ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doptelet 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains avatrombopag maleate equivalent to 20 mg of avatrombopag.

Excipient with known effect

Each film-coated tablet contains 120.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale yellow, round biconvex film-coated 7.6 mm tablet debossed with “AVA” on one side and “20” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).

4.2 Posology and method of administration

Posology

Treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases. Doptelet should be taken at the same time of day (e.g., in the morning or evening) with food, including when taking the dose less frequently than once daily.

Chronic liver disease

Obtain a platelet count prior to the administration of Doptelet therapy and on the day of a procedure to ensure an adequate increase in platelet count, and no unexpectedly high increase in platelet count in the patient populations specified in sections 4.4 and 4.5.

The recommended daily dose of avatrombopag is based on the patient’s platelet count (see Table 1). Dosing should begin 10 to 13 days prior to the planned procedure. The patient should undergo their procedure 5 to 8 days after the last dose of avatrombopag.

Table 1: Daily dose recommendation for avatrombopag

Platelet count ($\times 10^9$/L)	Once-daily dose	Duration of dosing
< 40	60 mg (Three 20 mg tablets)	5 days
≥ 40 to < 50	40 mg (Two 20 mg tablets)	5 days

Duration of treatment
Due to limited information, avatrombopag should not be taken for more than 5 days.

Missed doses
If a dose is missed, it should be taken as soon as it is remembered. Two doses should not be taken at one time to make up for a missed dose. The next dose should be taken at the usual time the next day.

Chronic immune thrombocytopenia

Use the lowest dose of Doptelet needed to achieve and maintain a platelet count ≥ 50×10^9/L as necessary to reduce the risk for bleeding. Do not use avatrombopag to normalise platelet counts. In clinical trials, platelet counts generally increased within 1 week after starting avatrombopag and decreased within 1 to 2 weeks after discontinuation.

Initial dose regimen
The recommended starting dose of Doptelet is 20 mg (1 tablet) once daily with food.

Monitoring and dose adjustment
After initiating therapy, assess platelet counts at least once weekly until a stable platelet count ≥ 50×10^9/L and ≤ 150×10^9/L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment.

Due to the potential risk of platelet counts above 400×10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks.

Dose adjustments (see Table 2 and Table 3) are based on the platelet count response. Do not exceed a daily dose of 40 mg (2 tablets).

Table 2: Avatrombopag dose adjustments for patients with primary chronic immune thrombocytopenia

Platelet count ($\times 10^9$/L)	Dose adjustment or action
< 50 after at least 2 weeks of avatrombopag treatment	• Increase *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
> 150 and ≤ 250	• Decrease *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
> 250	• Stop avatrombopag. • Increase platelet monitoring to twice weekly. • When platelet count is less than 100×10^9/L, decrease *One Dose Level* per Table 3 and reinitiate therapy.
< 50 after 4 weeks of avatrombopag 40 mg once daily	• Discontinue avatrombopag.
> 250 after 2 weeks of avatrombopag 20 mg weekly	• Discontinue avatrombopag.

Table 3: Avatrombopag dose levels for titration in patients with primary chronic immune thrombocytopenia

Dose[≠]	Dose Level
40 mg once daily	6
40 mg three times a week *AND* 20 mg on the four remaining days of each week	5
20 mg once daily*	**4**
20 mg three times a week	3
20 mg twice a week *OR* 40 mg once weekly	2
20 mg once weekly	1

*Initial dose regimen for all patients *except* those taking *moderate or strong dual inducers* or *moderate or strong dual inhibitors* of CYP2C9 and CYP3A4/5, or of CYP2C9 alone.

[≠] Patients taking avatrombopag less frequently than once daily should take the medicinal product in a consistent manner from week to week.

Dose Level 3: Three non-consecutive days a week, e.g. Monday, Wednesday and Friday
Dose Level 2: Two non-consecutive days a week, e.g. Monday and Friday
Dose Level 1: The same day each week, e.g. Monday

In the case of a missed dose, patients should take the missed dose of avatrombopag as soon as they remember. Patients should not take two doses at one time to make up for a missed dose, and should take the next dose per the current regimen.

Avatrombopag can be administered in addition to other ITP medicinal products. Platelet counts should be monitored when combining avatrombopag with other medicinal products for the treatment of primary ITP in order to avoid platelet counts outside of the recommended range, and to determine whether the dose of either medicinal product should be reduced.

Discontinuation
Discontinue avatrombopag if the platelet count does not increase to ≥ 50 × 10^9/L after 4 weeks of dosing at the maximum dose of 40 mg once daily. Discontinue Doptelet if the platelet count is greater than 250 × 10^9/L after 2 weeks of dosing at 20 mg once weekly.

Recommended dose with concomitant moderate or strong dual inducers or inhibitors of CYP2C9 and CYP3A4/5, or of CYP2C9 alone, in patients with chronic immune thrombocytopenia
The recommended starting doses of avatrombopag in patients with chronic immune thrombocytopenia receiving concomitant medicinal products are summarised in Table 4.

Table 4: Avatrombopag recommended starting dose for patients with primary chronic immune thrombocytopenia based on concomitant medications

Concomitant medicinal products	Recommended starting dose
Moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5, or of CYP2C9 alone (e.g., fluconazole)	20 mg (1 tablet) three times a week
Moderate or strong dual inducers of CYP2C9 and CYP3A4/5, or of CYP2C9 alone (e.g., rifampicin, enzalutamide)	40 mg (2 tablets) once daily

Special populations

Elderly
No dose adjustment is required for patients aged 65 years and older (see section 5.2).

Renal impairment
Avatrombopag is not renally excreted, therefore no dose adjustment is required in patients with mild or moderate renal impairment. Avatrombopag has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment.

Due to limited information available, the safety and efficacy of avatrombopag in patients with severe hepatic impairment (Child-Pugh class C, MELD score > 24) have not been established (see section 4.4). No dose adjustment is expected for these patients. Avatrombopag therapy should only be initiated in patients with severe hepatic impairment if the expected benefit outweighs the expected risks (see sections 4.4 and 5.2).

Coexisting medical conditions
Due to limited or no information available, the safety and efficacy of avatrombopag in adult patients with chronic ITP and human immunodeficiency virus [HIV], hepatitis C virus [HCV] or subjects with known systemic lupus erythematosus, acute hepatitis, active chronic hepatitis, cirrhosis, lymphoproliferative disease, myeloproliferative disorders, leukemia, myelodysplasia (MDS), concurrent malignant disease, and significant cardiovascular disease (e.g. Grade III/IV congestive heart failure, atrial fibrillation, status post coronary artery bypass or stent placement) have not been established.

Paediatric population

The safety and efficacy of avatrombopag in children aged less than 1 year have not been established. No data are available.
Currently available data for paediatric patients 1 year of age and older and less than 18 years are described in section 4.8 and 5.1.

