN等）を行うなど患者の状態を十分に観察すること。	腎障害の副作用が相互に増強されると考えられる。
メルファラン注射剤		機序は不明である。
非ステロイド性消炎鎮痛剤 ジクロフェナク ナプロキセン スリンダク インドメタシン等	腎障害があらわれやすくなるので、頻回に腎機能検査（クレアチニン、BUN等）を行うなど患者の状態を十分に観察すること。	腎障害の副作用が相互に増強されると考えられる。
	高カリウム血症があらわれるおそれがあるので、血清カリウム値に注意すること。	高カリウム血症の副作用が相互に増強されると考えられる。

薬剤名等	臨床症状・措置方法	機序・危険因子
アミオダロン カルシウム拮抗剤 　ジルチアゼム 　ニカルジピン 　ベラパミル マクロライド系抗生物質 　エリスロマイシン 　ジョサマイシン等 キヌプリスチン・ダルホプリスチン クロラムフェニコール アゾール系抗真菌剤 　フルコナゾール 　イトラコナゾール 　等 ノルフロキサシン HIVプロテアーゼ阻害剤 　リトナビル 　サキナビル等 コビシスタットを含有する製剤 卵胞・黄体ホルモン剤 ダナゾール ブロモクリプチン アロプリノール フルボキサミン イマチニブ ダサチニブ テラプレビル シメプレビル スチリペントール	本剤の血中濃度が上昇することがあるので、併用する場合には血中濃度を参考に投与量を調節すること。 また、本剤の血中濃度が高い場合、腎障害等の副作用があらわれやすくなるので、患者の状態を十分に観察すること。	代謝酵素の抑制又は競合により、本剤の代謝が阻害されると考えられる。
メトクロプラミド		胃腸運動が亢進し、胃内容排出時間が短縮されるため、本剤の吸収が増加すると考えられる。
アセタゾラミド カルベジロール ヒドロキシクロロキン メトロニダゾール		機序は不明である。
グレープフルーツジュース	本剤の血中濃度が上昇することがあるので、本剤服用時は飲食を避けることが望ましい。	グレープフルーツジュースが腸管の代謝酵素を阻害することによると考えられる。
リファンピシン チクロピジン 抗てんかん剤 　フェノバルビタール 　フェニトイン 　カルバマゼピン モダフィニル デフェラシロクス	本剤の血中濃度が低下することがあるので、併用する場合には血中濃度を参考に投与量を調節すること。特に、移植患者では拒絶反応の発現に注意すること。	これらの薬剤の代謝酵素誘導作用により本剤の代謝が促進されると考えられる。
オクトレオチド ランレオチド パシレオチド プロブコール		これらの薬剤が本剤の吸収を阻害すると考えられる。
テルビナフィン		機序は不明である。
エトラビリン	本剤の血中濃度に影響を与える可能性があるため、注意して投与すること。	エトラビリンの代謝酵素誘導作用により、本剤の血中濃度に変化が起こることがある。
セイヨウオトギリソウ（St. John's Wort，セント・ジョーンズ・ワート）含有食品	本剤の代謝が促進され血中濃度が低下するおそれがあるので、本剤投与時はセイヨウオトギリソウ含有食品を摂取しないよう注意すること。	セイヨウオトギリソウにより誘導された代謝酵素が本剤の代謝を促進すると考えられる。
副腎皮質ホルモン剤	高用量メチルプレドニゾロンとの併用により本剤の血中濃度上昇及び痙攣の報告がある。また、プレドニゾロンのクリアランスを低下させるとの報告もある。	相互に代謝を阻害すると考えられる。

薬剤名等	臨床症状・措置方法	機序・危険因子
ドセタキセル パクリタキセル	本剤又はこれらの薬剤の血中濃度が上昇する可能性があるので、併用する場合には血中濃度を参考に投与量を調節すること。	代謝酵素を競合することにより、本剤又はこれらの薬剤の代謝が阻害される可能性がある。
＊レテルモビル		レテルモビルのCYP3A阻害により本剤の血中濃度が上昇する可能性がある。また、本剤の有機アニオントランスポーター阻害によりレテルモビルの血中濃度が上昇する可能性がある。
エゼチミブ		機序は不明である。
オムビタスビル・パリタプレビル・リトナビル	本剤又はパリタプレビルの血中濃度が上昇する可能性があるので、併用する場合には血中濃度を参考に投与量を調節すること。	リトナビルのCYP3A4阻害及びパリタプレビルの有機アニオントランスポーター阻害により本剤の血中濃度が上昇すると考えられる。 本剤の有機アニオントランスポーター、乳癌耐性蛋白及びP糖蛋白阻害により、パリタプレビルの血中濃度が上昇すると考えられる。
コルヒチン [2.3、9.2、9.3参照]	本剤の血中濃度が上昇することがあるので、併用する場合には血中濃度を参考に投与量を調節すること。	機序は不明である。
	コルヒチンの血中濃度が上昇し、コルヒチンの作用が増強するおそれがあるので、患者の状態を十分に観察すること。なお、肝臓又は腎臓に障害のある患者にはコルヒチンを投与しないこと。	本剤のP糖蛋白阻害によりコルヒチンの血中濃度が上昇することがある。
トルバプタン チカグレロル レンバチニブ	これらの薬剤の血中濃度が上昇し、作用が増強するおそれがある。	本剤のP糖蛋白阻害によりこれらの薬剤の血中濃度が上昇することがある。
ダビガトラン エドキサバン	これらの薬剤の血中濃度が上昇し、抗凝固作用が増強するおそれがある。	本剤のP糖蛋白阻害によりこれらの薬剤の血中濃度が上昇することがある。
リファキシミン	リファキシミンの血中濃度が上昇し、作用が増強するおそれがある。	本剤のP糖蛋白、CYP3A4、有機アニオントランスポーター阻害によりリファキシミンの血中濃度が上昇することがある。
リオシグアト	リオシグアトの血中濃度が上昇するおそれがある。	P糖蛋白及び乳癌耐性蛋白阻害によりリオシグアトの血中濃度が上昇することがある。
グレカプレビル・ピブレンタスビル	これらの薬剤の血中濃度が上昇したとの報告がある。	本剤の有機アニオントランスポーター、P糖蛋白及び乳癌耐性蛋白阻害により、これらの薬剤の血中濃度が上昇すると考えられる。
レパグリニド	レパグリニドの血中濃度が上昇し、血糖降下作用が増強するおそれがある。	本剤が、レパグリニドのCYP3A4による代謝を阻害すること及び輸送蛋白質を阻害し肝細胞への取り込みを阻害することにより、レパグリニドの血中濃度が上昇すると考えられる。

薬剤名等	臨床症状・措置方法	機序・危険因子
カスポファンギン	カスポファンギンのAUCが増加したとの報告がある。また、併用により一過性のAST及びALTの増加が認められたとの報告がある。本剤が投与されている患者へのカスポファンギンの投与は、治療上の有益性が危険性を上回ると判断される場合のみとし、併用する場合は、肝酵素の綿密なモニタリングを考慮すること。	本剤がカスポファンギンの肝細胞への取り込みを抑制することによると考えられる。
HMG-CoA還元酵素阻害剤 シンバスタチン プラバスタチン等	筋肉痛、CK上昇、血中及び尿中ミオグロビン上昇を特徴とした急激な腎機能悪化を伴う横紋筋融解症があらわれやすいので、患者の状態を十分に観察すること。	HMG-CoA還元酵素阻害剤の血中からの消失が遅延すると考えられる。
ジゴキシン	ジゴキシンの血中濃度が上昇することがあるので、ジゴキシンの血中濃度を参考に投与量を調節するなどジギタリス中毒に注意すること。	ジゴキシンの腎からの排泄を抑制すると考えられる。
	高カリウム血症があらわれるおそれがあるので、血清カリウム値に注意すること。	高カリウム血症の副作用が相互に増強されると考えられる。
アンブリセンタン	本剤との併用によりアンブリセンタンの血中濃度が上昇しAUCが約2倍になるとの報告がある。	機序は不明である。
テオフィリン	テオフィリンの血中濃度が上昇するとの報告があるので、テオフィリンの血中濃度を参考に投与量を調節すること。	機序は不明である。
不活化ワクチン 不活化インフルエンザワクチン等	ワクチンの効果が得られないおそれがある。	免疫抑制作用によってワクチンに対する免疫が得られないおそれがある。
ニフェジピン	歯肉肥厚があらわれやすい。	歯肉肥厚の副作用が相互に増強されると考えられる。
カリウム保持性利尿剤 スピロノラクトン等 エプレレノン カリウム製剤 ACE阻害剤 アンジオテンシンⅡ受容体拮抗剤 β-遮断剤 ヘパリン	高カリウム血症があらわれるおそれがあるので、血清カリウム値に注意すること。	高カリウム血症の副作用が相互に増強されると考えられる。
利尿剤 チアジド系利尿剤 フロセミド等	高尿酸血症及びこれに伴う痛風があらわれやすいので、血中尿酸値に注意すること。	高尿酸血症の副作用が相互に増強されると考えられる。
ブロナンセリン ナルフラフィン	これらの薬剤の血中濃度が上昇し、作用が増強するおそれがある。	代謝酵素の競合により、これらの薬剤の代謝が阻害されると考えられる。
エベロリムス	エベロリムスのバイオアベイラビリティが有意に増加したとの報告がある。本剤の用量を変更する際には、エベロリムスの用量調節も行うこと。	代謝酵素の競合により、エベロリムスの代謝が阻害されると考えられる。
	エベロリムスが本剤の腎毒性を増強するおそれがある。	機序は不明である。
ミコフェノール酸モフェチル	ミコフェノール酸モフェチルの血中濃度が低下したとの報告がある。	ミコフェノール酸モフェチルの腸肝循環が阻害され血中濃度が低下すると考えられる。
アメナメビル	アメナメビルの血中濃度が低下し、作用が減弱するおそれがある。	機序は不明である。
外用活性型ビタミンD_3製剤 タカルシトール カルシポトリオール	血清カルシウム値が上昇する可能性がある。	本剤による腎機能低下があらわれた場合に、活性型ビタミンD_3による血清カルシウム値上昇がよりあらわれやすくなると考えられる。
エルトロンボパグ	エルトロンボパグの血中濃度が低下したとの報告[6]及び高値を示したとの報告[7]がある。	機序は不明である。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

〈効能共通〉

11.1.1 腎障害（5%以上）

腎機能障害は本剤の副作用として高頻度にみられる。主な発現機序は用量依存的な腎血管収縮作用によると考えられ、通常、減量又は休薬により回復する。BUN上昇、クレアチニン上昇を示し腎血流量減少、糸球体濾過値の低下がみられる。尿細管機能への影響としてカリウム排泄減少による高カリウム血症、尿酸排泄低下による高尿酸血症、マグネシウム再吸収低下による低マグネシウム血症がみられる。また、器質的な腎障害（尿細管萎縮、細動脈病変、間質の線維化等）があらわれることがある。移植後の大量投与や、腎疾患のある患者への使用あるいは腎毒性のある薬剤［10.1、10.2参照］との併用により起こりやすい。なお、腎移植後にクレアチニン、BUNの上昇がみられた場合は、本剤による腎障害か拒絶反応かを注意深く観察し、鑑別する必要がある。［8.4参照］

11.1.2 肝障害、肝不全（1%～5%未満）

肝機能障害、黄疸等の肝障害、肝不全があらわれることがあるので、AST、ALT、ALP、LDH、ビリルビンの上昇等の異常が認められた場合には、減量又は投与を中止するなど適切な処置を行うこと。［8.4参照］

11.1.3 可逆性後白質脳症症候群、高血圧性脳症等の中枢神経系障害（1%未満）

全身痙攣、意識障害、失見当識、錯乱、運動麻痺、小脳性運動失調、視覚障害、視神経乳頭浮腫、不眠等の症状があらわれた場合には、CT、MRIによる画像診断を行うとともに、本剤を減量又は中止し、血圧のコントロール、抗痙攣薬の投与等適切な処置を行うこと。［8.8参照］

11.1.4 感染症（1%～5%未満）

細菌、真菌あるいはウイルスによる重篤な感染症（肺炎、敗血症、尿路感染症、単純疱疹、帯状疱疹等）を併発することがある。アトピー性皮膚炎患者で黄色ブドウ球菌による皮膚感染を併発した場合は、適切な抗菌剤によってコントロールすること。また、B型肝炎ウイルスの再活性化による肝炎やC型肝炎の悪化があらわれることがある。強力な免疫抑制下では急激に重症化することがある。［8.5参照］

11.1.5 進行性多巣性白質脳症（PML）（頻度不明）

本剤の治療期間中及び治療終了後は患者の状態を十分に観察し、意識障害、認知障害、麻痺症状（片麻痺、四肢麻痺）、言語障害等の症状があらわれた場合は、MRIによる画像診断及び脳脊髄液検査を行うとともに、投与を中止し、適切な処置を行うこと。

11.1.6 BKウイルス腎症（頻度不明）

11.1.7 急性膵炎（1%未満）

初期症状として上腹部の激痛、発熱、血糖上昇、アミラーゼ上昇等があらわれることがあるので、このような場合には減量又は投与を中止し、適切な処置を行うこと。[8.4参照]

11.1.8 血栓性微小血管障害

溶血性尿毒症症候群（HUS：血小板減少、溶血性貧血、腎不全を主徴とする）（1%未満）、血栓性血小板減少性紫斑病（TTP）様症状（血小板減少、微小血管性溶血性貧血、腎機能障害、精神神経症状を主徴とする）（頻度不明）等の血栓性微小血管障害があらわれることがある。

11.1.9 溶血性貧血、血小板減少（各1%未満）

11.1.10 横紋筋融解症（1%未満）

筋肉痛、脱力感、CK上昇、血中及び尿中ミオグロビン上昇を特徴とする横紋筋融解症があらわれることがあるので、このような場合には減量又は投与を中止し、適切な処置を行うこと。

11.1.11 悪性腫瘍（1%未満）

他の免疫抑制剤と併用する場合に、過度の免疫抑制により悪性リンパ腫、リンパ増殖性疾患、悪性腫瘍（特に皮膚）の発現の可能性が高まることがある。[8.6参照]

〈ベーチェット病〉

11.1.12 神経ベーチェット病症状（1%～5%未満）

神経ベーチェット病症状（頭痛、発熱、情動失禁、運動失調、錐体外路症状、意識障害、髄液細胞増多等）が誘発又は悪化することがあるので、このような場合には減量又は投与を中止するなど適切な処置を行うこと。[8.10参照]

〈全身型重症筋無力症〉

11.1.13 クリーゼ（頻度不明）

使用に際しては患者の状態をよく観察し、このような症状があらわれた場合には人工呼吸器等の適切な処置を行うこと。

11.2 その他の副作用

	5%以上	1%～5%未満	1%未満	頻度不明
過敏症	-	-	発疹	-
循環器	-	血圧上昇	-	-
血液	-	-	貧血、白血球減少	-
消化器	-	悪心・嘔吐	消化管潰瘍、腹痛、胃部不快感、食欲不振、下痢、腹部膨満感	-
皮膚	多毛	-	脱毛、ざ瘡	-
精神神経系	-	振戦	頭痛、しびれ、めまい、眠気、異常感覚、末梢神経障害	片頭痛
代謝異常	-	糖尿・高血糖、高尿酸血症、高脂血症	高カリウム血症、低マグネシウム血症、体液貯留	-
感覚器	-	-	耳鳴、難聴	視力障害
筋骨格系	-	-	ミオパシー、筋痛、筋脱力、筋痙攣、関節痛	下肢痛
その他	-	歯肉肥厚	出血傾向（鼻出血、皮下出血、消化管出血、血尿）、熱感、のぼせ、発熱、けん怠感、浮腫、体重増加、女性化乳房	月経障害、良性頭蓋内圧亢進症

