Date: 28 January 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Doptelet

International non-proprietary name: avatrombopag as avatrombopag maleate

Pharmaceutical form: film-coated tablets

Dosage strength: 20 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Swedish Orphan Biovitrum AG

Marketing Authorisation No.: 67893

Decision and Decision date: approved on 23 November 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CLD	Chronic liver disease
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
ITP	Immune thrombocytopenia
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RH	Relative humidity
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TCP	Thrombocytopenia
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
TPO	Thrombopoietin

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance avatrombopag (as avatrombopag maleate) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo an invasive procedure.
Doptelet is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who have not responded to other treatments (e.g. corticoids, immunoglobulins).

2.2.2 Approved Indication

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 chronic immune thrombocytopenia (ITP) in adult patients who have shown insufficient response to at least one prior treatment (see section "Clinical efficacy").

2.2.3 Requested Dosage

Chronic liver disease
Before taking Doptelet and on the day of an intervention, the platelet count must be determined to ensure an appropriate and not an unexpectedly high increase in platelet levels in the patient populations mentioned in the sections "Warnings and precautions" and "Interactions".
Usual dosage
The recommended daily dose of avatrombopag is based on the patient's platelet count. Dosing should begin 10 to 13 days prior to the planned procedure. The patient should undergo the procedure 5 to 8 days after the last dose of avatrombopag.
(For full dosage recommendations, see *information for healthcare professionals*)

2.2.4 Approved Dosage

(see Appendix)

2.3 Regulatory History (Milestones)

Application	20 May 2020
Formal control completed	15 June 2020
List of Questions (LoQ)	8 October 2020
Answers to LoQ	23 December 2020
Predecision	25 March 2021
Answers to Predecision	17 May 2021
Labelling corrections	16 August 2021
Answers to Labelling corrections:	30 August 2021
Final Decision	23 November 2021
Decision	approval

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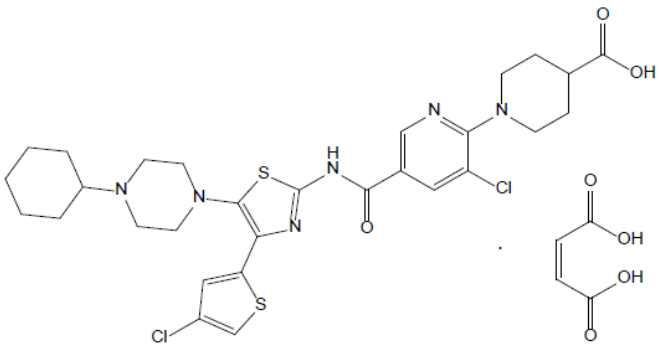
3 Medical Context

Thrombocytopenia (TCP) is a haematological disorder defined as platelet count of less than 100 x 10^9/L in peripheral blood. TCP is common in patients with chronic liver disease (CLD) including cirrhosis or fibrosis. While they have an increased bleeding risk, these patients require multiple invasive diagnostic and therapeutic procedures.
Chronic immune thrombocytopenia (ITP) is an acquired thrombocytopenia caused by autoantibody-mediated destruction of platelets. These autoantibodies may also affect megakaryocytes, with the consequence of decreased platelet production.
ITP can be classified as primary or secondary (resulting from an underlying disease such as HCV, HIV or a lymphoproliferative disease). Depending on its duration, ITP is classified as acute (newly diagnosed for 0-3 months), persistent (3-12 months) or chronic (≥12 months).
Shortcomings of the drugs currently available for treatment of CLD-associated TCP and chronic ITP include their toxicities and highly variable, transient treatment responses resulting in an unsatisfactory high relapse rate.