CYP2C9 loss-of-function polymorphisms
Avatrombopag exposure may increase in patients with CYP2C9*2 and CYP2C9*3 loss-of-function polymorphisms. Healthy subjects (n = 2) who were homozygous for these mutations (poor metabolizers) had approximately 2-fold higher exposure compared to subjects with wild-type CYP2C9.

Method of administration

Doptelet is for oral use, and the tablets should be taken with food (see section 5.2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Thrombotic/thromboembolic events

Patients with chronic liver disease are known to be at increased risk for thromboembolic events. Portal vein thrombosis has been reported at an increased frequency in patients with chronic liver disease who had platelet counts > 200 × 10^9/L receiving a thrombopoietin receptor agonist (see section 4.8). In patients with chronic immune thrombocytopenia, thromboembolic events (arterial or venous) occurred in 7% (9/128) of patients receiving avatrombopag (see section 4.8).

Doptelet was not studied in patients with prior thromboembolic events. Consider the potential increased thrombotic risk when administering Doptelet to patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (e.g. Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency), acquired risk factors (e.g. antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Doptelet should not be administered to patients with chronic liver disease or chronic immune thrombocytopenia in an attempt to normalise platelet counts.

QTc prolongation with concomitant medicinal products

At exposures similar to that achieved at the 40 mg and 60 mg dose, Doptelet did not prolong the QT interval to any clinically relevant extent. Mean QTc prolongation effects > 20 ms are not anticipated with the highest recommended therapeutic dosing regimen based on analysis of data from the pooled clinical trials in patients with chronic liver disease. However, caution must be exercised when Doptelet is co-administered with moderate or strong dual CYP3A4/5 and CYP2C9 inhibitors, or with moderate or strong CYP2C9 inhibitors, as these medicinal products can increase avatrombopag exposures. Caution must also be exercised in patients with loss-of-function polymorphisms of CYP2C9, as these can increase avatrombopag exposure.

Reoccurrence of thrombocytopenia and bleeding after cessation of treatment in patients with chronic immune thrombocytopenia

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with avatrombopag. Following discontinuation of avatrombopag, 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. There is an increased risk of bleeding if avatrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of treatment with avatrombopag. It is recommended that, if treatment with avatrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may

include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support.

Increased bone marrow reticulin

Increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines. Increased reticulin may be suggested by morphological changes in the peripheral blood cells and can be detected through bone marrow biopsy. Therefore, examinations for cellular morphological abnormalities using peripheral blood smear and complete blood count (CBC) prior to and during treatment with avatrombopag are recommended.

If a loss of efficacy and abnormal peripheral blood smear are observed in patients, administration of avatrombopag should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow biopsy, and the risk-benefit of avatrombopag and alternative ITP treatment options should be re-assessed.

Progression of existing myelodysplastic syndrome (MDS)

The effectiveness and safety of Doptelet have not been established for the treatment of thrombocytopenia due to MDS. Doptelet should not be used outside of clinical trials for the treatment of thrombocytopenia due to 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.

The diagnosis of ITP in adults and elderly patients should have been 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, for those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

Severe hepatic impairment

There is limited information on the use of avatrombopag in patients with severe (Child-Pugh class C, MELD score > 24) hepatic impairment. Avatrombopag should only be used in such patients if the expected benefit outweighs the expected risks (see sections 4.2 and 5.2).

Patients with severe hepatic impairment should be supported in line with clinical practice by close monitoring for early signs of worsening or new onset hepatic encephalopathy, ascites, and thrombotic or bleeding tendency, through monitoring of liver function tests, tests used for assessing clotting status and through imaging of portal vasculature as needed.

Patients with Child-Pugh class C liver disease who take avatrombopag prior to an invasive procedure, should be evaluated on the day of the procedure for an unexpectedly high increase in platelet count.

Use in patients with chronic liver disease undergoing invasive procedures

The objective of treatment with Doptelet is to increase platelet counts. While the benefit-risk profile for procedures that were not specifically included in the clinical trials is likely to be comparable, the efficacy and safety of avatrombopag have not been established in major surgeries like laparotomy, thoracotomy, open-heart surgery, craniotomy or excision of organs.

Retreatment for patients with chronic liver disease undergoing invasive procedures

There is limited information on the use of avatrombopag in patients previously exposed to avatrombopag.

Co-administration with interferon preparations

Interferon preparations have been known to reduce platelet counts, therefore, this should be considered when co-administering avatrombopag with interferon preparations.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

P-gp inhibitors

Concomitant use of avatrombopag with P-gp inhibitors resulted in alterations in exposure that were not clinically significant. No dose adjustment is recommended (see section 5.2).

CYP3A4/5 and CYP2C9 inhibitors

Concomitant use of avatrombopag with moderate or strong CYP3A4/5 and CYP2C9 dual inhibitors (e.g., fluconazole) increases avatrombopag exposure. Concomitant use of avatrombopag with moderate or strong CYP2C9 inhibitors is expected to increase avatrombopag exposure.

Chronic liver disease

The increase in avatrombopag exposure is not expected to have a clinically important effect on platelet counts due to the 5-day treatment duration, and no dose adjustment is recommended. However, these patients should be evaluated on the day of the procedure for an unexpectedly high increase in platelet count (see section 4.2 and 5.2).

Chronic immune thrombocytopenia

Reduce the starting dose of avatrombopag when used concomitantly with a moderate or strong dual inhibitor of CYP2C9 and CYP3A4/5 (see Table 4 and section 4.2). Reduction of the starting dose should also be considered for patients receiving a moderate or strong CYP2C9 inhibitor.
In patients starting moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5, or moderate or strong inhibitors of CYP2C9, while receiving avatrombopag, monitor platelet counts and adjust the avatrombopag dose as necessary (see Table 2, Table 3 and section 4.2).

CYP3A4/5 and CYP2C9 inducers

Concomitant use of moderate or strong CYP3A4/5 and CYP2C9 dual inducers (e.g., rifampicin, enzalutamide) reduces avatrombopag exposure, and may result in a decreased effect on platelet counts. Concomitant use of avatrombopag with moderate or strong CYP2C9 inducers is expected to reduce avatrombopag exposure.

Chronic liver disease

The decrease in avatrombopag exposure is not expected to have a clinically important effect on platelet counts due to the 5-day treatment duration. No dose adjustment is recommended (see section 5.2).

Chronic immune thrombocytopenia

Increase the recommended starting dose of Doptelet when used concomitantly with a moderate or strong dual inducer of CYP2C9 and CYP3A4/5 (see Table 4 and section 4.2). An increase in the starting dose should also be considered for patients receiving a moderate or strong CYP2C9 inducer. In patients starting moderate or strong dual inducers of CYP2C9 and CYP3A4/5, or moderate or strong inducers of CYP2C9, while receiving avatrombopag, monitor platelet counts and adjust dose as necessary (see Table 2, Table 3 and section 4.2).