ネオーラル内用液・カプセル、サンディミュン内用液・カプセル・注射液に関する使用成績調査を含む。

13. 過量投与

13.1 症状

悪心・嘔吐、傾眠、頭痛、頻脈、血圧上昇、腎機能低下等

13.2 処置

服用後短時間であれば催吐、活性炭投与、胃洗浄が有効である。シクロスポリンの血中濃度と症状の程度に相関性がみられるので、血中濃度をモニターし、必要により対症療法を行う。シクロスポリンは透析によりほとんど除去されない。

14. 適用上の注意

14.1 薬剤交付時の注意

PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 循環器障害：本剤との因果関係は確立されていないが、心不全等の重篤な循環器障害があらわれたとの報告がある。

15.1.2 長期にわたりPUVA療法を受けていた乾癬又はアトピー性皮膚炎患者に本剤を投与する場合、皮膚癌の発現リスクが増大する可能性があるので患者の皮膚の状態に注意すること。

15.1.3 海外でネフローゼ症候群の患者において、クレアチニンの上昇を伴わない腎臓の組織変化が報告されているので、本剤を1年以上の長期にわたり使用する際には、腎臓の組織学的検査を行うことが望ましい。

15.1.4 血中濃度測定用採血：血中濃度測定のための血液採取は末梢血を用いること。骨髄移植で中心静脈カテーテルによるルート採血を行った場合、その全血中シクロスポリン濃度は、末梢血中の濃度に比べて高いとの報告がある。

15.2 非臨床試験に基づく情報

15.2.1 ラットで、精細管障害を示す組織像（40mg/kg、経口投与）、精子運動能の低下（20mg/kg、経口投与）、精子数減少、精子運動能及び妊孕性の低下（1mg/kg、皮下投与）が認められたとの報告がある。

16. 薬物動態

16.1 血中濃度

16.1.1 移植後腎機能の安定した18例の腎移植患者に、それまで服用していたサンディミュンと同量の本剤又はサンディミュンをクロスオーバー法で投与した時（1日2回12時間毎）、全血中シクロスポリン濃度をRIA法により測定して比較した結果、単位投与量当たりの薬物動態パラメータは、表のとおりであった[8]。[1.3、7.1、8.2、8.3参照]

パラメータ	ネオーラル	サンディミュン	変化率（%）
$AUC_{0\text{-}12hr}$/Dose (ng·hr/mL/mg)	34.4±11.14	29.4±14.19	22.7±20.8
Cmax/Dose（ng/mL/mg）	11.00±2.944	8.61±4.701	45.6±47.9
Cmin/Dose（ng/mL/mg）	0.749±0.427	0.701±0.420	8.8±17.0
Tmax（hr）	1.1±0.21	1.6±1.57	-12.9±31.0

（平均値±S.D.）

16.1.2 サンディミュンで維持療法中の腎移植患者で、サンディミュンに吸収不良を示す20例に、それまで服用していたサンディミュンと同量の本剤又はサンディミュンをクロスオーバー法で投与した時（1日2回12時間毎）、全血中シクロスポリン濃度をRIA法により測定して比較した結果、単位投与量当たりの薬物動態パラメータは表のとおりであった[9]。（吸収不良例：dose normalized $AUC_{1\text{-}5hr}$が10ng・hr/mL/mg以下を参考基準値として症例検討会で判定）[1.3、7.1、8.2、8.3参照]

パラメータ	ネオーラル	サンディミュン	変化率（%）
$AUC_{0\text{-}12hr}$/Dose (ng·hr/mL/mg)	32.2±8.3	17.4±6.8	105.6±74.5
Cmax/Dose（ng/mL/mg）	10.49±3.00	3.93±1.87	248.6±239.8
Cmin/Dose（ng/mL/mg）	0.77±0.26	0.58±0.23	38.3±26.9
Tmax（hr）	1.4±0.5	2.4±1.1	-32.9±27.8

（平均値±S.D.）

16.2 吸収

本剤はサンディミュンと比較して胆汁分泌量や食事による影響を受けにくいとの報告がある[10,11]。

16.4 代謝

シクロスポリンは主としてチトクロームP450 3A4（CYP3A4）で代謝され、主要代謝物はモノヒドロキシ体、ジヒドロキシ体、N-脱メチル体であった[12~14]（外国人のデータ）。

16.5 排泄

シクロスポリンは主として胆汁を介して排泄される。腎機能が保たれている患者に^{3}H－シクロスポリンを経口投与した場合、尿中排泄率は6%で、未変化体としては投与量の0.1%であった（96時間値）[15]（外国人のデータ）。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈腎移植〉

17.1.1 国内臨床試験

新規投与例（生体腎47例、死体腎15例）における1年生着率及び生存率（Kaplan-Meier法）は、生体腎で94.8%及び100%、死体腎で93.3%及び100%であった。拒絶反応が発現した症例は、生体腎では51.1%（24例/47例）、死体腎では53.3%（8例/15例）であった。サンディミュンからの切り換え例では、検討した55例全体で移植腎の生着が維持された[16,17]。

〈肝移植〉

17.1.2 国内臨床試験

サンディミュンではシクロスポリンの血中濃度が不安定な患者12例及びタクロリムスの治療継続に問題がある患者8例を対象とし、それら薬剤からの切り換え試験を実施した結果、本剤の肝移植患者への使用に臨床上問題となる所見はなかった[18~20]。

〈心移植〉

17.1.3 外国臨床試験

ネオーラルとサンディミュンの新規心移植患者を対象とした多施設二重盲検群間比較試験における移植後6ヵ月までの成績では、国際心肺移植学会（ISHLT）の重症度基準でグレード3A以上の拒絶反応発現率は、ネオーラル群42.6%（80例/188例）、サンディミュン群41.7%（80例/192例）であった。また、生存率はネオーラル群93.1%（175例/188例）、サンディミュン群92.7%（178例/192例）であった。移植後6ヵ月までに7.1%（27例/380例）の患者が死亡したが、その主な原因は移植臓器廃絶（12例）、敗血症（4例）、悪性腫瘍（2例）であった[21]。

17.1.4 外国臨床試験

心移植患者139例の3剤併用療法（シクロスポリン＋アザチオプリン＋ステロイド）による長期成績では、急性拒絶反応は21例に25回（患者当たり0.18回）と従来の治療法（シクロスポリン＋ステロイド、患者当たり0.84回）に比べ発現頻度の減少がみられた。また、1年生存率は92%、3年生存率は85%、5年生存率は78%であった。一方、長期の安全性については従来の治療法に比べ、感染症、悪性腫瘍の発現率の低下を認めた[22]。

〈肺移植〉

17.1.5 外国臨床試験

片肺移植患者73例及び両肺移植患者58例の計131例における1年生存率は、それぞれ87%及び76%、2年生存率はそれぞれ87%及び73%であった。入院中に8%（11例/131例）の患者が死亡したが、その原因は敗血症（3例）、心臓病（3例）、アスペルギルス感染（2例）、原因不明の成人呼吸窮迫症候群（2例）、気道合併症（1例）であった[23]。

17.1.6 外国臨床試験

片肺又は両肺移植患者44例をATG（抗胸腺細胞免疫グロブリン）群（シクロスポリン＋アザチオプリン＋ステロイド＋ATG）と非ATG群（シクロスポリン＋アザチオプリン＋ステロイド）に無作為に割り付け比較検討した結果、肺生検によるグレードⅡ以上の急性拒絶反応の発現率は、ATG群で23%（5例/22例）、非ATG群で55%（12例/22例）とATG群で有意（p＝0.03）に少なかった。また、1年及び2年生存率はATG群で68%及び64%、非ATG群では73%及び68%であった。一方、移植後の感染症あるいは悪性腫瘍の発現率は両群で同様であった[24]。

〈膵移植〉

17.1.7 外国臨床試験

膵腎同時移植患者476例の1年、5年及び10年生存率は、それぞれ96.5%、88.9%及び79.5%であった。また、移植膵の1年、5年及び10年生着率は、それぞれ87.9%、78.9%及び68.4%、移植腎では、それぞれ88.4%、81.0%及び63.5%であった。移植後の死亡の主な原因は、心又は脳血管障害（46%）、敗血症（16%）、悪性腫瘍（13%）であった[25]。

17.1.8 外国臨床試験

膵腎同時移植患者50例をATG群（シクロスポリン＋アザチオプリン＋ステロイド＋ATG）と非ATG群（シクロスポリン＋アザチオプリン＋ステロイド）に無作為に割り付け比較検討した結果、移植後1年までの移植膵に対する急性拒絶反応は両群ともなく、移植腎に対する急性拒絶反応はATG群36%（9例/25例）、非ATG群76%（19例/25例）とATG群で有意（p＜0.01）に少なかった[26]。

〈小腸移植〉

17.1.9 外国臨床試験

海外において、小腸移植におけるシクロスポリンの拒絶反応の抑制効果に関して報告されている[27,28]。

〈骨髄移植〉

17.1.10 国内臨床試験

新規投与例に対して、サンディミュン注射剤及び本剤を投与して検討した結果、グレード2以上の急性移植片対宿主反応（GVHD）の累積発症率（Kaplan-Meier法）は血縁での移植で22.3%、非血縁で26.7%であった[29]。

〈ベーチェット病〉

17.1.11 国内臨床試験

新規投与例（16例）での検討では、改善率（「改善」以上）は81.3%（13例/16例）であった[30]。

〈乾癬〉

17.1.12 国内臨床試験

新規投与例（16例）の全例で皮疹の改善効果が認められた。サンディミュンからの切り換え例での検討では、27例全例で効果が維持された[31,32]。

〈再生不良性貧血、赤芽球癆〉

17.1.13 国内臨床試験

重症再生不良性貧血、赤芽球癆患者への新規投与の5例では、再生不良性貧血の1例で「Minimal response」、赤芽球癆の1例で輸血状況に著明改善がみられた。サンディミュンからの切り換え例（19例）では、18例で減量・休薬を要さず臨床効果は維持された[33]。

17.1.14 国内第Ⅱ/Ⅲ相試験

中等症以上のATG未治療の再生不良性貧血患者を対象としたエルトロンボパグの国内臨床試験において、ATG、シクロスポリン及びエルトロンボパグの3剤を併用した結果、奏効率は70.0%（7例/10例）であった。なお、奏効率は寛解（輸血非依存かつ血球数の改善）が得られた患者の割合と定義した[34]。

17.1.15 国内第Ⅱ/Ⅲ相試験

中等症以上かつ血小板数30,000/μL未満のATG治療を受けたが治療抵抗性若しくは再発又はATG治療が受けられない再生不良性貧血患者を対象としたエルトロンボパグの国内臨床試験において、シクロスポリン投与中の患者の75.0%（6例/8例）に投与開始26週時に血液学的反応率の改善が認められた。なお、血液学的反応率は1系統以上の血球に改善［血小板数が≥20,000/μL増加又は血小板輸血非依存、ヘモグロビン値が≥1.5g/dL増加（投与前値が9g/dL未満の場合）又は赤血球輸血量の減少、好中球数が≥

100%（投与前値が500/μL未満の場合）又は≥500/μL増加のうち、1つ以上該当］を認めた患者の割合と定義した[7]。

〈ネフローゼ症候群〉

17.1.16 国内臨床試験

新規投与例では、頻回再発型患者で改善率（「改善」以上）が69.2%（9例/13例）、ステロイド抵抗性患者で改善率が75.0%（9例/12例）であった。サンディミュンからの切り換え例では、頻回再発型患者の18例、ステロイド抵抗性患者の13例のいずれの症例でも効果が維持された[35]。

〈アトピー性皮膚炎〉

17.1.17 国内第Ⅲ相試験

成人の最重症のアトピー性皮膚炎患者を対象に、ネオーラル3mg/kg/日（2～5mg/kg/日）を1日2回に分けて8週間経口投与するプラセボとの比較試験を実施した。最終重症度スコアのベースラインからの変化率の群間差（ネオーラル群−プラセボ群、以下同様）の平均値（95%信頼区間）は−30.3%（−41.1%～−19.6%）であり、投与群間に有意差が認められた（p＜0.001、対応のないt検定）。また、最終罹病範囲スコアのベースラインからの変化率の群間差の平均値（95%信頼区間）は−21.8%（−32.8%～−10.9%）であり、投与群間に有意差が認められた（p＜0.001、対応のないt検定）。以上より、ネオーラル群のプラセボ群に対する有意な重症度及び罹病範囲スコア改善が検証された[36]。

評価項目 投与群	例数	ベースライン 平均値±S.D.	ベースラインからの変化率 平均値±S.E.	変化率の群間差 平均値	95%信頼区間	p値
重症度スコア						
ネオーラル群	44	54.0±16.30	−63.0±3.43	−30.3	(−41.1～−19.6)	<0.001
プラセボ群	45	51.1±16.13	−32.6±4.18			
罹病範囲スコア						
ネオーラル群	44	74.2±14.60	−41.4±4.08	−21.8	(−32.8～−10.9)	<0.001
プラセボ群	45	69.0±12.75	−19.5±3.71			

重症度スコア：4項目の臨床所見（紅斑・浮腫（浸潤）、丘疹、湿潤、痒疹・苔癬化）を8ヵ所の身体部分ごとに4段階（0−3）で点数化（最大値96）
罹病範囲スコア：8ヵ所の身体部分（全身に対する比率）ごとに4段階（0、1/3、2/3、3/3）で点数化（最大値100）

〈川崎病の急性期〉

＊17.1.18 国内第Ⅲ相試験

川崎病の静注用免疫グロブリン不応予測患者を対象に、免疫グロブリンの静脈内投与とアスピリンの経口投与の併用群（IVIG群）と、IVIG群の治療に加えて、ネオーラル5mg/kg/日（原則として投与3日目の1回目投与直前に血中トラフ値を測定し、60～200ng/mLを目標として投与量の調節を可能とした）を1日2回に分けて5日間経口投与する群（ネオーラル群）との非盲検比較試験を実施した。主要評価項目である冠動脈病変の合併割合は、IVIG群の31.0%（27例/87例）に対し、ネオーラル群は14.0%（12例/86例）であり、ネオーラル群で有意に低かった（Mantel-Haenszel 検定、p=0.0101）。初期治療反応例のうち再燃※例の割合は、IVIG群13.0%（7例/54例）、ネオーラル群32.4%（23例/71例）であった。副作用発現頻度は、ネオーラル群では13.8%（12例/87例）であった。主な副作用は、ネオーラル群では蕁麻疹3.4%（3例/87例）、及び川崎病3.4%（3例/87例）であった[37]。［7.2.3参照］