4 Quality Aspects

4.1 Drug Substance

INN: Avatrombopag
Chemical name: 1-(3-Chloro-5-{[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)-1,3-thiazol-2-yl]carbamoyl}pyridin-2-yl)piperidine-4-carboxylic acid maleate
Molecular formula: $C_{33}H_{38}Cl_2N_6O_7S_2$ ($C_{29}H_{34}Cl_2N_6O_3S_2 \cdot C_4H_4O_4$)
Molecular mass: 765.73 (avatrombopag maleate), 649.95 (avatrombopag)
Molecular structure:



Physicochemical properties:
Avatrombopag is a white to off white powder with a nonchiral structure. The compound is practically insoluble in water and is nonhygroscopic. Avatrombopag exhibits polymorphism. The commercial manufacturing process provides the anhydrous Form-C of avatrombopag.

Synthesis:
The synthesis of avatrombopag consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps and intermediates.

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Specification:
The drug substance specification includes tests for description (appearance), identity, water content, assay, related substances, maleic acid content, residue on ignition, particle size, residual solvents and microbial purity. The applied limits are justified and in line with the relevant guidelines and the European Pharmacopoeia, where applicable. The analytical methods are adequately described and the noncompendial methods are fully validated in accordance with the ICH guidelines.

Stability:
The stability of avatrombopag was investigated with three commercial scale batches, which were manufactured by the proposed commercial manufacturing site. The stability samples were stored under long term conditions (25°C/60% rh) and accelerated conditions (40°C/75% rh) as defined in the corresponding ICH guideline on stability studies. Based on these studies, an adequate retest period was defined for avatrombopag.

4.2 Drug Product

Description and composition:
Doptelet is available as round, biconvex, yellow, debossed ("AVA" on one side, "20" on the other side) film-coated tablets. Each tablet contains 20 mg of avatrombopag (as 23.6 mg avatrombopag maleate). The core tablets are composed of the well-known excipients lactose monohydrate, microcrystalline cellulose, crospovidone type B, silica (colloidal, anhydrous), and magnesium stearate. The film-coating consists of polyvinyl alcohol, talc, macrogol, titanium dioxide and iron oxide yellow.

Pharmaceutical development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including principles of quality by design as described in ICH Guidelines Q8 to Q11.

Manufacture:
Doptelet tablets are manufactured with a standard granulation process. Control of the manufacturing process is ensured through defined operating parameters based on the results of the development studies. In addition, in-process controls with adequate acceptance criteria have been established.

Specification:
The drug product specifications include tests for description, identification, assay, related substances, dissolution, uniformity of dosage units and microbial purity. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug product.

Container-Closure System:
Doptelet tablets are packaged in polyamide and polyvinyl chloride laminated aluminium film with push-through aluminium and polyethylene terephthalate foil blisters.

Stability:
Appropriate stability data from three commercial scale batches of Doptelet tablets were provided. The stability study was carried out according to ICH stability guidelines. Based on the results of this study, a shelf-life of 60 months was established. The product should not be stored above 30°C.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application of Doptelet®, Swissmedic Nonclinical Assessment conducted an abridged evaluation, which was based on the European Medicines Agency (EMA) assessment report (EPAR, dated 26 April 2019) provided by the applicant. The pivotal juvenile animal study with the new active substance avatrombopag, which was not discussed in the EPAR, was reviewed in detail. No new or unexpected toxicities were detected in juvenile rats administered avatrombopag once daily from postnatal day 7 for 10 weeks when compared to adult animals.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Doptelet® (avatrombopag) in the proposed indication. The pharmacological and toxicological profile has been sufficiently characterised in nonclinical species (mice, rats and cynomolgus monkeys), although avatrombopag appears only to be pharmacologically active in humans and chimpanzees. Therefore, the nonclinical studies cannot predict the risks related to the pharmacological effect of avatrombopag. The stomach was the main target organ of toxicity for avatrombopag in both rats (including juvenile rats) and monkeys. The histological changes, accompanied by elevation of serum gastrin, were dose related and characterised by glandular epithelial degeneration, regenerative hyperplasia and atrophy of glandular mucosa. These findings were reversible even after chronic treatment in both species. In clinical studies, there was no clear stomach-related finding to suggest a gastric safety signal in patients. The lowest safety margin of 3 times the exposure at the maximum recommended human dose was seen in cynomolgus monkeys. This is low but acceptable for the proposed indications and considering the short treatment duration of 5 days.