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with avatrombopag in clinical trials included corticosteroids, danazol, dapsone, and intravenous immunoglobulin (IVIg). Platelet counts should be monitored when combining avatrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of avatrombopag in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Doptelet is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There are no data on the presence of avatrombopag in human milk, the effects on the breastfed child, or the effects on milk production. It is unknown whether avatrombopag or its metabolites are excreted in human milk. Avatrombopag was present in the milk of lactating rats, see section 5.3. A risk to the breast-feeding child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Doptelet therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of avatrombopag on human fertility has not been established, and a risk cannot be ruled out. In animal studies, avatrombopag had no effect on male and female fertility or early embryogenesis in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Doptelet has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Chronic liver disease

The safety of avatrombopag was evaluated in two randomised, double-blind, placebo-controlled trials, ADAPT-1 and ADAPT-2, in which 430 patients with chronic liver disease and thrombocytopenia received either avatrombopag (n = 274) or placebo (n = 156), and had 1 post-dose safety assessment.

Chronic immune thrombocytopenia

The safety of avatrombopag in adult patients was evaluated in three controlled trials and one uncontrolled trial which enrolled 161 patients with chronic immune thrombocytopenia. The pooled safety data from these four trials includes 128 patients who were exposed to avatrombopag for a median duration of 29 weeks.

The safety of avatrombopag in paediatric patients ≥ 1 to < 18 years of age with persistent or chronic thrombocytopenia was evaluated in a randomized, placebo-controlled trial with a 12-week double-blind Core Phase followed by an optional open-label Extension Phase in which patients could receive avatrombopag for up to 2 years. The safety data from the Core Phase includes 54 patients who were exposed to avatrombopag for a median duration of 12 weeks. The overall safety profile in paediatric patients treated with avatrombopag is comparable to that in adult patients.

Tabulated list of adverse reactions

Adverse reactions are classified by Preferred Term and System Organ Class, and by frequency. Frequencies are defined as: 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); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Chronic liver disease study population

System organ class (MedDRA terminology*)	**Common**	**Uncommon**	**Not known**
Blood and lymphatic system disorders		Anaemia	
Immune system disorders			Hypersensitivity
Vascular disorders		Portal vein thrombosis	
Musculoskeletal & connective tissue disorders		Bone pain Myalgia	
General disorders and administration site conditions	Fatigue	Pyrexia	

* Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Chronic primary immune thrombocytopenia study population

System organ class MedDRA terminology	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Furuncle, Thrombophlebitis septic, Upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	Myelofibrosis
Blood and lymphatic system disorders	Common	Thrombocytopenia, Anaemia, Splenomegaly
	Uncommon	Leukocytosis
Immune system disorders	Not known	Hypersensitivity
Metabolism and nutrition disorders	Common	Hyperlipidaemia, Decreased appetite
	Uncommon	Dehydration, Hypertriglyceridaemia, Increased appetite, Iron deficiency
Psychiatric disorders	Uncommon	Mood swings

System organ class MedDRA terminology	Frequency	Adverse reaction
Nervous system disorders	Very common	Headache
	Common	Dizziness, Head discomfort, Migraine, Paraesthesia
	Uncommon	Cerebrovascular accident, Cognitive disorder, Dysgeusia, Hypoaesthesia, Sensory disturbance, Transient ischaemia attack
Eye disorders	Uncommon	Abnormal sensation in eye, Eye irritation, Eye pruritus, Eye swelling, Lacrimation increased, Ocular discomfort, Photophobia, Retinal artery occlusion, Vision blurred, Visual impairment
Ear and labyrinth disorders	Uncommon	Ear pain, Hyperacusis
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension
	Uncommon	Deep vein thrombosis, Jugular vein thrombosis, Vasoconstriction
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis, Dyspnoea
	Uncommon	Haemoptysis, Nasal congestion, Pulmonary embolism
Gastrointestinal disorders	Common	Nausea, Diarrhoea, Vomiting, Abdominal pain upper, Flatulence
	Uncommon	Abdominal discomfort, Abdominal distension, Abdominal pain lower, Anorectal varices, Constipation, Eructation, Gastrooesophageal reflux disease, Glossodynia, Haemorrhoids, Paraesthesia oral, Swollen tongue, Tongue disorder
Hepatobiliary disorders	Uncommon	Portal vein thrombosis
Skin and subcutaneous tissue disorders	Common	Rash, Acne, Petechiae, Pruritis
	Uncommon	Alopecia, Dry skin, Ecchymosis, Hyperhidrosis, Pigmentation disorder, Rash pruritic, Skin haemorrhage, Skin irritation
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Back pain, Pain in extremity, Myalgia, Musculoskeletal pain
	Uncommon	Arthropathy, Limb discomfort, Muscle spasms, Muscular weakness, Musculoskeletal chest pain
Renal and urinary disorders	Uncommon	Haematuria
Reproductive system and breast disorders	Uncommon	Menorrhagia, Nipple pain
General disorders and administration site conditions	Very common	Fatigue
	Common	Asthenia
	Uncommon	Chest discomfort, Hunger, Pain, Peripheral swelling

System organ class MedDRA terminology	Frequency	Adverse reaction
Investigations	Common	Blood glucose increased, Platelet count increased**, Blood glucose decreased, Blood triglycerides increased, Blood lactate dehydrogenase increased, Platelet count decreased, Alanine aminotransferase increased, Blood gastrin increased
	Uncommon	Aspartate aminotransferase increased, Blood pressure increased, Heart rate irregular, Hepatic enzyme increased

* Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.
** In the clinical trial in paediatric patients, thrombocytosis was reported in one patient during the Core Phase of the study and in one patient during the open-label Extension Phase.

Description of selected adverse reactions

Thromboembolic events

In the ADAPT-1 and ADAPT-2 clinical trials in patients with thrombocytopenia and chronic liver disease, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n = 1/274 of patients receiving avatrombopag) which was reported 14 days after treatment with Doptelet ended. This adverse reaction was assessed as non-serious.

In the four pooled clinical trials in adult patients with chronic immune thrombocytopenia, thromboembolic events were observed in 7% (9/128) of patients. The only thromboembolic event which occurred in more than 1 individual patient was cerebrovascular accident, occurring in 1.6% (2/128). In paediatric patients with persistent or chronic immune thrombocytopenia, thromboembolic events occurred in 1.4% (1/73) of patients receiving avatrombopag.

Thrombocytopenia following discontinuation of treatment in patients with chronic immune thrombocytopenia

In the 4 pooled clinical trials in patients with chronic immune thrombocytopenia, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8.6% (11/128) of patients treated with avatrombopag.

Hypersensitivity reactions

Hypersensitivity reactions including pruritus, rash, swelling face, and swollen tongue.

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

There is no specific antidote for overdose with avatrombopag. Should overdose occur or be suspected, Doptelet dosing should be stopped and platelet count should be carefully monitored since avatrombopag increases platelet count in a dose-dependent fashion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics, ATC code: B02BX08

Mechanism of action

Avatrombopag is an orally active, small molecule thrombopoietin (TPO) receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production.