※IVIG投与の開始時点から48時間後に体温37.5℃未満となった後、再び川崎病の主要症状の発現とともに発熱し、他の発熱性疾患が否定的であった場合

17.2 製造販売後調査等

〈腎移植〉

17.2.1 特別調査

サンディミュンから本剤への切り換え症例における切り換え後の副作用発現率は4.71%（13例/276例）で、特異的な副作用の発現は認めなかった。切り換え後の血中トラフ値測定時の1日平均投与量は174.10±3.38mg/日（3.18±0.07mg/kg/日）から165.55±2.78mg/日（3.00±0.05mg/kg/日）と有意に低下した（p＜0.001）。切り換え後の血中トラフ値も有意に低下した（p＜0.05）が、AUC、Cmaxに有意差は認められなかった。また、切り換え症例における移植腎の生着を有効とした有効率は99.6%（275例/276例）であった[38]。

項目	症例数	切り換え前 （平均値±S.E.）	切り換え後 （平均値±S.E.）
血中トラフ値（ng/mL）	262	97.80±2.56	91.96±2.51※
Cmax（ng/mL）	41	502.91±43.20	546.69±30.41
AUC（ng･h/mL）	10	1,471.46±329.77	1,411.06±235.94

※p＜0.05（t検定：切り換え前と切り換え後の比較）

18. 薬効薬理

18.1 作用機序

本剤の作用機序は直接的な細胞障害性によるものではなく、リンパ球に対し特異的かつ可逆的に作用し、強力な免疫抑制作用を示す。本剤は主にヘルパーT細胞の活性化を抑制するが、サプレッサーT細胞の活性化を阻害しないことが示されている。

本剤はT細胞においてシクロフィリンと複合体を形成し、T細胞活性化のシグナル伝達において重要な役割を果たしているカルシニューリンに結合し、カルシニューリンの活性化を阻害する。これによって脱リン酸化による転写因子NFATの細胞質成分の核内移行が阻止され、インターロイキン-2に代表されるサイトカインの産生が抑制される。

18.2 マイトジェン刺激によるリンパ球増殖抑制作用

本剤は種々のマイトジェンにより刺激活性化されたリンパ球の増殖反応を抑制する（マウス脾細胞 *in vitro*）。

18.3 インターロイキン-2等のサイトカイン産生抑制作用

本剤はT細胞増殖因子であるインターロイキン-2等のサイトカインの産生を抑制することが示されている（マウス脾細胞 *in vitro*、*ex vivo*）。

18.4 ヘルパーT細胞に対する選択的抑制作用

本剤は主として、ヘルパーT細胞の活性化を抑制するが、サプレッサーT細胞の活性化を阻害しないことが示されている（ヒト末梢血リンパ球 *in vitro*）。

18.5 移植モデルへの作用

本剤は動物において、腎（ウサギ、イヌ）、肝（イヌ）、骨髄（ウサギ、ラット）、心（ブタ）、肺（イヌ）、膵（イヌ）、小腸（イヌ）の同種移植片の生着又は生存期間を延長させ、骨髄移植における移植片対宿主反応の予防（ウサギ）及び治療（ラット）効果を示す。

18.6 実験的自己免疫性ブドウ膜炎（EAU）への作用

本剤は網膜可溶性抗原（S抗原）によって引き起こされる実験的自己免疫性ブドウ膜炎（EAU）の発症及び免疫反応を抑制することが示されている（ラット）。

18.7 乾癬患者皮膚移植ヌードマウスへの作用

乾癬患者の皮膚をヌードマウスに移植すると非投与対照マウスでは錯角化、表皮肥厚、乳頭腫症などの乾癬特有の組織所見を示すのに対し、本剤投与マウスではこれらの組織学的特徴を示さない。

18.8 再生不良性貧血改善作用

再生不良性貧血患者骨髄細胞より樹立したTリンパ球クローンは造血前駆細胞の*in vitro*におけるコロニー形成を抑制し、本剤はこのTリンパ球クローンによるコロニー形成抑制を緩和した。

18.9 抗GBM腎炎モデルへの作用

本剤は抗糸球体基底膜（GBM）抗体投与により作成した腎炎モデルラットにおいて尿中蛋白排泄、尿中NAG活性、血清コレステロール値を低下させ、腎臓の組織所見を改善させる。この作用は白血球サブセットの糸球体浸潤の抑制並びに抗体産生の抑制によることが示唆されている。

18.10 アトピー性皮膚炎モデルへの作用

本剤をアトピー性皮膚炎モデルマウス（NC/Ngaマウス）に経口投与した試験において、対照群に比べて皮膚炎スコアが有意な低値を示した。また、そう痒行動回数は対照群と比較すると本剤投与群で低値を示す傾向が認められた。病理組織学的検査では対照群と比較して表皮のびらん・潰瘍の病変程度が総じて軽度であった。

19．有効成分に関する理化学的知見

一般的名称

シクロスポリン（Ciclosporin）

化学名

cyclo｛-［(*2S*,*3R*,*4R*,*6E*)-3-Hydroxy-4-methyl-2-methylaminooct-6-enoyl］-L-2-aminobutanoyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-｝

分子式

$C_{62}H_{111}N_{11}O_{12}$

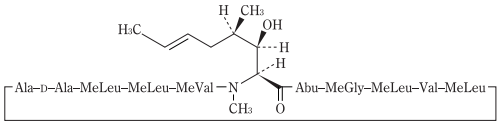
分子量

1202.61

性状

白色の粉末で、アセトニトリル、メタノール又はエタノール（95）に極めて溶けやすく、ジエチルエーテルに溶けやすく、水にほとんど溶けない。

化学構造式



Abu＝(2*S*)-2-アミノ酪酸
MeGly＝*N*-メチルグリシン
MeLeu＝*N*-メチルロイシン
MeVal＝*N*-メチルバリン

20．取扱い上の注意

〈内用液〉

約20℃以下で保存するとゼリー状になることがある。その場合には20℃以上の室温にて溶解後使用すること。

〈カプセル〉

吸湿によりカプセルが軟化したり、含有するエタノールが揮発することがあるので、服用直前までPTP包装のまま保存すること。

22．包装

〈ネオーラル内用液10%〉

50mL［1瓶］

〈ネオーラル10mgカプセル〉

100カプセル［10カプセル（両面アルミニウムPTP）×10］

〈ネオーラル25mgカプセル〉

100カプセル［5カプセル（両面アルミニウムPTP）×20］

〈ネオーラル50mgカプセル〉

100カプセル［5カプセル（両面アルミニウムPTP）×20］

23．主要文献

1）Baxi, L.V. et al.：Am. J. Obstet. Gynecol. 1993;169（1）:33-34 ［20180291］
2）Burrows, D.A. et al.：Obstet. Gynecol. 1988 ;72（3）:459-461 ［20180292］
3）Lowenstein, B.R. et al.：Am. J. Obstet. Gynecol. 1988;158（3）: 589-590 ［20180293］
4）Flechner,S.M. et al.：Am. J. Kidney Dis. 1985 ;5（1）: 60-63 ［19966522］
5）Coscia, L.A. et al.：Best Pract. Res. Clin. Obstet. Gynaecol. 2014;28（8）:1174-1187 ［20180295］
6）社内資料：エルトロンボパグとシクロスポリンの薬物相互作用（201583試験） ［20160747］
7）社内資料：国内第Ⅱ/Ⅲ相臨床試験（ETB115E1201試験） ［20170501］
8）高原史郎ほか：今日の移植.1999;12（Suppl.）:5-24 ［20000066］
9）高原史郎ほか：今日の移植.1999;12（Suppl.）:25-41 ［20000067］
10）社内資料：肝移植患者における安全性、耐容性及び薬物動態学的プロフィール ［20000085］
11）社内資料：高脂肪食の薬物動態に対する影響 ［20000086］
12）Kronbach,T.et al.：Clin.Pharmacol.Ther.1988;43（6）:630-635 ［20000317］
13）Combalbert,J.et al.：Drug Metab.Dispos.1989;17（2）:197-207 ［19966834］
14）Wood,A.J.et al.：Transplant.Proc.1983;15（4）（Suppl.1/2）:2409-2412 ［20049036］
15）Beveridge,T.：Cyclosporin A；Pharmacokinetics and metabolism of Cyclosporin A.1982;35-44 ［19966455］
16）打田和治ほか：今日の移植.1999;12（Suppl.）:65-77 ［20000069］
17）大島伸一ほか：今日の移植.1999;12（Suppl.）:43-64 ［20000068］
18）橋倉泰彦ほか：今日の移植.1999;12（Suppl.）:99-107 ［20000072］
19）橋倉泰彦ほか：今日の移植.1999;12（Suppl.）:109-115 ［20000073］
20）猪股裕紀洋ほか：今日の移植.1999;12（Suppl.）:117-123 ［20000074］
21）Eisen,H.J.et al.：Transplantation.1999;68（5）:663-671 ［20006172］
22）Olivari,M.T.et al.：Circulation.1990 ;82（5/Suppl.IV）:276-280 ［20006173］
23）Cooper,J.D.et al.：J.Thorac.Cardiovasc.Surg.1994;107（2）:460-471 ［20006174］
24）Palmer,S.M.et al.：Chest.1999;116（1）:127-133 ［20006368］
25）Odorico,J.S.et al.：Clinical Transplants.1997;1998:157-166 ［20006175］
26）Cantarovich,D.et al.：Kidney Int.1998;54（4）:1351-1356 ［20006369］
27）Grant,D.et al.：Lancet.1990 ; 335 :181-184 ［20006176］
28）Jan,D.et al.：J.Pediatr.Surg.1999 ;34（5）:841-844 ［20123825］
29）村田誠ほか：今日の移植.1999;12（Suppl.）:87-98 ［20000071］
30）Fujino,Y.et al.：Jpn.J.Ophthalmol.1999;43（4）:318-326 ［19995252］
31）原田昭太郎ほか：西日本皮膚科.1998;60（6）:832-841 ［19990057］
32）原田昭太郎ほか：西日本皮膚科.1998;60（6）:842-848 ［19990058］
33）溝口秀昭ほか：Biotherapy.1998;12（11）:1459-1472 ［19986782］
34）社内資料：国内第Ⅱ/Ⅲ相臨床試験（ETB115E1202試験） ［20170502］
35）小山哲夫ほか：腎と透析.1998;45（6）:823-836 ［19990014］
36）ネオーラルによるアトピー性皮膚炎治療研究会：臨床皮膚科.2009;63（1）:73-82 ［20090397］
＊37）社内資料：国内第Ⅲ相臨床試験（CHI-CsA-004試験）［20190564］
38）社内資料：ネオーラルの腎移植に対する特別調査 ［20085663］

24．文献請求先及び問い合わせ先

ノバルティスファーマ株式会社　ノバルティスダイレクト
〒105-6333 東京都港区虎ノ門1-23-1

NOVARTIS DIRECT
0120-003-293
受付時間：月～金 9：00～17：30
（祝日及び当社休日を除く）
www.novartis.co.jp

26．製造販売業者等

26.1 製造販売

ノバルティス ファーマ株式会社
東京都港区虎ノ門 1－23－1

最新の添付文書を参照すること

改訂案（2023年4月時点）

日本標準商品分類番号	873999

貯法：室温保存

有効期間：3年

経口造血刺激薬/トロンボポエチン受容体作動薬
エルトロンボパグ オラミン錠

劇薬、処方箋医薬品
（注意－医師等の処方箋により使用すること）

レボレード®錠12.5mg
レボレード®錠25mg
REVOLADE® Tablets

	12.5mg	25mg
承認番号	22200AMX00960000	22200AMX00961000
販売開始	2010年12月	2010年12月

NOVARTIS

®登録商標

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	レボレード錠12.5mg	レボレード錠25mg
有効成分	1錠中エルトロンボパグオラミン15.9mg（エルトロンボパグとして12.5mg）	1錠中エルトロンボパグオラミン31.9mg（エルトロンボパグとして25mg）
添加剤	結晶セルロース、D-マンニトール、デンプングリコール酸ナトリウム、ステアリン酸マグネシウム、ポビドン、ヒプロメロース、酸化チタン、マクロゴール400、ポリソルベート80	

3.2 製剤の性状

販売名	レボレード錠12.5mg			レボレード錠25mg		
性状	白色円形のフィルムコーティング錠			白色円形のフィルムコーティング錠		
外形						
識別コード	GSMZ1 12.5			GSNX3 25		
大きさ（約）	直径：7.9mm 厚さ：3.5mm 質量：184mg			直径：10.3mm 厚さ：4.2mm 質量：364mg		

4. 効能又は効果

○慢性特発性血小板減少性紫斑病
○再生不良性貧血

5. 効能又は効果に関連する注意

〈慢性特発性血小板減少性紫斑病〉

5.1 他の治療にて十分な効果が得られない場合、又は忍容性に問題があると考えられる場合に使用すること。

5.2 血小板数、臨床症状からみて出血リスクが高いと考えられる場合に使用すること。

〈再生不良性貧血〉

5.3 診療ガイドライン等の最新の情報を参考に、本剤の投与が適切と判断される患者に投与すること。[17.1.4~~、17.1.5~~-17.1.6参照]

6. 用法及び用量

〈慢性特発性血小板減少性紫斑病〉

通常、成人には、エルトロンボパグとして初回投与量12.5mgを1日1回、食事の前後2時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1日最大投与量は50mgとする。

〈再生不良性貧血〉

抗胸腺細胞免疫グロブリンで未治療の場合

抗胸腺細胞免疫グロブリンとの併用において、通常、成人及び12歳以上の小児には、エルトロンボパグとして75mgを1日1回、6歳以上12歳未満の小児には、エルトロンボパグとして37.5mgを1日1回、食事の前後2時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。

既存治療で効果不十分な場合

通常、成人には、エルトロンボパグとして初回投与量25mgを1日1回、食事の前後2時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜増減する。また、1日最大投与量は100mgとする。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後2時間を避けて空腹時に服用すること。[16.2.1参照]

7.2 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用すると本剤の血中濃度が低下するので、本剤服用の前4時間及び後2時間はこれらの摂取を避けること。[10.2、16.2.1、16.7.1参照]

〈慢性特発性血小板減少性紫斑病〉

7.3 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記7.3.1-7.3.7を参照の上、調節すること。本剤の投与開始時及び用量調節時には血小板数及び末梢血塗抹標本検査を含む全血球計算を、血小板数が安定する（血小板数50,000/μL以上が少なくとも4週間）までは毎週、安定した後は毎月検査することが望ましい。

7.3.1 本剤は治療上必要最小限の用量で使用すること。

7.3.2 本剤の効果は、通常1～2週間であらわれるので、効果の確認のためには少なくとも2週間は同一用量を維持すること。ただし、肝障害のある患者では、血小板数が定常状態に達するまでの期間が長くなるため、効果の確認のためには少なくとも3週間は同一用量を維持すること。

7.3.3 血小板数50,000/μLを目安とし、血小板数がそれを下回る場合には増量を考慮すること。

7.3.4 血小板数が50,000/μL～200,000/μLの場合には、出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮すること。

7.3.5 血小板数が200,000/μL～400,000/μLの場合には本剤を減量すること。

7.3.6 血小板数が400,000/μLを超えた場合には本剤を休薬すること。この場合血小板数の測定は週に2回実施することが望ましい。休薬後、血小板数が150,000/μLまで減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で投与を再開すること。