Doptelet® should not pose a risk to the environment if used and disposed of appropriately. However, the updated ERA was requested as a post-approval requirement.

All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The clinical pharmacology data of this application have been evaluated based on previous regulatory decisions by EMA and FDA. The available assessment reports and respective product information from these authorities were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology, see section 8.1 of this report.

6.2 Dose Finding and Dose Recommendation

With regard to the primary data of this application related to the treatment of TCP in patients with CLD, Swissmedic based its evaluation on the assessments of FDA and EMA. Accordingly, the present SwissPAR relating to clinical aspects of TCP in patients with CLD refers to the publicly available Assessment Report Doptelet, EMA/CHMP/322871/2019, dated 26 April 2019 and the FDA Clinical Review report dated 20 February 2018.
Swissmedic focused its assessment on the data related to treatment of chronic immune thrombocytopenia.

The applicant submitted one pivotal, Phase 3, multicentre, randomised, double-blind, placebo-controlled study (302) for evaluation of efficacy in patients with chronic ITP.
In this study, patients with chronic ITP received a starting dose of 20 mg once daily, with subsequent titration based on platelet response (minimum dose of 5 mg to maximum dose of 40 mg once daily).

49 patients were randomised 2:1 to receive either Doptelet (N=32) or placebo (N=17) treatment for 6 months, with similar mean [SD] baseline platelet counts in both treatment groups (14.1 [8.6] x 10^9/L and 12.7 [7.8] x 10^9/L, respectively). The median age was 44 years (8.2% were ≥65 years of age), 63% were female, and 94% were Caucasian. The median duration of exposure was 26 weeks for patients treated with Doptelet and 6 weeks for patients treated with placebo.
The primary endpoint was the cumulative number of weeks in which the platelet count was ≥ 50 x 10^9/L during the 6-month treatment period in the absence of rescue therapies. Patients in the Doptelet group had a longer duration of platelet counts ≥ 50 x 10^9/L in the absence of rescue medication than those who received placebo (median 12.4 [0, 25] vs 0 [0, 2] weeks, respectively, $p < 0.0001$).

6.3 Safety

The pooled safety data from four clinical studies in adult patients with chronic ITP demonstrated that the most common adverse events (≥ 10%) were headache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae and nasopharyngitis. The nature and frequency of the reported adverse events are considered consistent with those expected after treatment of chronic ITP patients with thrombopoietin (TPO) receptor agonists. There were no new relevant safety findings.

6.4 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Clinical data in a limited number of adult patients with chronic ITP and a median duration of exposure of 29.1 weeks demonstrated efficacy of Doptelet treatment during the planned follow-up. Doptelet increased the platelet count rapidly and maintained the effect without rescue therapy. The safety profile of Doptelet is acceptable and comparable to that of other TPO receptor agonists. The main uncertainty regarding the missing data on the long-term efficacy and safety profile can be addressed during the post-authorisation period.

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Overall, the benefit-risk ratio for Doptelet treatment in adult patients with chronic ITP has been assessed to be positive.

6.5 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Doptelet, film-coated tablets was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

DOPTELET

Composition

Active substances

Avatrombopag or avatrombopag maleate

Excipients

Tablet core:
Lactose monohydrate 120.8 mg
Microcrystalline cellulose (E460)
Crospovidone (E1202)
Silica colloidal (E551)
Magnesium stearate (E470b)

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

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

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 chronic immune thrombocytopenia (ITP) in adult patients who have shown insufficient response to at least one prior treatment (see section "Clinical efficacy").

Dosage/Administration

Dosage

Treatment should be initiated and supervised by 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, even if the dose is taken 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 the «Warnings and precautions» and «Interactions» sections.

Usual dosage

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 the procedure 5 to 8 days after the last dose of avatrombopag.