Clinical efficacy and safety

Chronic liver disease studies

The efficacy and safety of avatrombopag for the treatment of adult patients with chronic liver disease and a platelet count $< 50 \times 10^9$/L who were scheduled to undergo a procedure were studied in 2 identically-designed multicenter, randomised, double-blind, placebo-controlled Phase 3 studies (ADAPT-1 and ADAPT-2). In each study, patients were assigned to the low baseline platelet count cohort ($< 40 \times 10^9$/L) or the high baseline platelet count cohort (≥ 40 to $< 50 \times 10^9$/L) based on their platelet count at baseline. Patients were then randomised 2:1 to either avatrombopag or placebo.

Patients in the low baseline platelet count cohort received 60 mg avatrombopag or matching placebo once daily for 5 days, and patients in the high baseline platelet count cohort received 40 mg avatrombopag or matching placebo once daily for 5 days. Eligible patients were scheduled to undergo their procedure (low bleeding risk procedures, such as endoscopy and colonoscopy (60.8%); moderate bleeding risk, such as liver biopsy and chemoembolization for HCC (17.2%); or high bleeding risk, such as dental procedures and radiofrequency ablation (22.1%)) 5 to 8 days after their last dose of treatment. Patient populations were similar between the low and high baseline platelet count cohorts, and consisted of 66% male and 35% female; median age 58 years and 61% White, 34% Asian, and 3% Black. A total of 24.8% of patients were ≥ 65 years of age, 4.6% ≥ 75 years of age, and only 1 (0.2%) ≥ 85 years of age. Patients' MELD scores ranged from < 10 (37.5%), 10 to 14 (46.3%) and from > 14 to < 24 (16.2%), and included patients with CTP Class A (56.4%), Class B (38.1%), and Class C (5.6%).

In ADAPT-1, a total of 231 patients were randomised; 149 patients to the avatrombopag group and 82 patients to the placebo group. In the low baseline platelet count cohort, the mean baseline platelet count for the avatrombopag-treated group was 31.1×10^9/L and for placebo-treated patients was 30.7×10^9/L. In the high baseline platelet count cohort, the mean baseline platelet count for the avatrombopag-treated patients was 44.3×10^9/L and for placebo-treated patients was 44.9×10^9/L.

In ADAPT-2, a total of 204 patients were randomised; 128 patients to the avatrombopag treatment group and 76 patients to the placebo treatment group. In the low baseline platelet count cohort, the mean baseline platelet count for the avatrombopag-treated group was 32.7×10^9/L and for placebo-treated patients was 32.5×10^9/L. In the high baseline platelet count cohort, the mean baseline platelet count for the avatrombopag-treated patients was 44.3×10^9/L and for placebo-treated patients was 44.5×10^9/L.

Responders were defined as patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomisation and up to 7 days following a scheduled procedure. Results are shown in Table 5.

Table 5: Efficacy results by baseline platelet count cohort and treatment group – ADAPT-1 and ADAPT-2

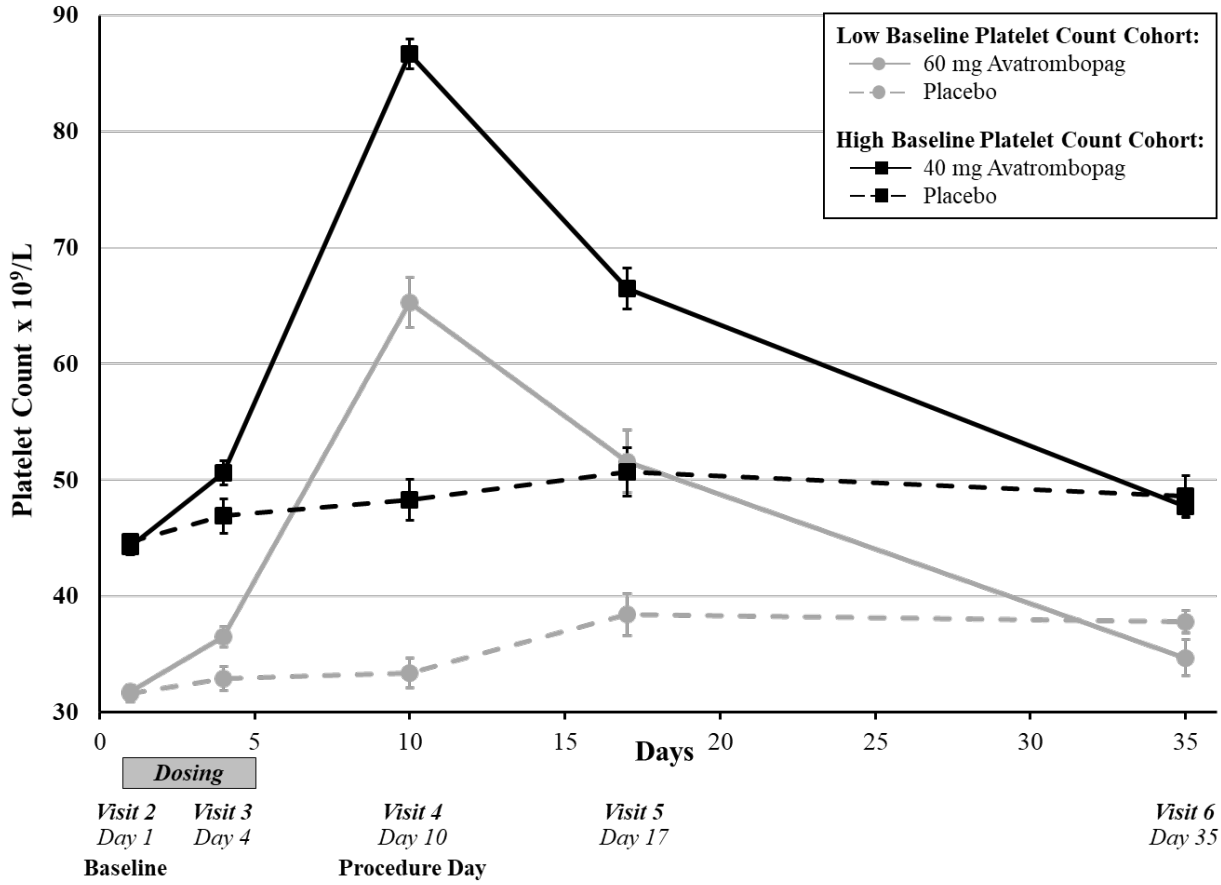
Low baseline platelet count cohort (< 40 × 10^9/L)				
Category	**ADAPT-1**		**ADAPT-2**	
	Placebo (n = 48)	**Avatrombopag 60 mg (n = 90)**	**Placebo (n = 43)**	**Avatrombopag 60 mg (n = 70)**
Proportion of subjects not requiring a platelet transfusion or rescue procedure for bleeding				
Responders *95% CI*[a]	**23%** *(11, 35)*	**66%** *(56, 75)*	**35%** *(21, 49)*	**69%** *(58, 79)*
P-value[b]	**< 0.0001**		**0.0006**	
Proportion of subjects who achieved a platelet count ≥ 50 × 10^9/L on procedure day				
Responders *95% CI*[a]	**4%** *(0, 10)*	**69%** *(59, 79)*	**7%** *(0, 15)*	**67%** *(56, 78)*
P-value[b]	**< 0.0001**		**< 0.0001**	
Change in platelet count from baseline to procedure day				
Mean (SD) × 10^9/L	**0.8** (6.4)	**32.0** (25.5)	**3.0** (10.0)	**31.3** (24.1)
Median × 10^9/L	0.5	28.3	0.5	28.0
P-value[c]	**< 0.0001**		**< 0.0001**	