7.3.7 本剤の投与量を調節する場合には、通常、12.5mg/日ずつとする。

7.4 本剤を1日50mg、4週間投与しても血小板数が増加せず、臨床的に問題となる出血傾向の改善が認められない場合には、本剤の投与中止を考慮すること。

〈再生不良性貧血〉

7.5 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記7.6、7.6.1-7.6.~~5~~4、7.7、7.7.1-7.7.4を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日（抗胸腺細胞免疫グロブリンで未治療の6歳以上12歳未満の小児は12.5mg/日）ずつとする。用量調節時には少なくとも2週間は同一用量を維持すること。

7.6 抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合

~~7.6.1 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。[17.1.4参照]~~

7.6.~~2~~1 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の~~添付文書~~電子添文を熟読すること。

7.6.~~3~~2 血小板数が200,000/μLを超えた場合には本剤の減量を考慮すること。

7.6.~~4~~3 血小板数が400,000/μLを超えた場合には本剤を休薬すること。休薬後、血小板数が200,000/μL未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

7.6.~~5~~4 本剤を26週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

7.7 既存治療で効果不十分な患者に投与する場合

7.7.1 血小板数50,000/μLを目安とし、血小板数がそれを下回る場合には増量を考慮すること。

7.7.2 血小板数が100,000/μL～200,000/μLの場合には減量を考慮すること。

7.7.3 血小板数が200,000/μLを超えた場合には少なくとも1週間は本剤を休薬すること。休薬後、血小板数が50,000/μL未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

7.7.4 本剤を16週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

7.8 3血球系統の改善（目安として、輸血非依存下で血小板数50,000/μLを超える、輸血非依存下でヘモグロビン値10g/dLを超える、好中球数1,000/μLを超える）が8週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が更に8週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数30,000/μL未満、ヘモグロビン値9g/dL未満、好中球数500/μL未満に低下した場合には休薬前の投与量で投与を再開してもよい。

8. 重要な基本的注意

〈効能共通〉

8.1 本剤は、血液疾患の治療に十分な経験を持つ医師のもとで使用すること。

8.2 本剤の投与により肝機能障害があらわれることがあるので、本剤の投与開始前及び用量調節時は2週間毎、用量の変更がなければ1ヵ月毎に肝機能検査（AST、ALT、ビリルビン等）を実施すること。[11.1.1参照]

8.3 血小板数が正常範囲以下であっても血栓塞栓症が認められているため、血小板数にかかわらず血栓塞栓症の発現に注意すること。また、血小板数が正常範囲を超えると、血栓塞栓症のリスクが増加する可能性があるので、観察を十分に行い、血小板数が治療の目標とするレベルを超えた場合には、本剤の減量又は休薬を考慮する等注意すること。[11.1.2参照]

8.4 本剤の投与中止後2週間以内に血小板数が投与開始前の値まで低下し、出血を生じることがあるので、本剤の投与中止後4週間程度は頻回に血小板数を測定すること。[11.1.3参照]

8.5 本剤を含むトロンボポエチン受容体作動薬には、骨髄のレチクリン線維の形成及び線維化を進行させる可能性があるので、本剤の投与開始前には末梢血塗抹標本検査を行い、細胞の形態学的異常を確認すること。また、本剤の投与中は、毎月白血球分画を含む全血球計算を検査し、未熟細胞又は異型細胞が観察された場合には、末梢血塗抹標本検査を行い、形態学的異常（涙滴赤血球、有核赤血球、未熟白血球等）の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、本剤の投与を中止し、骨髄生検（染色による骨髄線維化の評価等）の実施を考慮すること。[11.1.4参照]

8.6 トロンボポエチン受容体作動薬には、既存の骨髄異形成症候群等の血液悪性腫瘍を進行させる可能性がある。

8.7 げっ歯類を用いた毒性試験において、白内障がみられた。また、臨床試験において白内障が報告されているので、白内障に対する眼科的な検査を定期的に行うことが望ましい。

〈再生不良性貧血〉

8.8 重症再生不良性貧血患者を対象とした海外臨床試験において、本剤投与後に染色体異常が認められた例や骨髄異形成症候群及び急性骨髄性白血病への移行例が報告されている。再生不良性貧血患者への本剤の投与中は、定期的に白血球分画を含む全血球計算及び末梢血塗抹標本検査を行い、幼若細胞や形態学的異常の発現を確認し、血球減少の有無も確認すること。これらの異常が認められた場合には、骨髄検査（染色体異常の評価を含む）の実施を考慮し、本剤の投与継続の可否を判断すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 アンチトロンビンⅢ欠損、抗リン脂質抗体症候群等の血栓塞栓症の素因のある患者

血栓塞栓症があらわれるおそれがある。

9.2 腎機能障害患者

血小板数の推移に加えて安全性についても慎重に観察すること。腎機能障害患者を対象に有効性及び安全性を指標とした臨床試験は実施していない。[16.6.1参照]

9.3 肝機能障害患者

肝機能障害が悪化するおそれがある。また、血中濃度-時間曲線下面積（AUC）が増加する可能性がある。[16.6.2参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。胎児の血小板への影響は不明である。動物試験（ラット）において母体毒性用量で胚致死、胎児体重の低値及び低頻度の頸肋（変異）の増加が報告されている。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。動物試験（ラット）で乳汁中への移行が示唆されている。

9.7 小児等

〈慢性特発性血小板減少性紫斑病〉

9.7.1 小児等を対象とした臨床試験は実施していない。

〈再生不良性貧血〉

9.7.2 免疫抑制療法で未治療の低出生体重児、新生児、乳児又は6歳未満の幼児を対象とした臨床試験は実施していない。既存治療で効果不十分の小児等を対象とした臨床試験は実施していない。[17.1.6参照]

9.8 高齢者

患者の状態を観察しながら注意して投与すること。一般に生理機能が低下している。

10. 相互作用

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
ロスバスタチン [16.7.2参照]	ロスバスタチンの血中濃度が上昇したとの報告がある[1]。 ロスバスタチンの減量を考慮し、患者の状態を慎重に観察すること。	本剤がOATP1B1及びBCRPを阻害する可能性がある。
制酸剤 乳製品 多価陽イオン（鉄、カルシウム、アル	同時に服用すると本剤の吸収が著しく妨げられることがあるので、本剤投与の前4時間及び	本剤はこれら多価陽イオンと錯体を形成する。

ミニウム、マグネシウム、セレン、亜鉛等）含有製剤等［7.2、16.2.1,16.7.1参照］	後 2 時間はこれらの摂取を避けること[2,3]。	
ロピナビル･リトナビル配合剤［16.7.3参照］	本剤の AUC が減少したとの報告があるので[4]、ロピナビル･リトナビル配合剤と併用する場合には、注意すること。	機序は不明であるが、ロピナビル･リトナビル配合剤が本剤の代謝酵素を誘導する可能性がある。
シクロスポリン［16.7.4参照］	本剤の AUC 及び Cmax が減少したとの報告がある[5]。また、本剤の血中濃度が高値を示したとの報告がある[6]。シクロスポリンと併用する場合には、注意すること。	機序は不明である。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 肝機能障害

AST（~~2~~3.3%）、ALT（~~7~~16.7%）、ALP（~~6~~5.6%）、ビリルビン（~~1~~3~~2~~5.6%）の増加等があらわれることがある。［8.2参照］

11.1.2 血栓塞栓症

肺塞栓症（頻度不明）、深部静脈血栓症（頻度不明）、一過性脳虚血発作（~~2~~1.1%）、心筋梗塞（頻度不明）、虚血性脳卒中（頻度不明）等があらわれることがある。［8.3参照］

11.1.3 出血（頻度不明）

［8.4参照］

11.1.4 骨髄線維化（頻度不明）

［8.5参照］

11.2 その他の副作用

	~~5%以上~~	5%未満	頻度不明
消化器	~~悪心~~	~~―~~悪心、腹痛、~~嘔~~吐	~~嘔吐、~~下痢、口内乾燥
皮膚	~~―~~	発疹、皮膚変色	脱毛症
筋骨格	~~筋痛~~	~~―~~筋肉痛、四肢痛	背部痛、筋骨格系胸痛、筋骨格痛
感染症		~~―~~	咽頭炎、尿路感染
その他	~~頭痛~~	頭痛、疲労、浮動性めまい、血小板数増加、低カリウム血症、白内障	~~咽頭炎、尿路感染~~

12. 臨床検査結果に及ぼす影響

エルトロンボパグは赤～褐色であるため、臨床検査に影響を及ぼす可能性がある。本剤を投与された患者において、血清の変色や総ビリルビン及びクレアチニン検査に影響が認められたとの報告がある。

13. 過量投与

13.1 症状

本剤 5,000mg を過量投与した症例では、軽度の発疹、一過性の徐脈、疲労、AST 及び ALT 上昇が報告され、血小板数は 929,000/μL まで増加した。

13.2 処置

吸収を抑えるために、カルシウム、アルミニウム、マグネシウム等の多価陽イオンを含有する製剤の経口投与を考慮すること。また、血小板数の検査を頻回に行い、患者の状態を十分に観察すること。

14. 適用上の注意

14.1 薬剤交付時の注意

PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15.2 非臨床試験に基づく情報

本剤はヒト及びチンパンジー以外のトロンボポエチン受容体に対し親和性をもたず、ヒト及びチンパンジー以外の動物に対して薬理活性を示さない。このため毒性試験において、薬理活性に付随する影響は評価されていない。

16. 薬物動態

16.1 血中濃度

日本人健康成人男性を対象に、本剤 25、50 あるいは 75mg を空腹時単回及び反復経口投与した時、本剤は速やかに吸収され、投与後 3～4 時間（中央値）で最高血漿中濃度（Cmax）に達した。単回及び反復投与時の曝露量（Cmax 及び AUC）は、投与量の増加に対し、ほぼ線形的に増加した。また、本剤は反復投与開始後約 7 日で定常状態に達すると考えられた。表-1 に薬物動態パラメータを示した[7,8]。

表-1　健康成人に単回及び 10 日間反復経口投与した時の薬物動態パラメータ

投与量（mg）	例数	Cmax（μg/mL）	AUC[a)]（μg･hr/mL）	tmax（hr）	$t_{1/2}$（hr）	CL/F（L/hr）
単回投与						
25	10	3.56±1.13	55.4±23.2	3.0（2.0-5.0）	29.6±5.0	0.534±0.256
50	10	6.44±2.14	106.6±32.4	3.0（1.5-5.0）	31.0±5.9	0.525±0.218
75	10	8.39±2.84	134.9±37.4	3.0（2.0-6.0）	32.4±7.6	0.604±0.201
反復投与						
25	10	4.83±1.17	58.9±18.4	3.0（1.5-5.0）	39.7±3.2	0.478±0.196
50	9	10.6±2.38	133.8±33.6	4.0（2.0-5.0）	51.3±12.2	0.396±0.102
75	10	12.78±2.84	164.2±35.5	4.0（2.0-5.0）	47.8±11.5	0.476±0.102

算術平均値±標準偏差、tmax は中央値（範囲）

a）単回投与：$AUC_{0-\infty}$、反復投与：$AUC_{0-\tau}$

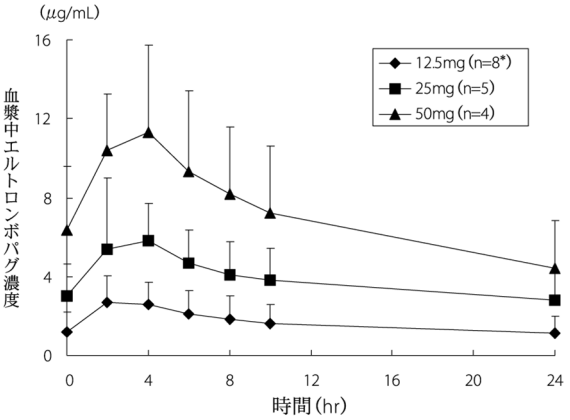
日本人特発性血小板減少性紫斑病患者に本剤12.5、25あるいは50mgを投与した時の定常状態における薬物動態パラメータを表-2に、血漿中エルトロンボパグ濃度推移を図-1に示した[9,10]。

表-2　日本人特発性血小板減少性紫斑病患者の定常状態における薬物動態パラメータ

投与量（mg）	例数	Cmax（μg/mL）	tmax（hr）	$AUC_{0-\tau}$（μg･hr/mL）	$t_{1/2}$[b)]（hr）
12.5	8	2.99±1.25	3.19（2.00-4.17）	41.64±24.36[a)]	19.5±7.16[a)]
25	5	6.78±2.62	4.00（2.00-4.00）	92.53±41.12	27.0±7.66
50	4	11.88±3.93	2.97（1.92-4.17）	171.6±75.24	18.2±4.94

算術平均値±標準偏差、tmax は中央値（範囲）

a）n＝7　b）24 時間までのポイントから算出のため、参考値



*：24 時間のポイントのみ　n＝7

図-1　日本人特発性血小板減少性紫斑病患者の定常状態における血漿中エルトロンボパグ濃度推移（平均値±標準偏差）

なお、日本人及び外国人の成績を用いた母集団薬物動態解析の結果、エルトロンボパグの $AUC_{0-\tau}$は、非東アジア系特発性血小板減少性紫斑病患者（主に白人）と比較して、東アジア系特発性血小板減少性紫斑病患者で約 87%高値を示した。また、日本人特発性血小板減少性紫斑病患者の $AUC_{0-\tau}$は、非東アジア系特発性血小板減少性紫斑病患者の $AUC_{0-\tau}$（母集団薬物動態解析推定値）に比べ、約 85%高値を示した[11,12]。

母集団薬物動態解析の結果、女性特発性血小板減少性紫斑病患者における AUC0-τは、男性に比べて約 50%高かった。また、年齢は本剤の薬物動態に影響を及ぼさなかった[11]。

抗胸腺細胞免疫グロブリンに治療抵抗性若しくは再発又は抗胸腺細胞免疫グロブリン治療が受けられない中等症以上の日本人再生不良性貧血患者に本剤 25mg を投与した時の定常状態における薬物動態パラメータを表-3 に示した[6]。

表-3　日本人再生不良性貧血患者の定常状態における薬物動態パラメータ

投与量（mg）	例数	Cmax（μg/mL）	tmax（hr）	$AUC_{0-\tau}$[a]（μg･hr/mL）
25	5	6.41±4.20	2.00（1.90-7.58）	99.20±119.0

算術平均値±標準偏差、tmax は中央値（範囲）
a）n＝3

16.2 吸収

16.2.1 食事の影響

健康成人に本剤 50mg を、乳製品を含む高カロリー、高脂肪の食事（カルシウム 427mg 含有）とともに単回経口投与した時、空腹時に比べて $AUC_{0-\infty}$は 59%、Cmax は 65%低下した。また、本剤 75mg を高脂肪又は低脂肪のカルシウム含有量の低い（50mg 未満）食事とともに投与した時、いずれもエルトロンボパグの $AUC_{0-\infty}$及び Cmax に影響を与えなかった[2]（外国人データ）。