Table 1 Daily dose recommendation for avatrombopag

Platelet count (x 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

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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 x 10^9/L as necessary to reduce the risk for bleeding. Do not use avatrombopag to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 week after starting treatment with 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. For patients taking moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5, or moderate or strong inhibitors of CYP2C9, the starting dose needs to be adjusted (see Table 4 and «Interactions» section).

Monitoring and dose adjustment

After initiating therapy, assess platelet counts at least once weekly until a stable platelet count between ≥ 50 x 10^9/L and ≤ 150 x 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 is also necessary after dose adjustments during the treatment.

Due to the potential risk of platelet counts above 400 x 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, monitor platelet counts at least once per month. 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 film-coated tablets).

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

Platelet count (x10^9/L)	**Dose adjustment or action**
< 50 after at least 2 weeks of treatment with Doptelet	• 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	• Suspend Doptelet. • Increase platelet monitoring to twice weekly. • When platelet count is less than 100 x 10^9/L, decrease one *dose level* per Table 3 and reinitiate therapy.
< 50 after 4 weeks of treatment with Doptelet 40 mg once daily	• Discontinue Doptelet.
> 250 after 2 weeks of treatment with Doptelet 20 mg weekly	• Discontinue Doptelet.

Table 3: Avatrombopag dose levels for titration in patients with 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 inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5 or CYP2C9 alone (see Table 4 and «Interactions» section).
≠ Patients taking avatrombopag less frequently than once daily should take the medication in a consistent manner from week to week:
Dose level 3: Three non-consecutive days a week, e.g., Monday, Wednesday, 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

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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.

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 a medication should be reduced.

Discontinuation of treatment

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

Recommended dosage with concomitant moderate or strong dual inducers or inhibitors of CYP2C9 and CYP3A4/5 or CYP2C9 alone in patients with chronic immune thrombocytopenia

The recommended starting doses of avatrombopag in patients with chronic immune thrombocytopenia receiving concomitant medications are summarised in Table 4.

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

Concomitant medications	**Recommended starting dose**
Moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5 or CYP2C9 alone (e.g., fluconazole)	20 mg (1 tablet) three times a week

Moderate or strong dual inducers of CYP2C9 and CYP3A4/5 or CYP2C9 alone (e.g., rifampicin, enzalutamide)	40 mg (2 tablets) once daily

Special populations

Elderly patients

No dose adjustment is required for patients aged 65 years and older (see «Pharmacokinetics» section).

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 «Pharmacokinetics» section), dose adjustment is not recommended, however.

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 « Warnings and precautions» section). 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 « Warnings and precautions» and «Pharmacokinetics» sections).

Coexisting medical conditions

Due to limited or unavailable data, the safety and efficacy of avatrombopag in adult patients with ITP with the following coexisting medical conditions has not been established: patients with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or patients with known systemic lupus erythematosus, acute hepatitis, active chronic hepatitis, cirrhosis, lymphoproliferative disease, myeloproliferative disorders, leukaemia, myelodysplasia (MDS), concurrent malignant diseases, and significant cardiovascular disease (e.g., grade III/IV heart failure, atrial fibrillation, status post coronary artery bypass or stent placement).

Children and adolescents

The safety and efficacy of avatrombopag in children aged less than 18 years have not been established. No data are available.

CYP2C9 loss-of-function polymorphisms

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

Mode of administration

Doptelet is for oral use, and the film-coated tablets should be taken once daily with food (see «Pharmacokinetics» section).

Contraindications

Hypersensitivity to avatrombopag or to any of the excipients listed under Composition.

Warnings and precautions

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 x 10^9/L receiving a thrombopoietin receptor agonist (see «Undesirable effects» section).

In patients with chronic immune thrombocytopenia, thromboembolic events (arterial or venous) occurred in 7% (9/128) of patients receiving avatrombopag (see «Undesirable effects» section).