High baseline platelet count (≥ 40 to < 50 × 10^9/L)				
Category	**ADAPT-1**		**ADAPT-2**	
	Placebo (n = 34)	**Avatrombopag 40 mg (n = 59)**	**Placebo (n = 33)**	**Avatrombopag 40 mg (n = 58)**
Proportion of subjects not requiring a platelet transfusion or rescue procedure for bleeding				
Responders *95% CI*[a]	**38%** *(22, 55)*	**88%** *(80, 96)*	**33%** *(17, 49)*	**88%** *(80, 96)*
P-value[b]	**< 0.0001**		**< 0.0001**	
Proportion of subjects who achieved a platelet count ≥ 50 × 10^9/L on procedure day				
Responders *95% CI*[a]	**21%** *(7, 34)*	**88%** *(80, 96)*	**39%** *(23, 56)*	**93%** *(87, 100)*
P-value[b]	**< 0.0001**		**< 0.0001**	
Change in platelet count from baseline to procedure day				
Mean (SD) × 10^9/L	**1.0** (9.3)	**37.1** (27.4)	**5.9** (14.9)	**44.9** (33.0)
Median × 10^9/L	0.0	33.0	3.3	41.3
P-value[c]	**< 0.0001**		**< 0.0001**	

a Two-sided 95% confidence interval based on normal approximation.
b Cochran-Mantel-Haenszel Test.
c Wilcoxon Rank Sum Test.

A measured increase in platelet counts was observed in both avatrombopag treatment groups over time beginning on Day 4 post-dose, which peaked on Day 10-13 and then returned to near baseline values by Day 35 (Figure 1); mean platelet count remained greater than or equal to 50 × 10^9/L on Day 17 (Visit 5).

Figure 1: Mean platelet count (+/- standard error) by days from start of dosing by baseline platelet count cohort and treatment group - pooled ADAPT-1 and ADAPT-2



The efficacy of avatrombopag was similar across various subgroups for the pooled Phase 3 study population (ADAPT-1 and ADAPT-2). The proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding was generally similar across the various subgroups.

Chronic immune thrombocytopenia studies

The efficacy of Doptelet in adult patients with chronic immune thrombocytopenia was evaluated in a Phase 3, multicentre, randomised, double-blind, placebo-controlled trial (Study 302). Patients had previously received one or more prior chronic immune thrombocytopenia therapies and had an average of screening and baseline platelet counts $< 30 \times 10^9$/L. Patients were centrally stratified by splenectomy status, baseline platelet count (≤ 15 or $> 15 \times 10^9$/L), and use of concomitant chronic immune thrombocytopenia medicinal products, and then randomised (2:1) to receive either avatrombopag or placebo for 6 months. Patients received a starting dose of 20 mg once daily, with doses subsequently titrated based on platelet response.

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 29% of placebo patients and 34% of avatrombopag patients had a prior splenectomy.

Forty-nine patients were randomised, 32 to avatrombopag and 17 to placebo, with similar mean [SD] baseline platelet counts in the 2 treatment groups (14.1 [8.6] × 10^9/L and 12.7 [7.8] × 10^9/L, respectively). The median age was 44 years, 63% were female, and 94% were Caucasian, 4% Asian and 2% Black. A total of 8.2% of patients were ≥ 65 years of age, and no patients were ≥ 75 years of age. The median duration of exposure was 26 weeks for avatrombopag-treated patients and 6 weeks for placebo-treated patients. The primary efficacy outcome in this trial was the cumulative number of weeks in which the platelet count was ≥ 50 × 10^9/L during the 6-month treatment period in the absence of rescue therapy. Avatrombopag-treated patients had a longer duration of platelet counts ≥ 50 × 10^9/L in the absence of rescue therapy than those who received placebo (median 12.4 [0, 25] vs 0 [0, 2] weeks, respectively, p < 0.0001) (see Table 6).

Table 6: Cumulative number of weeks of platelet response - Study 302

Primary efficacy outcome	Avatrombopag (n = 32)	Placebo (n = 17)
Cumulative number of weeks with a platelet response*		
Mean (SD)	12.0 (8.75)	0.1 (0.49)
Median	12.4	0.0
Min, Max	0, 25	0, 2
p-value of Wilcoxon rank sum test	< 0.0001	

* Cumulative number of weeks of platelet response is defined as the total numbers of weeks in which the platelet count was ≥ 50 × 10^9/L during 6 months of treatment in the absence of rescue therapy.

In addition, a larger proportion of patients in the avatrombopag treatment group had platelet counts ≥ 50 × 10^9/L at Day 8 compared to placebo (21/32; 66% vs 0/17; 0.0%, respectively; 95% CI (47, 86); p < 0.0001). Though few subjects were receiving concomitant ITP medicinal products at baseline, a larger proportion of patients in the avatrombopag treatment group had a reduction in use of concomitant ITP medicinal products from baseline compared to placebo (5/15; 33% vs 0/7; 0.0%, respectively; 95% CI (12, 62); p = 0.1348).

Persistent or chronic immune thrombocytopenia study in paediatric patients

The efficacy of Doptelet was evaluated in paediatric patients ≥ 1 to < 18 years of age with persistent or chronic immune thrombocytopenia in a randomized, double-blind, placebo-controlled trial. A 12-week randomized treatment phase (Core Phase) was followed by an optional Extension Phase in which all patients received avatrombopag.

Patients were required to have had a diagnosis of primary ITP for ≥ 6 months and had an insufficient response to at least one previous treatment. The study enrolled 75 patients randomized 3:1 avatrombopag: placebo in 3 age cohorts: ≥ 12 to < 18 years of age (n = 29); ≥ 6 to < 12 years of age (n = 28); and ≥ 1 to < 6 years of age (n = 18).

The primary endpoint was durable platelet response, defined as the proportion of patients achieving at least 6 out of 8 weekly platelet counts ≥ 50×10^9/L during the last 8 weeks of the 12-week Treatment Period in the Core Phase in the absence of rescue medication.

The alternative primary endpoint (analysed as a secondary endpoint) was platelet response, defined as the proportion of subjects achieving at least 2 consecutive platelet assessments ≥ 50×10^9/L in the Core Phase in the absence of rescue medication.