（参考）

健康成人にエルトロンボパグの経口懸濁液用粉末（以下、PfOS）製剤 25mg（国内未承認）を高カルシウム食（カルシウム約 448mg）摂取 2 時間前に単回投与した時のエルトロンボパグの $AUC_{0-\infty}$及び Cmax は、空腹時投与と比べてそれぞれ 20%及び 14%低下した。一方、高カルシウム食摂取 2 時間後に PfOS 製剤 25mg を単回投与した時、エルトロンボパグの $AUC_{0-\infty}$及び Cmax は、空腹時投与と比べてそれぞれ 47%及び 48%低下した[3]（外国人データ）。[7.1、7.2、10.2 参照]

16.3 分布

本剤は *in vitro* 試験の結果、2～100μg/mL の濃度範囲で 99.9%以上がヒト血漿蛋白質と結合し、主な結合蛋白質はアルブミンであった。

本剤は BCRP の基質であったが、P-糖蛋白質（Pgp）及び OATP1B1 の基質ではないことが確認された。また、本剤は *in vitro* 試験で OATP1B1 及び BCRP を阻害（IC_{50}値：いずれも約 2.7μM）した。

16.4. 代謝

本剤は *in vitro* 試験の結果、最大 100μM の濃度で CYP1A2、CYP2A6、CYP2C19、CYP2D6、CYP2E1、CYP3A4/5 及び CYP4A9/11 の活性を阻害しなかったが、CYP2C8（パクリタキセル）及び CYP2C9（ジクロフェナク）の活性を阻害し、IC_{50}値はそれぞれ 24.8μM（11μg/mL）及び 20.2μM（8.9μg/mL）であった[13]。

健康成人男性に本剤 75mg を反復経口投与した時、本剤は CYP1A2、CYP2C19、CYP2C9 及び CYP3A4 の活性を阻害及び誘導しなかった[14]（外国人データ）。

本剤は *in vitro* 試験の結果、UGT1A1、UGT1A3、UGT1A4、UGT1A6、UGT1A9、UGT2B7 及び UGT2B15 の活性を阻害（IC_{50}値：3.0～33μM）した[13]。

健康成人男性に本剤の ^{14}C-標識体 75mg を経口投与した時、酸化体、グルクロン酸抱合体、グルタチオン抱合体又はシステイン抱合体に代謝された（外国人データ）。また、*in vitro* 試験の結果、本剤の酸化的代謝には CYP1A2 及び CYP2C8 が、グルクロン酸抱合には UGT1A1 及び UGT1A3 が関与していると考えられた[13]。

16.5 排泄

本剤の主な排泄経路は糞中であり、本剤の ^{14}C-標識体 75mg を単回経口投与後 168 時間までに、平均で投与量の 30.7%が尿中に、投与量の 58.9%が糞中に排泄された。尿中に未変化体（エルトロンボパグ）は認められず、糞中には投与量の約 20%が未変化体として排泄された[15]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

腎機能障害患者に本剤 50mg を単回経口投与した時のエルトロンボパグの $AUC_{0-\infty}$の幾何平均値は健康成人と比べて軽度の腎機能障害患者（CLcr：50～80mL/min）で 32%、中等度の腎機能障害患者（CLcr：30～49mL/min）で 36%、重度の腎機能障害患者（CLcr：30mL/min 未満）で 60%低かった。しかしながら、健康成人及び軽度～重度の腎機能障害患者の $AUC_{0-\infty}$の範囲（最小値～最大値）は、順に 32.65～99.32、22.54～83.51、21.10～109.95、3.44～117.54μg･hr/mL とばらつきが大きかった[16,17]（外国人データ）。[9.2 参照]

16.6.2 肝機能障害患者

肝機能障害患者に本剤 50mg を単回経口投与した時のエルトロンボパグの $AUC_{0-\infty}$の幾何平均値は健康成人と比べて軽度の肝機能障害患者（Child-Pugh スコア：5～6）で 41%、中等度の肝機能障害患者（Child-Pugh スコア：7～9）で 93%、重度の肝機能障害患者（Child-Pugh スコア：10 以上）で 80%高かった。しかしながら、健康成人及び軽度～重度の肝機能障害患者の $AUC_{0-\infty}$の範囲（最小値～最大値）は、順に 34.46～174.99、35.86～127.74、57.64～263.22、32.26～263.51μg･hr/mL とばらつきが大きかった[16,17]（外国人データ）。[9.3 参照]

16.6.3 小児等

免疫抑制療法で未治療の日本人小児再生不良性貧血患者に、抗胸腺細胞免疫グロブリン及びシクロスポリンとの併用において 6 歳以上 12 歳未満の患者に本剤 37.5mg を、12 歳以上 18 歳未満の患者に本剤 75mg を投与した時のエルトロンボパグの定常状態における薬物動態パラメータを表-4 に示した[18]。

表-4　日本人小児再生不良性貧血患者の定常状態における薬物動態パラメータ

年齢	投与量（mg）	例数	Cmax（μg/mL）	tmax（hr）	$AUC_{0-\tau}$（μg･hr/mL）
6 歳以上 12 歳未満[a]	37.5	3	17.7±8.36	3.93（1.87-3.95）	352±194
12 歳以上 18 歳未満[b]	75	2	42.3（40.6,44.0）	3.06（2.12,4.00）	713（705,721）

a）算術平均値±標準偏差、tmax は中央値（範囲）
b）算術平均値（個別値）、tmax は中央値（個別値）

16.7 薬物相互作用

16.7.1 制酸剤

健康成人に、本剤 75mg と多価陽イオン（水酸化アルミニウム及び炭酸マグネシウム）を含む制酸剤を単回併用投与した時、エルトロンボパグの $AUC_{0-\infty}$及び Cmax はともに約 70%低下した[2]（外国人データ）。[7.2、10.2 参照]

16.7.2 ロスバスタチン

健康成人に本剤 75mg 投与の定常状態時に、OATP1B1 及び BCRP の基質であるロスバスタチン 10mg を単回併用投与した時、単独投与時に比べてロスバスタチンの $AUC_{0-\infty}$は 55%、Cmax は 103%増加した（n＝39）。層別解析の結果、アジア人では、$AUC_{0-\infty}$は 32%、Cmax は 61%増加した（n＝21）。なお、ロスバスタチンは、本剤の薬物動態に影響を及ぼさなかった[1]（外国人データ）。[10.2 参照]

16.7.3 ロピナビル/リトナビル配合剤

健康成人にロピナビル 400mg/リトナビル 100mg 配合剤 1 日 2 回反復投与時に、本剤 100mg を単回併用投与した時、単独投与時に比べてエルトロンボパグの $AUC_{0-\infty}$は 17%低下した（n＝40）[4]（外国人データ）。[10.2 参照]

16.7.4 シクロスポリン

健康成人に本剤 50mg 単回投与時に、シクロスポリン 200mg を単回併用投与した時、単独投与時に比べてエルトロンボパグの $AUC_{0-\infty}$及び Cmax はそれぞれ 18%及び 25%低下した（n＝37 及び n＝39）。また、シクロスポリン 600mg を単回併用投与した時、単独投与時に比べてエルトロンボパグの $AUC_{0-\infty}$及び Cmax はそれぞれ 24%及び 39%低下した（n＝33 及び n＝37）[5]（外国人データ）。

既存治療で効果不十分な再生不良性貧血患者に本剤 50mg を 1 日 1 回反復投与した時のエルトロンボパグのトラフ値（平均値）は、シクロスポリン非併用患者（n＝12）と比べてシクロスポリン 25～250mg を 1 日 2 回反復併用投与した患者で 73%高値を示した（n＝8）[6]（日本人データ）。[10.2 参照]

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈慢性特発性血小板減少性紫斑病〉

17.1.1 国内第 II/III 相試験

既治療の慢性特発性血小板減少性紫斑病患者（血小板数が 30,000/μL 未満）23 例を対象として、二重盲検下で本剤 12.5 又は 25mg を 1 日 1 回空腹時に、7 週間投与した。投与は 12.5mg から開始し、投与 3 週目の血小板数に応じて 25mg に用量調節した。その結果、投与 6 週目における本剤の有効率（血小板数が 50,000/μL 以上、400,000/μL 以下に増加した患者の割合［95%信頼区間］）は 60%［32.29,83.66］であり、プラセボ（0%［0.00,36.94］）に比べて明らかな血小板数増加効果が認められた。

二重盲検期終了後は、本剤の投与期間が 26 週間になるように本剤を継続投与した。用量は血小板数に応じて 12.5、25 又は 50mg に調節した。その結果、投与 5 週目から 26 週目までの血小板数（中央値）は 50,000/μL を超えて推移し、血小板数の増加に伴い出血症状が改善した（図-1、2）[9,10]。

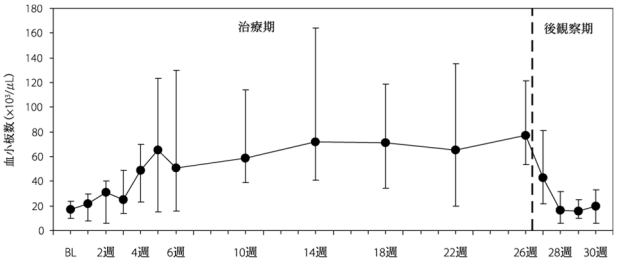


図-1　血小板数（中央値）の推移：TRA108109 試験
Bars represent the 25th and 75th percentiles

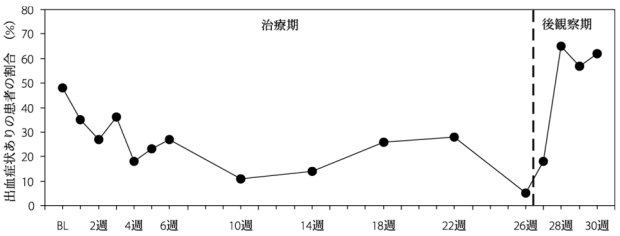


図-2　出血症状がみられた患者の割合の推移：TRA108109 試験

副作用発現頻度は本剤投与群で 48%（11/23 例）であった。主な副作用は、疲労、ALT 増加、血小板数増加、低カリウム血症各 9%（2/23 例）であった。

17.1.2 国内第 III 相試験

上記 23 例中 19 例が国内長期継続投与試験に移行した。用量は血小板数に応じて 12.5～50mg に調節し、19 例中 10 例では異なる用量の組み合わせや投与間隔の調節も行った。その結果、長期継続投与試験でも血小板数の増加と出血症状の改善が示された。投与期間の中央値は 833.0 日（範囲：301～981 日）であった（最終報告時）[18-19,20]。

国内長期継続投与試験に移行した 26%（5/19 例）に副作用が報告された。主な副作用は、白内障、胸痛各 11%（2/19 例）であった（最終報告時）。

17.1.3 海外第 III 相試験

既治療の慢性特発性血小板減少性紫斑病患者（血小板数が 30,000/μL 未満）197 例を対象として、本剤 25、50 又は 75mg を 1 日 1 回空腹時に、26 週間投与する二重盲検試験を実施した（本剤 135 例、プラセボ 62 例）。投与は 50mg から開始し、血小板数に応じて 25、50 又は 75mg に用量調節した。その結果、本剤群のプラセボ群に対する血小板数増加効果のオッズ比[99%信頼区間]は 8.2[3.59,18.73]であり、有意に高かった（p〈0.001）。また、本剤群の血小板数（中央値）は、投与 1 週目より増加し、投与 2～26 週目まで 50,000/μL を超えて推移した（図-4）。本剤投与により出血症状（WHO Bleeding Scale を用いて評価、Grade2～4）が認められた患者の割合について、本剤群のプラセボ群に対するオッズ比［95%信頼区間］は 0.35［0.19,0.64］であり、本剤群の方が有意に低下した（p＜0.001）[20-21,22]。

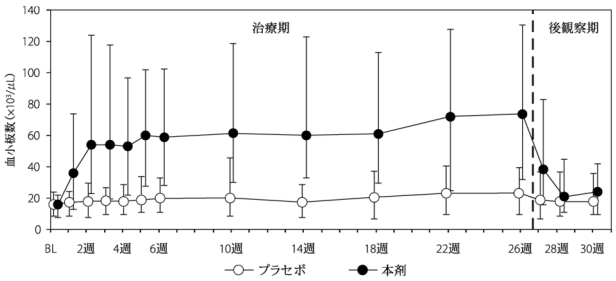


図-3　血小板数（中央値）の推移

副作用発現頻度は、本剤投与群で 37%（50/135 例）であった。主な副作用は、頭痛 11%（15/135 例）、ALT 増加 4%（6/135 例）、悪心 4%（6/135 例）、白内障 4%（5/135 例）、下痢 3%（4/135 例）であった。

（本剤の国内承認用量は 12.5～50mg を 1 日 1 回投与である。）

〈再生不良性貧血〉

17.1.4 国内第Ⅱ/Ⅲ相試験（成人）

抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者（中等症以上）10 ~~名~~例を対象として、抗胸腺細胞免疫グロブリン/シクロスポリンに本剤を併用投与した。抗胸腺細胞免疫グロブリン/シクロスポリン開始後、15 日目から初回投与量として本剤 75mg を 1 日 1 回空腹時に経口投与し、血小板数に応じて 2 週間ごとに 25mg ずつ減量した。その結果、投与 26 週時の奏効率［95%信頼区間］は 70.0%［34.8,93.3］であった。なお、奏効率は寛解（輸血非依存かつ血球数の改善）が得られた患者の割合と定義した[~~22~~23]。

副作用発現頻度は 50.0%（5/10 例）であった。主な副作用は、筋肉痛 30.0%（3/10 例）、血中ビリルビン増加、悪心各 20.0%（2/10 例）であった。［5.3~~、7.6.1~~参照］

17.1.5 国内第Ⅱ/Ⅲ相試験（成人）

抗胸腺細胞免疫グロブリンに治療抵抗性若しくは再発又は抗胸腺細胞免疫グロブリン治療が受けられない再生不良性貧血患者（中等症以上）21 ~~名~~例を対象として、初回投与量として本剤 25mg を 1 日 1 回空腹時に経口投与し、血小板数に応じて 2 週間ごとに 25mg ずつ、最大 100mg/日まで用量調節した。その結果、投与 26 週時における血液学的反応率［95%信頼区間］は、47.6%［25.7,70.2］であった。なお、血液学的反応率は 1 系統以上の血球に改善[血小板数が≥20,000/μL 増加又は血小板輸血非依存、ヘモグロビン値が≥1.5g/dL 増加（投与前値が 9g/dL 未満の場合）又は赤血球輸血量の減少、好中球数が≥100%（投与前値が 500/μL 未満の場合）又は≥500/μL 増加のうち、1 つ以上該当]を認めた患者の割合と定義した。投与継続により血球系統（血小板、赤血球及び好中球）の更なる改善を認め、投与 26 週時~~点~~で 2 系統に改善を認めた 4 ~~名~~例では投与 52 週時~~点~~には 3 系統が改善した[6]。

副作用発現頻度は 57.1%（12/21 例）であった。主な副作用は、血中 ALP 増加、血中ビリルビン増加、肝機能異常、高ビリルビン血症、発疹が各 9.5%（2/21 例）であった。［5.3 参照］