Table 7: Durable Platelet Response and Platelet Response - Phase 3 Trial in Paediatric Patients with Persistent or Chronic ITP

Endpoint	Avatrombopag (n = 54)	Placebo (n = 21)
Durable platelet response, n% (primary)		
Yes	15 (27.8)	0
No	39 (72.2)	21 (100.0)
Difference of proportion (avatrombopag – placebo) (95% CI)	27.8 (15.8, 39.7)	
Cochran-Mantel-Haenszel (avatrombopag vs. placebo) p-value	p = 0.0077[a]	
Platelet response, n% (alternative primary)		
Yes	44 (81.5)	0
No	10 (18.5)	21 (100.0)
Difference of proportion (avatrombopag – placebo) (95% CI)	81.5 (71.1, 91.8)	
Cochran-Mantel-Haenszel (avatrombopag vs. placebo) p-value	p < 0.0001[a]	

[a] Denotes p-value from Fisher's Exact Test, which was used in place of Cochran-Mantel-Haenszel test due to sparse number of responders in the strata.
Note: The Cochran-Mantel-Haenszel test is adjusted for age cohort and baseline platelet counts.

The proportion of subjects who required rescue therapy was significantly lower (p = 0.0008) in the avatrombopag group (7.4%) than in the placebo (42.9%) group.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Doptelet in all subsets of the paediatric population in thrombocytopenia secondary to liver disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The plasma concentration-time profiles following the oral administration of avatrombopag were characterised by a short lag time (0.5 – 0.75 hours) with peak exposure at 6 – 8 hours post dose. In a multiple-dose pharmacokinetic study in healthy volunteers, steady state was reached by day 5 of dosing. Open label, randomised, cross-over replicate design clinical trials were conducted in healthy subjects to assess the effects of high-fat and low-fat food on the bioavailability and pharmacokinetic variability of avatrombopag. Administration with either type of food did not have any clinically important effects on rate (C_{max}) or extent (AUC) of avatrombopag exposure. However, there was a significant reduction (by approximately 50%) in the between- and within-subject variability of avatrombopag AUC and C_{max} when administered with food (see sections 4.2 and 4.5).

Food interaction

Coadministration of avatrombopag with either a high-fat or low-fat meal did not result in clinically important changes in rate or extent of absorption of avatrombopag. However, administration of avatrombopag with both a high and low-fat meal reduced intersubject and intrasubject pharmacokinetic variability of avatrombopag by approximately 50%. Therefore, avatrombopag is recommended to be administered with food (see section 4.2).

Distribution

In vitro studies suggest that avatrombopag is highly bound to human plasma proteins (> 96%). The apparent volume of distribution of avatrombopag in patients with thrombocytopenia and chronic liver disease based on population pharmacokinetic analysis is approximately 180 L, and the apparent volume of distribution with patients with chronic immune thrombocytopenia is approximately 235 L, suggesting that avatrombopag is extensively distributed.

Biotransformation

The oxidative metabolism of avatrombopag is mainly mediated by CYP2C9 and CYP3A4/5. Avatrombopag is a substrate for p-glycoprotein (P-gp) mediated transport, although no clinically important differences in platelet count elevations are expected when avatrombopag is co-administered with a strong P-gp inhibitor. Based on *in vitro* studies, no other transporting proteins (OATP1B1, OATP1B3, OCT2, OAT1, and OAT3) are expected to play a significant role in the disposition of avatrombopag.

Table 8: Drug interactions: Changes in pharmacokinetics of avatrombopag in the presence of co-administered medicinal product

Co-administered medicinal product*	**Geometric mean ratio [90% CI] of avatrombopag PK with/without co administered drug (No Effect = 1.00)**	
	$AUC_{0\text{-}inf}$	**C_{max}**
Strong CYP3A inhibitor		
Itraconazole	1.37 (1.10, 1.72)	1.07 (0.86, 1.35)
Moderate CYP3A and CYP2C9 inhibitor		
Fluconazole	2.16 (1.71, 2.72)	1.17 (0.96, 1.42)
Moderate CYP2C9 and strong CYP3A inducer		
Rifampin	0.57 (0.47, 0.62)	1.04 (0.88, 1.23)
P-gp inhibitor		
Cyclosporine	0.83 (0.65, 1.04)	0.66 (0.54, 0.82)
P-gp and moderate CYP3A inhibitor		
Verapamil	1.61 (1.21, 2.15)	1.26 (0.96, 1.66)

* at steady state, except for cyclosporine which was administered as a single dose

Effect of avatrombopag
Avatrombopag does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A, does not induce CYP1A, CYP2B6, CYP2C, and CYP3A, and weakly induces CYP2C8 and CYP2C9 *in vitro.*

Avatrombopag inhibits organic anion transporter (OAT) 1 and 3 and breast cancer resistance protein (BCRP) but not organic anion transporter polypeptide (OATP) 1B1 and 1B3, and organic cation transporter (OCT) 2 *in vitro.*

Effect of transporting proteins
Avatrombopag is a substrate for P-glycoprotein (P-gp) mediated transport (see Table 8).
Avatrombopag is not a substrate for OATP1B1, OATP1B3, OCT2, OAT1, and OAT3.

Elimination

The predominant route of avatrombopag excretion is via faeces. Following administration of a single 20 mg ^{14}C-avatrombopag dose to healthy male volunteers, 88% of the dose was recovered in faeces and 6% in urine. Of the 88% of drug-related material in the faeces, 77% was identified as parent (34%) and the 4-hydroxy metabolite (44%). No metabolites of avatrombopag were detected in plasma.

The mean plasma elimination half-life (%CV) of avatrombopag is approximately 19 hours (19%). The mean (%CV) of the clearance of avatrombopag is estimated to be 6.9 L/hr (29%).

Linearity

Avatrombopag demonstrated dose-proportional pharmacokinetics after single doses from 10 mg (0.5-times the lowest approved dose) to 80 mg (1.3-times the highest recommended dose).

Special populations

Elderly
Population pharmacokinetic analysis of avatrombopag plasma concentrations from clinical trials with healthy subjects and patients with thrombocytopenia due to chronic liver disease or healthy subjects and patients with ITP, that included 11% (84/787) and 4% (24/577) of the study population ≥ 65 years of age, respectively, suggested that avatrombopag exposures are not affected by age (see section 4.2).

Racial or ethnic groups
Population pharmacokinetic analysis of avatrombopag plasma concentrations from the clinical trials with healthy subjects, patients with thrombocytopenia due to chronic liver disease, and patients with ITP indicated that avatrombopag exposures were similar across the different races studied.

Renal impairment
Human studies demonstrated that the renal route is not a major pathway for either unchanged avatrombopag or its metabolite's elimination. Based on the known metabolic profile of avatrombopag and the fact that only 6% of the dose is excreted in urine, the likelihood of effects of renal impairment on pharmacokinetics of avatrombopag is considered to be very low (see sections 4.2 and 4.8).
The population pharmacokinetic analysis of avatrombopag in healthy subjects and subjects with thrombocytopenia due to chronic liver disease indicated similar exposures between healthy subjects and subjects with mild and moderate renal impairment (CrCL ≥ 30 mL/min, Cockcroft-Gault).

Pharmacokinetics and pharmacodynamics of avatrombopag have not been investigated in patients with severe renal impairment (CrCL < 30 mL/min, Cockcroft-Gault) including patients requiring haemodialysis.

Hepatic impairment
A population pharmacokinetic analysis evaluated avatrombopag plasma exposures in patients with mild to moderate hepatic impairment based on Model for End-Stage Liver Disease (MELD) scores and Child-Turcotte-Pugh scores. No clinically important difference in avatrombopag exposures were observed between patients with Child-Turcotte-Pugh Scores (Range = 5 to 12) or MELD scores (Range = 4 to 23) and healthy subjects. Avatrombopag plasma exposure was comparable in patients with chronic liver disease secondary to viral hepatitis (n = 242), non-alcoholic steatohepatitis (n = 45) and alcoholic liver disease (n = 49) in the pivotal Phase 3 studies, and also comparable to that in healthy subjects (n = 391). Due to the limited information available, avatrombopag should only be used in Child-Pugh class C patients when the expected benefit outweighs the expected risks.

5.3 Preclinical safety data

Avatrombopag does not stimulate platelet production in mice, rats, monkeys, or dogs because of the unique TPO receptor specificity. Therefore, data from these animal studies do not fully model potential adverse effects related to platelet count increases due to avatrombopag in humans.

Effects in non-clinical trials were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. The primary toxicity of avatrombopag in pivotal repeated-dose studies was in the stomach at high doses with adequate safety margins when compared to the exposure at the maximum recommended human dose; these effects were reversible even in the chronic toxicity studies.

Carcinogenesis

In two-year carcinogenicity studies in mice and rats, neuroendocrine cell (enterochromaffin-like cell, ECL cell) gastric tumours (carcinoids) occurred in the stomach at high doses. The gastric carcinoids were considered likely due to prolonged hypergastrinemia observed in toxicity studies. Hypergastrinemia-related gastric carcinoids in rodents are generally considered to be of low risk or relevance to humans.

Avatrombopag was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberrations assay or in an *in vivo* rat bone marrow micronucleus assay.

Animal toxicology and/or pharmacology

In 4-week or longer repeated-dose toxicity studies, treatment-related gastric lesions were observed in mice, rats, and cynomolgus monkeys. In these species, avatrombopag was associated with histopathologic changes in the fundic mucosa of the glandular stomach, characterised by degeneration of the glandular epithelium with a decrease in matured parietal cells. This effect was not associated with inflammatory response or any evidence of erosion or ulcer formation. The severity of gastric lesions was dependent on the dose and duration of avatrombopag administration and showed a clear trend towards reversibility during the recovery period. The exposures (AUC) at doses that showed no gastric lesions across the species were 3- to 33-fold higher than the exposures in humans at the maximum recommended human dose (MRHD).

Reproductive and developmental toxicity

Avatrombopag did not affect fertility or early embryonic development in male rats at exposures 22-times, or in female rats at exposures 114-times, the AUC observed in patients at the recommended dose of 60 mg once daily.

Excretion in milk

Avatrombopag was present in milk of lactating rats after oral administration of radioactive labeled avatrombopag. The pharmacokinetic parameters of avatrombopag in milk were similar to those in plasma with an exposure ratio of avatrombopag-related radioactivity (milk to plasma) of 0.94.

Juvenile animal studies

In a 10-week juvenile toxicology study in rats, avatrombopag was administered at doses ranging from 20 to 300 mg/kg/day. There were no test article-related mortality or clinical signs at doses up to 300 mg/kg/day. In the stomach, dose-dependent degeneration, regenerative hyperplasia, and atrophy of the glandular epithelium occurred at 100 and 300 mg/kg/day; exposures at 100 mg/kg/day in male rats were 14-times the AUC in patients at the maximum recommended dose of 60 mg once daily. Avatrombopag did not cause gastric changes in male juvenile rats at exposures 7 times the AUC observed in patients at the maximum recommended dose of 60 mg once daily. An increased incidence

of background focal mineralization was also observed in the kidneys of females at 300 mg/kg/day (female rat exposure was 50-times the human exposure based on AUC at the 60 mg daily dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose (E460(i))
Crospovidone type B (E1202)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Film coating

Poly(vinyl alcohol) (E1203)
Talc (E553b)
Macrogol 3350 (E1521)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (polyamide and polyvinyl chloride-laminated aluminium film with push-through aluminium and polyethylene terephthalate foil) containing either 10 or 15 film-coated tablets. Each carton contains one blister of 10 or 15 film-coated tablets or two blisters of 15 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

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1373/001
EU/1/19/1373/002
EU/1/19/1373/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2019
Date of latest renewal: 09 February 2024

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. MANUFACTURER(S) 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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Swedish Orphan Biovitrum AB (publ)
Norra Stationsgatan 93
113 64 Stockholm
Sweden

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

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Doptelet 20 mg film-coated tablets
avatrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains avatrombopag maleate equivalent to 20 mg of avatrombopag.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
15 film-coated tablets
30 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 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

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

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1373/001
EU/1/19/1373/002
EU/1/19/1373/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Doptelet 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Doptelet 20 mg tablets
avatrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Doptelet 20 mg film-coated tablets
avatrombopag

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 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 Doptelet is and what it is used for

Doptelet contains an active substance called avatrombopag. It belongs to a group of medicines called thrombopoietin receptor agonists.

Doptelet is used in adults with chronic liver disease to treat low platelet count (called thrombocytopenia) before having a medical procedure where there is a risk of bleeding.

Doptelet is used to treat adults with low platelet counts due to primary chronic immune thrombocytopenia (ITP) when a prior treatment for ITP (such as corticosteroids or immunoglobulins) has not worked well enough.
Doptelet works by helping to increase the number of platelets in the blood. Platelets are blood cells that help the blood to clot and so reduce or prevent bleeding.

2. What you need to know before you take Doptelet

Do not take Doptelet
- if you are allergic to avatrombopag or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or pharmacist before taking Doptelet.

Warnings and precautions
Talk to your doctor or pharmacist before taking Doptelet if:
- you are at risk of blood clots in your veins or arteries, or members of your family have had blood clots.
- you have another blood condition known as myelodysplastic syndrome (MDS); taking Doptelet may worsen MDS.

You may be at **higher risk of blood clots** as you get older or if:
- you have had to stay in bed for a long time
- you have cancer
- you are taking the contraceptive birth control pill or hormone replacement therapy

- you have recently had surgery or been injured
- you are very overweight
- you smoke
- you have advanced chronic liver disease.

If any of the above applies to you, or you are not sure, talk to your doctor or pharmacist before taking Doptelet.

Blood tests for platelet count
If you stop taking Doptelet, your platelet count is likely to become low as before treatment or even lower, with a risk of bleeding. This may happen within days. The platelet count will be monitored, and your doctor will discuss appropriate precautions with you.

Tests to check your bone marrow
In people who have problems with their bone marrow, medicines like Doptelet 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 a test to directly check your bone marrow during treatment with Doptelet.