17.1.6 国際共同第Ⅱ相試験（成人、小児）

免疫抑制療法で未治療の 6 歳以上の東アジア人再生不良性貧血患者（重症以上）36 例（日本人小児 5 例を含む）を対象として、抗胸腺細胞免疫グロブリン/シクロスポリン開始日より本剤を併用投与した。初回投与量として本剤 75mg（6 歳以上 12 歳未満の患者には本剤 37.5mg）を 1 日 1 回空腹時に経口投与し、血小板数に応じて 2 週間ごとに 25mg ずつ（6 歳以上 12 歳未満の患者では 12.5mg ずつ）減量した。その結果、投与 26 週時の完全奏効率［95%信頼区間］、奏効率［95%信頼区間］は 16.7%[6.4,32.8]、77.8%[60.8,89.9]であった。また、日本人小児 5 例における投与 26 週時の完全奏効率［95%信頼区間］、奏効率[95%信頼区間]は 20.0%[0.5,71.6]、80.0%[28.4,99.5]であった。なお、完全奏効率は完全奏効［好中球数が>1,000/μL、血小板数が>100,000/μL、ヘモグロビン値が>10g/dL のすべてを満たす］が得られた患者の割合、奏効率は完全奏効又は部分奏効［好中球数が≥500/μL、血小板数が≥20,000/μL、網赤血球数が≥20,000/μL のうち 2 項目以上を満たすが、完全奏効の基準には不十分である］の基準を満たした患者の割合と定義した。

副作用発現頻度は 83.3%（30/36 例）であった。主な副作用は、ALT 増加、高ビリルビン血症が各 30.6%(11/36 例)、γ－GTP 増加が 19.4%（7/36 例）であった。また、日本人小児 5 例の副作用発現頻度は

80.0%（4/5例）であった。主な副作用はALT増加40.0%（2/5例）であった[18)]。［5.3、9.7.2参照］

18. 薬効薬理

〈効能共通〉

18.1 作用機序

ヒトトロンボポエチン受容体との特異的な相互作用を介して、トロンボポエチンのシグナル伝達経路の一部を活性化することにより巨核球及び骨髄前駆細胞の増殖及び分化を促進させる[23~~19~~24)]。

18.2 血小板産生促進作用

18.2.1 *In vitro*において、ヒト巨核球系細胞株の増殖を促進させ、ヒト骨髄前駆細胞の巨核球への分化を誘導した[23~~19~~24)]。

18.2.2 チンパンジーへの5日間経口投与により、最終投与の6～10日後に血小板数は約2倍に増加した[23~~19~~24)]。

18.3 正常血小板機能に及ぼす影響

ヒト正常血小板においてアデノシン二リン酸誘発の血小板凝集に影響を及ぼさず、P-セレクチンの発現を誘導しなかった[24~~20~~25)]。

〈再生不良性貧血〉

18.4 造血促進作用

*In vitro*及び*in vivo*において、ヒト骨髄幹細胞及び前駆細胞の増殖及び分化を促進させ、多系統の血球が増加した[25~~21~~26)]。

19. 有効成分に関する理化学的知見

一般名：エルトロンボパグ　オラミン（Eltrombopag Olamine）

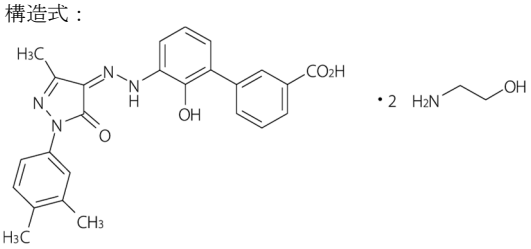
化学名：3'-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid bis(2-aminoethanol)

分子式：$C_{25}H_{22}N_4O_4 \cdot 2\ (C_2H_7NO)$

分子量：564.63

性　状：赤色～褐色の粉末

構造式：



分配係数（log P）：4.05

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

〈レボレード錠12.5mg〉

70錠［7錠（両面アルミニウムPTP）×10］

〈レボレード錠25mg〉

70錠［7錠（両面アルミニウムPTP）×10］

23. 主要文献

1) Allred,A.J.et al.：Br.J.Clin.Pharmacol. 2011; 72 (2) : 321-329 [20152521]

2) Williams,D.D.et al.：Clin.Ther. 2009; 31 (4) : 764-776 [20152327]

3) Wire,M.B.et al.：Clin.Ther. 2012; 34 (3) : 699-709 [20152652]

4) Wire,M.B.et al.：Antimicrob.Agents Chemother. 2012; 56 (6) : 2846-2851 [20152670]

5) 社内資料：エルトロンボパグとシクロスポリンの薬物相互作用（201583試験）（2017年8月25日承認、CTD2.7.2-2.1.1） [20160747]

6) 社内資料：国内第Ⅱ/Ⅲ相臨床試験（ETB115E1201試験）（2017年8月25日承認、CTD2.7.6-4.2.1） [20170501]

7) Shida,Y.et al.：臨床薬理2011; 42 (1) : 11-20 [20154538]

8) 社内資料：国内第Ⅰ相臨床試験（TRA104603試験,TRA105580試験）（2010年10月27日承認、CTD2.7.2.2.2.1.1, 2.7.2.2.2.1.2） [20160020]

9) Tomiyama,Y.et al.：J.Thromb.Haemost.2012; 10 (5) : 799-806 [20152644]

10) 社内資料：国内第Ⅱ/Ⅲ相臨床試験（TRA108109試験）（2010年10月27日承認、CTD2.7.3.3.2.1.1,2.7.3.3.2.1.2,2.7.4.2.1.1.3.1.1） [20155833]

11) Gibiansky,E.et al.：J.Clin.Pharmacol. 2011; 51 (6) : 842-856 [20152522]

12) 社内資料：母集団薬物動態解析（2010年10月27日承認、CTD2.7.2.3.2.1.2, 2.7.2.3.3） [20160021]

13) 社内資料:代謝(2010年10月27日承認、CTD2.7.2.2.1,2.7.2.2.2.1.5, 2.7.2.2.2.4.2) [20160022]

14) Jenkins,J.et al.：Eur.J.Clin.Pharmacol. 2010; 66 (1) : 67-76 [20152334]

15) 社内資料：排泄（2010年10月27日承認、CTD2.7.2.2.2.1.5） [20160023]

16) Bauman,J.W.et al.：J.Clin.Pharmacol. 2011; 51 (5) : 739-750 [20152523]

17) 社内資料：腎障害又は肝障害患者における薬物動態（2010年10月27日承認、CTD2.7.2.2.2.3） [20160024]

18) 社内資料：国際共同第Ⅱ相臨床試験（ETB115G2201試験）（XXXX年X月XX日承認、CTD2.5.4.2.2,2.7.4.7付録-Table 7-3,2.7.6.4.2.1） [20230108]

~~18~~19) Katsutani,S.et al.：Int.J.Hematol. 2013; 98 (3) : 323-330 [20152700]

~~19~~20) 社内資料：国内第Ⅲ相臨床試験（TRA111433試験） [20155834]

~~20~~21) Cheng,G.et al.：Lancet 2011; 377 (9763) :393-402
Department of Error：Lancet. 2011; 377 (9763) : 382 [20152366]

~~21~~22) 社内資料：海外第Ⅲ相臨床試験（TRA102537試験；RAISE試験）（2010年10月27日承認、CTD2.7.4.7付録-表2.7.4.7-5, 2.7.6-TRA102537試験） [20155835]

~~22~~23) 社内資料：国内第Ⅱ/Ⅲ相臨床試験（ETB115E1202試験）（2017年8
月25日承認、CTD2.7.6-4.2.2） [20170502]

~~23~~24) Erickson-Miller,C.L.et al.：Stem Cells 2009; 27 (2) : 424-430 [20152326]

~~24~~25) Erhardt,J.A.et al.：Exp.Hematol. 2009; 37 (9) ; 1030-1037 [20152344]

~~25~~26) Sun,H.et al.：Stem Cell Res. 2012; 9 (2) : 77-86 [20170519]

24. 文献請求先及び問い合わせ先

ノバルティスファーマ株式会社　ノバルティスダイレクト

〒105-6333 東京都港区虎ノ門1-23-1

NOVARTIS DIRECT

0120-003-293

受付時間：月～金 9：00～17：30

（祝祭日及び当社休日を除く）

www.novartis.co.jp

26. 製造販売業者等

26.1 製造販売

ノバルティスファーマ株式会社

東京都港区虎ノ門1-23-1

目　　次

目　　次 2
1　用法及び用量欄 3
1.1　用法及び用量 3
1.2　用法及び用量の設定根拠 3
2　用法及び用量に関連する注意欄 5
2.1　用法及び用量に関連する注意 5
2.2　用法及び用量に関連する注意の設定根拠 7
3　参考文献 9

1　用法及び用量欄

1.1　用法及び用量

〈慢性特発性血小板減少性紫斑病〉
通常、成人には、エルトロンボパグとして初回投与量 12.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、血小板数、症状に応じて適宜増減する。また、1 日最大投与量は 50mg とする。
〈再生不良性貧血〉
抗胸腺細胞免疫グロブリンで未治療の場合
抗胸腺細胞免疫グロブリンとの併用において、通常、成人及び 12 歳以上の小児には、エルトロンボパグとして 75mg を 1 日 1 回、6 歳以上 12 歳未満の小児には、エルトロンボパグとして 37.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。
既存治療で効果不十分な場合
通常、成人には、エルトロンボパグとして初回投与量 25mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜増減する。また、1 日最大投与量は 100mg とする。
（下線：追加）

1.2　用法及び用量の設定根拠

抗ヒト胸腺細胞免疫グロブリン（ATG）で未治療の小児再生不良性貧血（AA）に対するエルトロンボパグ オラミン（以下，ETB115）の用法・用量（案）は，CETB115G2201 試験（以下，G2201 試験）の成績に基づき設定した。

G2201 試験では，ETB115 の初回投与量を 12 歳以上の小児には 75 mg を 1 日 1 回，6 歳以上 12 歳未満の小児には 37.5 mg を 1 日 1 回とし，その後は血小板数に応じて適宜減量した。これは，免疫抑制療法で未治療の重症 AA 患者を対象とした NIH 12-H-0150／CETB115AUS01T 試験（以下，150 試験）での東アジア人患者に対する用法・用量と同一である。150 試験では，コホート 1［ETB115 を Day 14 から 6 ヵ月目までウマ ATG/シクロスポリン（CsA）と併用］及びコホート 2（ETB115 を Day 14 から 3 ヵ月目までウマ ATG/CsA と併用）よりもコホート 3（ETB115 を Day 1 から 6 ヵ月目までウマ ATG/CsA と併用）で高い有効性が得られ（コホート 1，2，3 の 6 ヵ月時点の CR 率及び奏効率はそれぞれ 33%及び 80%，26%及び 87%，58%及び 94%），かつ安全性プロファイルも許容可能であった（1.13.1-2-2.7.3-3.4 項，2.7.4-6.1 項）。米国では 150 試験の成績に基づき，成人及び小児（2 歳以上）重症 AA 患者に対し，当該試験のコホート 3 で設定された用法・用量で免疫抑制療法との併用による一次治療として承認されている。

以上を踏まえ，G2201 試験では 150 試験のコホート 3 と同様に，Day 1 から ETB115，ウサギ ATG（Day 1～5 のみ），及び CsA を併用投与した。

小児 AA に対する製造販売承認事項一部変更承認申請（以下，一変申請）にあたり，G2201 試験の成績に基づき，ETB115 とウサギ ATG / CsA 療法の併用投与により，日本人小児重症 AA 患者で，日本人成人 AA 患者［CETB115E1202 試験（以下，E1202 試験）］と同程度の有効性・安全性が認められるかを検討することで，ETB115 の小児 AA 患者に対する有用性を評価した。その結果，小児でも成人と同程度の血液学的奏効及び輸血に対する効果が認められ，小児に対しても有効性が期待できると考えた（2.5-6.2 項）。また，安全性に関しても小児特有の懸念は認められなかった（2.5-6.3 項）。PK について，成人被験者に 75 mg を投与した場合と比較し，6 歳以上 12 歳未満の被験者に 37.5 mg を投与した場合及び 12 歳以上 18 歳未満の被験者に 75 mg を投与した場合で大きな違いはなかった（2.5-3 項）。各試験の被験者数は限られており検討には限界があるものの，ETB115 は成人 AA 患者と同様に，小児 AA 患者に対しても有用であると考える。なお，G2201 試験には中等症の患者が含まれないが，成人 AA 患者では重症度の違いによって ETB115 の有効性に問題となる傾向は認められておらず，小児でも成人と同様に中等症以上の患者に対して有効性が期待できると考える（2.5-6.2 項）。以上のことから，一変申請時の国内添付文書（案）では，米国の添付文書で規定された東アジア人小児患者に対する用法・用量と同様に，ATG で未治療の小児 AA 患者に対する ETB115 の用法・用量（案）を「抗胸腺細胞免疫グロブリンとの併用において、通常、成人及び 12 歳以上の小児には、エルトロンボパグとして 75mg を 1 日 1 回、6 歳以上 12 歳未満の小児には、エルトロンボパグとして 37.5mg を 1 日 1 回、食事の前後 2 時間を避けて空腹時に経口投与する。なお、患者の状態に応じて適宜減量する。（下線部：追記）」とすることは妥当であると判断した。

2　用法及び用量に関連する注意欄

2.1　用法及び用量に関連する注意

〈効能共通〉

7.1 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後 2 時間を避けて空腹時に服用すること。［16.2.1 参照］

7.2 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用すると本剤の血中濃度が低下するので、本剤服用の前 4 時間及び後 2 時間はこれらの摂取を避けること。［10.2、16.2.1、16.7.1 参照］

〈慢性特発性血小板減少性紫斑病〉

7.3 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記 7.3.1-7.3.7 を参照の上、調節すること。本剤の投与開始時及び用量調節時には血小板数及び末梢血塗抹標本検査を含む全血球計算を、血小板数が安定する（血小板数 50,000/μL 以上が少なくとも 4 週間）までは毎週、安定した後は毎月検査することが望ましい。

7.3.1 本剤は治療上必要最小限の用量で使用すること。

7.3.2 本剤の効果は、通常 1～2 週間であらわれるので、効果の確認のためには少なくとも 2 週間は同一用量を維持すること。ただし、肝障害のある患者では、血小板数が定常状態に達するまでの期間が長くなるため、効果の確認のためには少なくとも 3 週間は同一用量を維持すること。

7.3.3 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。

7.3.4 血小板数が 50,000/μL～200,000/μL の場合には、出血のリスクを低下できる治療上必要最小限の用量となるよう、適宜減量も考慮すること。

7.3.5 血小板数が 200,000/μL～400,000/μL の場合には本剤を減量すること。

7.3.6 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。この場合血小板数の測定は週に 2 回実施することが望ましい。休薬後、血小板数が 150,000/μL まで減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で投与を再開すること。

7.3.7 本剤の投与量を調節する場合には、通常、12.5mg/日ずつとする。

7.4 本剤を 1 日 50mg、4 週間投与しても血小板数が増加せず、臨床的に問題となる出血傾向の改善が認められない場合には、本剤の投与中止を考慮すること。

〈再生不良性貧血〉

7.5 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記 7.6、7.6.1-7.6.~~5~~4、7.7、7.7.1-7.7.4 を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日（抗胸腺細胞免疫グロブリンで未治療の 6 歳以上 12 歳未満の小児は 12.5mg/日）ずつとする。用量調節時には少なくとも 2 週間は同一用量を維持すること。

7.6 抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合

~~7.6.1 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。［17.1.4 参照］~~

7.6.~~2~~1 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の~~添付文書~~電子添文を熟読すること。

7.6.~~3~~2 血小板数が 200,000/μL を超えた場合には本剤の減量を考慮すること。

7.6.~~4~~3 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。休薬後、血小板数が 200,000/μL 未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

7.6.~~5~~4 本剤を 26 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

7.7 既存治療で効果不十分な患者に投与する場合

7.7.1 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。

7.7.2 血小板数が 100,000/μL～200,000/μL の場合には減量を考慮すること。

7.7.3 血小板数が 200,000/μL を超えた場合には少なくとも 1 週間は本剤を休薬すること。休薬後、血小板数が 50,000/μL 未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

7.7.4 本剤を 16 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

7.8　3 血球系統の改善（目安として、輸血非依存下で血小板数 50,000/μL を超える、輸血非依存下でヘモグロビン値 10g/dL を超える、好中球数 1,000/μL を超える）が 8 週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が更に 8 週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数 30,000/μL 未満、ヘモグロビン値 9g/dL 未満、好中球数 500/μL 未満に低下した場合には休薬前の投与量で投与を再開してもよい。

（下線：追加，取り消し線：削除）

2.2　用法及び用量に関連する注意の設定根拠

〈効能共通〉
7.1 本剤は食事とともに服用すると血中濃度が低下することがあるので、食事の前後 2 時間を避けて空腹時に服用すること。［16.2.1 参照］
7.2 制酸剤、乳製品、多価陽イオン（鉄、カルシウム、アルミニウム、マグネシウム、セレン、亜鉛等）含有製剤等とともに服用すると本剤の血中濃度が低下するので、本剤服用の前 4 時間及び後 2 時間はこれらの摂取を避けること。［10.2、16.2.1、16.7.1 参照］
（現行の記載から変更なし）

成人 AA の承認時に設定した記載であり，本一変申請においても同様の注意喚起が必要であると考え，設定した。

〈再生不良性貧血〉
7.5 本剤の投与中は、血液検査及び肝機能検査を定期的に実施し、本剤の用量は下記 7.6、7.6.1-7.6.~~5~~4、7.7、7.7.1-7.7.4 を参照の上、調節すること。本剤の投与量を調節する場合には、通常、25mg/日（抗胸腺細胞免疫グロブリンで未治療の 6 歳以上 12 歳未満の小児は 12.5mg/日）ずつとする。用量調節時には少なくとも 2 週間は同一用量を維持すること。
（下線：追加，取り消し線：削除）

G2201 試験の免疫抑制療法で未治療の小児に対する ETB115 の用法・用量は，150 試験の東アジア人に対する用法・用量に基づき 75 mg/日（6 歳以上 12 歳未満の小児は 37.5 mg/日）で開始し，血小板数に応じて 2 週間ごとに 25 mg（6 歳以上 12 歳未満の小児は 12.5 mg）ずつ調節することとした（2.5-1.2.2.2.項）。その結果，小児でも成人と同程度の血液学的奏効及び輸血に対する効果が認められ（2.5-6.2 項），安全性に関しても小児特有の懸念は認められなかった（2.5-6.3 項）。これを踏まえ，「（抗胸腺細胞免疫グロブリンで未治療の 6 歳以上 12 歳未満の小児は 12.5mg/日）」を追記することは妥当と判断した。なお，米国では免疫抑制療法で未治療の東アジア人重症 AA 患者に対して 150 試験の東アジア人に対する用法・用量と同様の用法・用量が承認されている。

7.6 抗胸腺細胞免疫グロブリンで未治療の患者に投与する場合
~~7.6.1 抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。［17.1.4 参照］~~
（取り消し線：削除）

150 試験のコホート 1 及びコホート 2 では，ATG と ETB115 の肝毒性の重複が懸念されたため，ATG 投与開始後 14 日目より ETB115 の投与を開始した。この規定は，ATG の投与開始から

ALT 上昇が発現するまでの期間の中央値（範囲）が 5（1～10）日であったとの報告に基づき（Killick et al. 1997），ATGの一過性の肝毒性との重複を避けるために設定された。コホート 1及びコホート 2 の成績を踏まえて，ATG 投与開始と同時に ETB115 の投与を開始するコホート 3 が新たに追加された。その結果，コホート 1 及びコホート 2 と比べ，コホート 3 で高い有効性が得られた。また，コホート 3 で認められた肝機能検査値異常の多くは一過性の事象であり，ETB115 の一時的な減量又は中止により管理可能であったことから，米国では ATG と ETB115 を Day 1 から同時に開始することが認められている。

一方，国内で実施された未治療で中等症以上の成人 AA 患者を対象とした E1202 試験では，試験計画時点で実施されていた 150 試験のコホート 1 及びコホート 2 を参考に，ATG 投与後 15 日目より ETB115 を投与開始した。成人 AA に対する承認審査の過程において，ETB115 の投与開始タイミングに関する注意喚起の記載要否について議論された結果，E1202 試験の試験デザインに基づき承認時国内添付文書には注意喚起が記載された。

G2201 試験では，高い有効性が認められた 150 試験のコホート 3 を参考に，ATG と ETB115 を同時に投与開始することとした。その結果，G2201 試験の全体集団及び日本人小児いずれにおいても，血液学的奏効及び輸血に対する効果が認められた（2.7.6-4.2.1 項，2.5-4.2.2 項）。肝機能異常の有害事象は，全体集団で，投与開始後 7 日以内及び投与開始後 8 日以上 14 日以内にそれぞれ 8 名（22.2%），11 名（30.6%）に発現した（SCS Appendix 2-Japan-Table PUG-2.1.1）。治験治療の中止に至った肝機能異常は，2 名（薬物性肝障害及び肝機能異常 各 1 名）に発現したものの，両被験者ともに治験治療の中止後に回復した。中止に至った 2 名以外ではほとんどの事象が経過観察あるいは休薬又は減量により消失した。

以上より，成人及び小児 AA を対象に，ATG と同時に ETB115 の投与を開始することは可能であると考え，用法及び用量に関連する注意から「抗胸腺細胞免疫グロブリンの投与により肝機能障害があらわれることがあるので、抗胸腺細胞免疫グロブリン投与後、一定期間経過後に本剤の投与を開始すること。［17.1.4 参照］」を削除することは妥当であると判断した。

7.6.~~2~~1 抗胸腺細胞免疫グロブリンの投与に際しては、併用薬剤の~~添付文書~~電子添文を熟読すること。

7.6.~~3~~2 血小板数が 200,000/μL を超えた場合には本剤の減量を考慮すること。

7.6.~~4~~3 血小板数が 400,000/μL を超えた場合には本剤を休薬すること。休薬後、血小板数が 200,000/μL 未満に減少した場合には、休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

7.6.~~5~~4 本剤を 26 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

7.7　既存治療で効果不十分な患者に投与する場合

7.7.1 血小板数 50,000/μL を目安とし、血小板数がそれを下回る場合には増量を考慮すること。

7.7.2 血小板数が 100,000/μL～200,000/μL の場合には減量を考慮すること。

7.7.3 血小板数が 200,000/μL を超えた場合には少なくとも 1 週間は本剤を休薬すること。休薬後、血小板数が 50,000/μL 未満に減少した場合には休薬前の投与量よりも原則として一段階用量を減量した上で本剤の投与を再開すること。

7.7.4 本剤を 16 週間投与しても血球数の改善が認められない場合には本剤の投与を中止すること。

7.8　3 血球系統の改善（目安として、輸血非依存下で血小板数 50,000/μL を超える、輸血非依存下でヘモグロビン値 10g/dL を超える、好中球数 1,000/μL を超える）が 8 週間以上持続した場合には本剤の投与量を最大で半量まで減量すること。減量後の投与量で血球改善が更に 8 週間以上持続した場合には、本剤を休薬し、血球数を観察すること。休薬後に血小板数 30,000/μL 未満、ヘモグロビン値 9g/dL 未満、好中球数 500/μL 未満に低下した場合には休薬前の投与量で投与を再開してもよい。

（下線：追加，取り消し線：削除）

成人 AA の承認時に設定したもので，本一変申請においても同様の注意喚起が必要であると考え，設定した。なお，7.6.2 項は，「医薬品，医療機器等の品質，有効性及び安全性の確保等に関する法律（医薬品医療機器等法）」の改正に基づき，「添付文書」から「電子添文」へ記載整備した。

3　参考文献

Killick SB, Marsh JC, Booth JC, et al. (1997) Liver function abnormality following treatment with antithymocyte globulin for aplastic anaemia. Bone Marrow Transplant; 19(3):249-51. (available upon request)

目　　次

目　　次 2
1　使用上の注意（案）及びその設定根拠 3
2　「9.7 小児等」欄 3
2.1　「9.7 小児等」 3
2.2　「9.7 小児等」の設定根拠 3
3　「11. 副作用」欄 3
3.1　「11.1 重大な副作用」欄 3
3.1.1　「11.1 重大な副作用」 3
3.1.2　「11.1 重大な副作用」の設定根拠 4
3.2　「11.2 その他の副作用」欄 4
3.2.1　「11.2 その他の副作用」 4
3.2.2　「11.2 その他の副作用」の設定根拠 4

1　使用上の注意（案）及びその設定根拠

小児再生不良性貧血に関する承認事項一部変更承認申請にあたり，今回改訂する「9.7 小児等」及び「11.副作用」の注意事項及びその設定根拠を以下に示す。それ以外の「使用上の注意」の記載は，改訂不要と判断した。

2　「9.7 小児等」欄

2.1　「9.7 小児等」

〈慢性特発性血小板減少性紫斑病〉

9.7.1 小児等を対象とした臨床試験は実施していない。

〈再生不良性貧血〉

9.7.2 免疫抑制療法で未治療の低出生体重児，新生児，乳児又は 6 歳未満の幼児を対象とした臨床試験は実施していない。既存治療で効果不十分の小児等を対象とした臨床試験は実施していない。［17.1.6 参照］

（下線部：追記）

2.2　「9.7 小児等」の設定根拠

免疫抑制療法で未治療の重症再生不良性貧血患者を対象とした国際共同第 II 相試験（以下，G2201 試験）は 6 歳以上の患者を対象として実施しており，低出生体重児，新生児，乳児又は 6 歳未満の幼児を対象とした臨床試験は実施していないことから設定した。

既存治療で効果不十分の小児等を対象とした臨床試験は実施していないことから設定した。

3　「11. 副作用」欄

3.1　「11.1 重大な副作用」欄

3.1.1　「11.1 重大な副作用」

11.1.1 肝機能障害

AST（~~23~~.3%），ALT（~~7~~16.7%），ALP（~~6~~5.6%），ビリルビン（~~13~~25.6%）の増加等があらわれることがある。［8.2 参照］

11.1.2 血栓塞栓症

肺塞栓症（頻度不明），深部静脈血栓症（頻度不明），一過性脳虚血発作（~~2~~1.1%），心筋梗塞（頻度不明），虚血性脳卒中（頻度不明）等があらわれることがある。［8.3 参照］

11.1.3 出血（頻度不明）

［8.4 参照］

11.1.4 骨髄線維化（頻度不明）

［8.5 参照］

（取り消し線部：削除，下線部：追記）

3.1.2 「11.1 重大な副作用」の設定根拠

G2201 試験の結果，小児特有の新たな重大な副作用は認められず，現行添付文書に基づき設定した。

重大な副作用及びその他の副作用の発現頻度は，慢性特発性血小板減少性紫斑病患者を対象とした国内第Ⅱ/Ⅲ相試験（TRA108109 試験），慢性特発性血小板減少性紫斑病患者を対象とした国内第Ⅲ相試験（TRA111433 試験），既存治療で効果不十分な中等症以上の再生不良性貧血患者を対象とした国内第Ⅱ/Ⅲ相試験（E1201 試験），抗胸腺細胞免疫グロブリンで未治療の中等症以上の再生不良性貧血患者を対象とした国内第Ⅱ/Ⅲ相試験（E1202 試験）及び G2201 試験を併合した副作用集計結果（添付資料番号 5.3.5.3-3）に基づく。

3.2 「11.2 その他の副作用」欄

3.2.1 「11.2 その他の副作用」

	~~5%以上~~	5%未満	頻度不明
消化器	~~悪心~~	―悪心，腹痛，嘔吐	~~嘔吐，~~下痢，口内乾燥
皮膚	―	発疹，皮膚変色	脱毛症
筋骨格	~~筋痛~~	―筋肉痛，四肢痛	背部痛，筋骨格系胸痛，筋骨格痛
感染症		―	咽頭炎，尿路感染
その他	~~頭痛~~	頭痛，疲労，浮動性めまい，血小板数増加，低カリウム血症，白内障	~~咽頭炎，尿路感染~~―

（取り消し線部：削除，下線部：追記）

3.2.2 「11.2 その他の副作用」の設定根拠

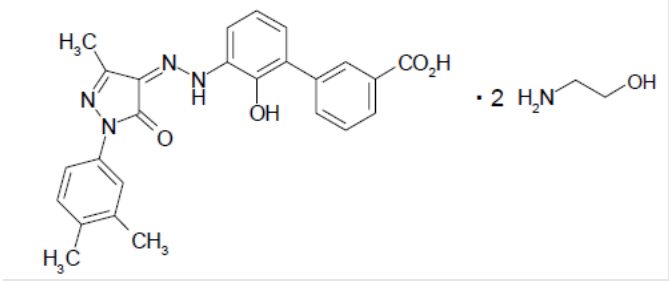
ETB115 の企業中核データシート（v.3.1）で副作用としている事象の内，G2201 試験で副作用として認められた事象（腹痛，皮膚変色*，四肢痛，浮動性めまい）を新たに追記した。

副作用集計結果に基づき，悪心，筋痛及び頭痛は，発現頻度の区分を 5%以上から 5%未満に変更し，嘔吐は，頻度不明から 5%未満に変更した。なお筋痛は，MedDRA ver. 25.0 に従い，筋肉痛に記載整備した。

*皮膚変色の集計条件（MedDRA PTs）：皮膚変色，黄色皮膚，皮膚色素過剰

今回の承認申請で追加すべき資料はないため，該当資料なし

＜現行＞

化学名・別名	3'-{(2Z)-2-[1-(3,4-ジメチルフェニル)-3-メチル-5-オキソ-1,5-ジヒドロ-4H-ピラゾール-4-イリデン]ヒドラジノ}-2'-ヒドロキシビフェニル-3-カルボン酸ビス(2-アミノエタノール)
構造式	
効能・効果	1. 慢性特発性血小板減少性紫斑病 2. 再生不良性貧血
用法・用量	1. 慢性特発性血小板減少性紫斑病の場合 通常，成人には，エルトロンボパグとして初回投与量 12.5 mg を 1 日 1 回，食事の前後 2 時間を避けて空腹時に経口投与する。なお，血小板数，症状に応じて適宜増減する。また，1 日最大投与量は 50 mg とする。 2. 再生不良性貧血の場合 抗胸腺細胞免疫グロブリンで未治療の場合 抗胸腺細胞免疫グロブリンとの併用において，通常，成人には，エルトロンボパグとして 75 mg を 1 日 1 回，食事の前後 2 時間を避けて空腹時に経口投与する。なお，患者の状態に応じて適宜減量する。 既存治療で効果不十分な場合 通常，成人には，エルトロンボパグとして初回投与量 25 mg を 1 日 1 回，食事の前後 2 時間を避けて空腹時に経口投与する。なお，患者の状態に応じて適宜増減する。また，1 日最大投与量は 100 mg とする。
劇薬等の指定	劇薬：原体・製剤 処方せん医薬品：製剤
市販名及び有効成分・分量	原体：エルトロンボパグ　オラミン 製剤：レボレード錠 12.5 mg，25 mg（1 錠中エルトロンボパグとして 12.5 mg，25 mg 含有）
毒性	単回投与 概略の致死量 (mg/kg)　経口 ラット♂♀　1000 イヌ♂♀　>300 反復投与