Children and adolescents
Do not give Doptelet to people less than 18 years old. The safety and effectiveness of this medicine in this age group is not known.

Other medicines and Doptelet
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you are taking other medicines for ITP, you may need to take a lower dose or to stop taking them while you are taking Doptelet.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Doptelet is not recommended in pregnancy and in women who are able to have children and are not using contraception.

If you are breast-feeding, ask your doctor or pharmacist for advice before taking Doptelet. This medicine can pass into breast milk. Your doctor will help you decide whether the benefit of breast-feeding outweighs any possible risks to your baby while you are breast-feeding.

Driving and using machines
Doptelet is not expected to affect you being able to drive, cycle or use tools or machines.

Doptelet contains lactose
Doptelet contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Doptelet

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you have chronic liver disease and low platelet count you should be scheduled to undergo your procedure 5 to 8 days after the last dose of Doptelet.

If you have chronic ITP your doctor will tell you how much Doptelet to take and how often to take it.

How much to take

If you have chronic liver disease and are scheduled for an invasive procedure
- Doptelet is available in 20 mg tablets. The usual recommended dose is either 40 mg (2 tablets) or 60 mg (3 tablets) every day for 5 days in a row.
- Your dose will depend on your platelet counts.
- Your doctor or pharmacist will tell you how many tablets to take and when to take them.

If you have chronic ITP
- The usual recommended starting dose is 20 mg (1 tablet) a day. If you are taking certain other medicines you may need a different starting dose.
- Your doctor or pharmacist will tell you how many tablets to take and when to take them.
- Your doctor will monitor your platelet count regularly and will adjust your dose as needed.

Taking this medicine

- Swallow the tablets whole and take with food at the same time each day that you take Doptelet.

If you have chronic liver disease and low platelet count
- Start taking Doptelet 10 to 13 days before your planned medical procedure.
- Your doctor or pharmacist will tell you how many tablets to take and when to take them.

If you have chronic ITP
- Your doctor or pharmacist will tell you how many tablets to take and when to take them.

If you take more Doptelet than you should
- Talk to a doctor or pharmacist straight away.

If you forget to take Doptelet
- Take your missed dose as soon as you remember, then take your next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Doptelet
Take Doptelet for as long as your doctor tells you. Do not stop taking Doptelet unless your doctor tells you to.

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.

Tell your doctor or pharmacist if you notice any of the following side effects.

The following side effects have been reported to be associated with treatment with Doptelet in adult patients with chronic liver disease:

Common (may affect up to 1 in 10 people)
- feeling tired

Uncommon (may affect up to 1 in 100 people)
- low red blood cell count (anaemia)
- blood clot in the portal vein (blood vessel that carries blood to the liver from the intestines) which may result in upper abdominal pain or swelling
- bone pain

- muscle aches
- fever

Not known (frequency cannot be estimated from the available data)
- allergic reactions including swollen face, swollen tongue, and skin changes such as rash and itching

The following side effects have been reported to be associated with treatment with Doptelet in adult patients with primary chronic ITP:

Very common (may affect more than 1 in 10 people)
- feeling tired
- headache

Common (may affect up to 1 in 10 people)
- back pain, muscle pain, joint pain, pain in arms or legs
- discomfort or pain of bones, muscles, ligaments, tendons, and nerves
- feeling sick (nausea), diarrhoea, vomiting, abdominal pain, digestive wind/gas
- dizziness, head discomfort, migraine
- decreased appetite
- weakness
- nose bleeds
- skin rash, itching, acne, red spots on skin
- feeling of tingling, prickling or numbness, commonly called “pins and needles”
- enlarged spleen
- shortness of breath
- elevated blood pressure
- tendency to bruise or bleed (low platelets)

Common side effects that may show up in blood tests
- increased fats (cholesterol, triglycerides)
- increased or decreased blood sugar (glucose)
- increased liver enzyme (alanine aminotransferase)
- increased lactate dehydrogenase
- increased gastrin
- decreased number of red blood cells (anaemia)
- increased or decreased number of platelets

Uncommon (may affect up to 1 in 100 people)
- redness, swelling and pain of a vein caused by a blood clot
- 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)
- blood clots in the veins which carry blood away from the brain
- narrowing of the blood vessels (vasoconstriction)
- 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
- blockage or narrowing of the vein that brings blood to the liver
- stroke or mini-stroke
- heart attack
- irregular heartbeat
- haemorrhoids
- dilation of the rectal veins
- inflammation (swelling) and infection of the nose, sinuses, throat, tonsils, or middle ear (upper respiratory tract infection)
- scarring of the bone marrow

- loss of water or body fluids (dehydration)
- increased appetite, hunger
- mood changes
- abnormal thinking
- changes in sense of taste, smell, hearing, vision
- eye problems including irritation, discomfort, itching, swelling, tearing, sensitivity to light, blurred vision, vision impaired, loss of vision
- ear pain
- increased sensitivity to everyday sounds
- coughing up blood
- nasal congestion
- abdominal pain, discomfort or swelling
- constipation
- belching
- acid reflux
- burning or stinging sensation in mouth
- numbness of the mouth, swollen tongue, tongue problems
- numbness
- hair loss
- boils
- dry skin
- dark purple spots on skin (blood leakage out of blood vessels, bruising)
- excessive sweating
- changes in skin color
- itchy rash
- skin irritation
- abnormality of a joint
- muscle cramps, muscle weakness
- blood in urine
- heavy menstrual period
- nipple pain
- chest pain
- pain
- swelling in legs or arms

Uncommon side effects that may show up in blood tests
- bacteria in the blood
- increased white blood cells
- decreased iron in blood
- increased liver enzyme (aspartate aminotransferase), abnormal liver tests

Not known (frequency cannot be estimated from the available data)
- allergic reactions including swollen face, swollen tongue, and skin changes such as rash and itching

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Doptelet

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 on each blister after 'EXP'. The expiry date refers to the last day of that month.

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 to protect the environment.

6. Contents of the pack and other information

What Doptelet contains

- The active substance is avatrombopag. Each film-coated tablet contains avatrombopag maleate equivalent to 20 mg of avatrombopag.

- The other ingredients are:
  Tablet core: lactose monohydrate (see section 2 "Doptelet contains lactose"); microcrystalline cellulose [E460(i)]; crospovidone type B [E1202]; silica, colloidal anhydrous [E551]; magnesium stearate [E470b].
  Film coating: poly(vinyl alcohol) [E1203]; talc [E553b]; macrogol 3350 [E1521]; titanium dioxide [E171]; iron oxide yellow [E172].

What Doptelet looks like and contents of the pack

Doptelet 20 mg film-coated tablets (tablets) are pale yellow, round, rounded on the upper and lower side, marked with "AVA" imprinted on one side and "20" on the other.

The tablets are supplied in cartons containing one or two aluminium blisters. Each blister contains either 10 or 15 tablets.

Marketing Authorisation Holder

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

Manufacturer

Swedish Orphan Biovitrum AB (publ)
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.