動物種	投与期間	投与経路	投与量 (mg/kg/日)	無毒性量 (mg/kg/日)	主な所見
ラット	28 週間	経口	3, 10, 30, 60	30	60：死亡，自発運動低下，異常呼吸，削痩，体重増加量・摂餌量↓，白内障，肝臓重量↑，肝細胞変性・壊死・空胞化・肥大，副腎皮質束状帯細胞空胞化・壊死，大腿骨・脛骨骨内膜過形成
イヌ	52 週間	経口	3, 10, 30	30	なし

副　作　用	慢性特発性血小板減少性紫斑病患者を対象とした国内臨床試験において，23 例中 11 例（48%）に臨床検査値異常を含む副作用が報告された。その主なものは，疲労，ALT（GPT）増加，血小板数増加，低カリウム血症各 2 例（9%）であった（承認時）。また，これら 23 例中 19 例がその後国内長期継続投与試験に移行した。移行した 19 例中 5 例（26%）に副作用が報告された。その主なものは，白内障，胸痛各 2 例（11%）であった。（最終報告時） 慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において，135 例中 50 例（37%）に臨床検査値異常を含む副作用が報告された。その主なものは，頭痛 15 例（11%），ALT（GPT）増加 6 例（4%），悪心 6 例（4%），白内障 5 例（4%），下痢 4 例（3%）であった。（承認時） 抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内臨床試験において，10 例中 5 例（50%）に臨床検査値異常を含む副作用が報告された。その主なものは，筋肉痛 3 例（30%），血中ビリルビン増加，悪心各 2 例（20%）であった。（承認時） 既存治療で効果不十分な再生不良性貧血患者を対象とした国内臨床試験において，21 例中 12 例（57%）に臨床検査値異常を含む副作用が報告された。その主なものは，血中 ALP 増加，肝機能異常，高ビリルビン血症，発疹が各 2 例（10%）であった。（承認時）
会　　社	ノバルティスファーマ株式会社　製剤：輸入

＜変更＞　下線部：追加，取り消し線：削除

化学名・別名	
構造式	
効能・効果	
用法・用量	1. 慢性特発性血小板減少性紫斑病~~の場合~~ 通常，成人には，エルトロンボパグとして初回投与量 12.5 mg を 1 日 1 回，食事の前後 2 時間を避けて空腹時に経口投与する。なお，血小板数，症状に応じて適宜増減する。また，1 日最大投与量は 50 mg とする。 2. 再生不良性貧血~~の場合~~ 抗胸腺細胞免疫グロブリンで未治療の場合 抗胸腺細胞免疫グロブリンとの併用において，通常，成人及び 12 歳以上の小児には，エルトロンボパグとして 75 mg を 1 日 1 回，6 歳以上 12 歳未満の小児には，エルトロンボパグとして 37.5 mg を 1 日 1 回，食事の前後 2 時間を避けて空腹時に経口投与する。なお，患者の状態に応じて適宜減量する。 既存治療で効果不十分な場合 通常，成人には，エルトロンボパグとして初回投与量 25 mg を 1 日 1 回，食事の前後 2 時間を避けて空腹時に経口投与する。なお，患者の状態に応じて適宜増減する。また，1 日最大投与量は 100 mg とする。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	慢性特発性血小板減少性紫斑病患者を対象とした国内臨床試験において，23 例中 11 例（48%）に臨床検査値異常を含む副作用が報告された。その主なものは，疲労，ALT ~~(GPT)~~ 増加，血小板数増加，低カリウム血症各 2 例（9%）であった（承認時）。また，これら 23 例中 19 例がその後国内長期継続投与試験に移行した。移行した 19 例中 5 例（26%）に副作用が報告された。その主なものは，白内障，胸痛各 2 例（11%）であった。（最終報告時） 慢性特発性血小板減少性紫斑病患者を対象とした海外臨床試験において，135 例中 50 例（37%）に臨床検査値異常を含む副作用が報告された。その主なものは，頭痛 15 例（11%），ALT ~~(GPT)~~ 増加 6 例（4%），悪心 6 例（4%），白内障 5 例（4%），下痢 4 例（3%）であった。（承認時） 抗胸腺細胞免疫グロブリンで未治療の再生不良性貧血患者を対象とした国内臨床試験において，10 例中 5 例（50%）に臨床検査値異常を含む副作用が報告された。その主なものは，筋肉痛 3 例（30%），血中ビリルビン増加，悪心各 2 例（20%）であった。（承認時） 既存治療で効果不十分な再生不良性貧血患者を対象とした国内臨床試験において，21 例中 12 例（57%）に臨床検査値異常を含む副作用が報告された。その主なものは，血中 ALP 増加，血中ビリルビン増加，肝機能異常，高ビリルビン血症，発疹が各 2 例（10%）であった。（承認時） 免疫抑制療法で未治療の東アジア人再生不良性貧血患者を対象とした国際共同試験において，36 例中 30 例（83%）に臨床検査値異常を含む副作用が報告された。その主なものは，ALT 増加，高ビリルビン血症が各 11 例（31%），γ－GTP 増加が 7 例（19%）であった。また，日本人小児では 5 例中 4 例（80%）に副作用が報告され，主な副作用は ALT 増加 2 例（40%）であった（申請時）
会社	

目　次

目　次 2
1　第 3 部 3
2　第 4 部 3
3　第 5 部 3

1　第 3 部

該当資料なし

2　第 4 部

該当資料なし

3　第 5 部

添付資料番号	Report No./Study No.	表　題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.2　全臨床試験一覧表							
5.2	－	全臨床試験一覧表	－	－	国内	評価	－
5.3　臨床試験報告書							
5.3.1　生物薬剤学試験報告書							
5.3.1.1　バイオアベイラビリティ（BA）試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.1.2　比較 BA 試験及び生物学的同等性（BE）試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.1.3　In Vitro-In Vivo の関連を検討した試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.1.4　生物学的及び理化学的分析法検討報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.2　ヒト生体試料を用いた薬物動態関連の試験報告書							
5.3.2.1　血漿蛋白結合試験報告書							

添付資料番号	Report No./Study No.	表　題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
－	－	該当資料なし	－	－	－	－	－
5.3.2.2　肝代謝及び薬物相互作用試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.2.3　他のヒト生体試料を用いた試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.3　臨床薬物動態（PK）試験報告書							
5.3.3.1　健康被験者における PK 及び初期忍容性試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.3.2　患者における PK 及び初期忍容性試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.3.3　内因性要因を検討した PK 試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.3.4　外因性要因を検討した PK 試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.3.5　ポピュレーション PK 試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.4　臨床薬力学（PD）試験報告書							
5.3.4.1　健康被験者における PD 試験及び PK/PD 試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.4.2　患者における PD 試験及び PK/PD 試験報告書							
－	－	該当資料なし	－	－	－	－	－
5.3.5　有効性及び安全性試験報告書							
5.3.5.1　申請する適応症に関する比較対照試験報告書							
－	－	該当資料なし	－	－	－	－	－

添付資料番号	Report No./Study No.	表　題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5.2　非対照試験報告書							
5.3.5.2-1	ETB115G2201	A non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia (REACTS)	2020 年 11 月 4 日～2022 年 6 月 10 日（データカットオフ） 本報告時点で継続中	中国，日本，韓国，台湾， 計 12 施設	国際共同	評価	あり
5.3.5.3　複数の試験成績を併せて解析した報告書							
5.3.5.3-1	SCE Appendix 1-Japan	SCE Appendix: Outputs for pediatric aplastic anemia submission in Japan	―	―	国内	評価	なし
5.3.5.3-2	SCS Appendix 1-Japan	SCS Appendix: Outputs for pediatric aplastic anemia submission in Japan	―	―	国内	評価	なし
5.3.5.3-3	SCS Appendix 2-Japan	Package insert / risk management plan / proper use guide / interview form /GCP inspection Appendix: Outputs for Japan submission	―	―	国内	評価	なし
5.3.5.4　その他の臨床試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.6　市販後の使用経験に関する報告書							
5.3.6-1	―	PERIODIC SAFETY UPDATE REPORT	Period covered: 2021 年 10 月 1 日 ～ 2022 年 9 月 30 日	―	海外	参考	あり
5.3.6-2	CETB115E1402	CETB115E1402_総括報告書	―	―	国内	参考	あり
5.3.6-3	CETB115B1401	CETB115B1401_総括報告書	―	―	国内	参考	あり
5.3.7　患者データ一覧表及び症例記録							
―	―	該当資料なし	―	―	―	―	―

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
5.4 参考文献　（評価／参考の別：参考資料）		
5.4-1	Alexander WS, Roberts AW, Nicola NA, et al. (1996) Deficiencies in progenitor cells of multiple hematopoietic lineages and defective megakaryocytopoiesis in mice lacking the thrombopoietic receptor c-Mpl. Blood; 87(6):2162-70.	海外
5.4-2	Camitta BM, Rappeport JM, Parkman R, et al. (1975) Selection of patients for bone marrow transplantation in severe aplastic anemia. Blood; 45(3):355-63.	海外
5.4-3	Campbell SD, de Morais SM, Xu JJ (2004) Inhibition of human organic anion transporting polypeptide OATP 1B1 as a mechanism of drug-induced hyperbilirubinemia. Chem Biol Interact; 150(2):179-87.	海外
5.4-4	Cui Y, König J, Leier I, et al. (2001) Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. J Biol Chem; 276(13):9626-30.	海外
5.4-5	Erickson-Miller CL, Kirchner J, Aivado M, et al. (2010) Reduced proliferation of non-megakaryocytic acute myelogenous leukemia and other leukemia and lymphoma cell lines in response to eltrombopag. Leuk Res; 34(9):1224-31.	海外
5.4-6	Geddis AE (2011) Congenital amegakaryocytic thrombocytopenia. Pediatr Blood Cancer; 57(2):199-203.	海外
5.4-7	Killick SB, Bown N, Cavenagh J, et al. (2016) Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol; 172(2):187-207.	海外
5.4-8	Kojima S, Ohara A, Tsuchida M, et al. (2002) Risk factors for evolution of acquired aplastic anemia into myelodysplastic syndrome and acute myeloid leukemia after immunosuppressive therapy in children. Blood; 100(3):786-90.	海外
5.4-9	Kosaka Y, Yagasaki H, Sano K, et al. (2008) Prospective multicenter trial comparing repeated immunosuppressive therapy with stem-cell transplantation from an alternative donor as second-line treatment for children with severe and very severe aplastic anemia. Blood; 111(3):1054-9.	海外
5.4-10	Marsh JC, Ball SE, Cavenagh J, et al. (2009) Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol; 147(1):43-70.	海外
5.4-11	Methia N, Louache F, Vainchenker W, et al. (1993) Oligodeoxynucleotides antisense to the proto-oncogene c-mpl specifically inhibit in vitro megakaryocytopoiesis. Blood; 82(5):1395-401.	海外
5.4-12	Olnes MJ, Scheinberg P, Calvo KR, et al. (2012) Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med; 367(1):11-9.	海外
5.4-13	Qian H, Buza-Vidas N, Hyland CD, et al. (2007) Critical role of thrombopoietin in maintaining adult quiescent hematopoietic stem cells. Cell Stem Cell; 1(6):671-84.	海外
5.4-14	Samarasinghe S and Webb DK (2012) How I manage aplastic anaemia in children. Br J Haematol; 157(1):26-40.	海外

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
5.4-15	Scheinberg P, Wu CO, Nunez O, et al. (2009) Treatment of severe aplastic anemia with a combination of horse antithymocyte globulin and cyclosporine, with or without sirolimus: a prospective randomized study. Haematologica; 94(3):348-54.	海外
5.4-16	Scheinberg P and Young NS (2012) How I treat acquired aplastic anemia. Blood; 120(6):1185-96.	海外
5.4-17	Scheinberg P (2018) Activity of eltrombopag in severe aplastic anemia. Blood Adv; 2(21):3054-62.	海外
5.4-18	Sun H, Tsai Y, Nowak I, et al. (2012) Eltrombopag, a thrombopoietin receptor agonist, enhances human umbilical cord blood hematopoietic stem/primitive progenitor cell expansion and promotes multi-lineage hematopoiesis. Stem Cell Res; 9(2):77-86.	海外
5.4-19	Townsley DM, Scheinberg P, Winkler T, et al. (2017) Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia. N Engl J Med; 376(16):1540-50.	海外
5.4-20	Wire MB, Li X, Zhang J, et al. (2018a) Modeling and Simulation Support Eltrombopag Dosing in Pediatric Patients With Immune Thrombocytopenia. Clin Pharmacol Ther; 104(6):1199-207.	海外
5.4-21	Young NS, Calado RT, Scheinberg P (2006) Current concepts in the pathophysiology and treatment of aplastic anemia. Blood; 108(8):2509-19.	海外
5.4-22	Young NS and Kaufman DW (2008) The epidemiology of acquired aplastic anemia. Haematologica; 93(4):489-92.	海外
5.4-23	Zeigler FC, de Sauvage F, Widmer HR, et al. (1994) In vitro megakaryocytopoietic and thrombopoietic activity of c-mpl ligand (TPO) on purified murine hematopoietic stem cells. Blood; 84(12):4045-52.	海外
5.4-24	小原明 (2008)　日本における小児再生不良性貧血など造血障害性疾患の現状-日本小児血液学会再生不良性貧血委員会疫学調査 1988-2005 年-. 日本小児血液学会雑誌; 22(1):53-62.	国内
5.4-25	小原直 (2020)　再生不良性貧血の参照ガイド. 臨床血液; 61(9):1071-9.	国内
5.4-26	小島勢二 (2014)　小児再生不良性貧血の治療. 臨床血液; 55(10):1769-76.	国内
5.4-27	特発性造血障害に関する調査研究班 (2020)　再生不良性貧血診療の参照ガイド 令和 1 年改訂版. （Internet）Available from: <http://zoketsushogaihan.umin.jp/file/2020/02.pdf> (Accessed 2 Mar 2023)	国内
5.4-28	日本造血細胞移植学会 (2018)　造血細胞移植ガイドライン 再生不良性貧血（小児）（第 3 版）. （Internet）Available from: <https://www.jstct.or.jp/uploads/files/guideline/02_05_aa_ped03.pdf> (Accessed 2 Mar 2023)	国内