Doptelet was not studied in patients with prior thromboembolic events. The potential increased thrombotic risk when administering Doptelet to patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, antithrombin deficiency, or protein C or S deficiency) must be considered. 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 medications

The effects of a single dose of 100 mg avatrombopag on the QTc interval was assessed in a comprehensive QT study. The results confirmed that the single dose of 100 mg avatrombopag had no effect on the QTc interval. 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, as well as with moderate or strong CYP2C9 inhibitors, as these medications 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 ratio of avatrombopag as well as the assessment of alternative ITP treatment options.

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 studies 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 the expansion and differentiation of thrombopoietic progenitor cells and platelet production. The TPO-R is

predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

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

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 studies 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 only 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.

Interactions

Avatrombopag does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A, does not induce CYP1A, CYP2B6, CYP2C, or 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, or organic cation transporter (OCT) 2 *in vitro*.

Avatrombopag is a substrate for P-glycoprotein (P-gp) mediated transport (see Table 3). Avatrombopag is not a substrate for OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.

Effects of other medicinal products on the pharmacokinetics of avatrombopag

Table 5 shows the geometric mean ratios (GMR) of the pharmacokinetic parameters with/without co-administration of other medicinal products, with a 90 % confidence interval (CI) respectively. In patients with thrombocytopenia as a result of chronic liver disease, concomitant medication is not contraindicated and no dose adjustments are required.

Table 5: Interactions with other medications: changes in the pharmacokinetics of avatrombopag in the presence of co-administered medications

Co-administered medication	**Geometric mean ratio [90 % CI] of avatrombopag PK with/without co-administered medication (no effect = 1.00)**		**Recommendation for co-administration in the treatment of ITP patients**
	AUC0-inf	**Cmax**	
Strong CYP3A inhibitor			
Itraconazol (200 mg bid for 1 day, 200 mg qd for 15 days) Avatrombopag (20 mg single dose)	1.37 (1.10, 1.72)	1.07 (0.86, 1.35)	No dose adjustment
Moderate CYP3A4/5 and CYP2C9 inhibitor			
Fluconazole (400 mg qd for 16 days) Avatrombopag (20 mg single dose)	2.16 (1.71, 2.72)	1.17 (0.96, 1.42)	Adjustment of the starting dose for the dual inhibitors of CYP2C9 and CYP3A4/5 required (see Table 4)
Moderate CYP2C9 and strong CYP3A4/5 inducer			
Rifampin (600 mg qd for 16 days) Avatrombopag (20 mg single dose)	0.57 (0.47, 0.62)	1.04 (0.88, 1.23)	Adjustment of the starting dose for the dual inducers of CYP2C9 and CYP3A4/5 required (see Table 4)
P-gp inhibitor			

Cyclosporine (400 mg single dose) Avatrombopag (20 mg single dose)	0.83 (0.65, 1.04)	0.66 (0.54, 0.82)	No dose adjustment
P-gp and moderate CYP3A inhibitor			
Verapamil (240 mg qd for 11 days) Avatrombopag (20 mg single dose)	1.61 (1.21, 2.15)	1.26 (0.96, 1.66)	No dose adjustment

CYP3A4/5 and CYP2C9 inhibitors

Concomitant use of avatrombopag with moderate or strong CYP3A4/5 and CYP2C9 dual inhibitors, such as fluconazole, increases avatrombopag exposure. Concomitant use of avatrombopag with moderate or strong CYP2C9 inhibitors is expected to increase avatrombopag exposure. In the treatment of ITP patients, adjustment of the starting dose is recommended (see Table 4).

CYP3A4/5 and CYP2C9 inducers

Concomitant use of moderate or strong CYP3A4/5 and CYP2C9 dual inducers, such as rifampicin, enzalutamide, reduces avatrombopag exposure, and may result in a decreased effect on platelet counts (see «Pharmacokinetics» section). Concomitant use of avatrombopag with moderate or strong CYP2C9 inducers is expected to reduce avatrombopag exposure. In the treatment of ITP patients, adjustment of the starting dose is recommended (see Table 4).

P-gp inhibitor

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

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 «Dosage/Administration» and «Pharmacokinetics» sections).

Chronic immune thrombocytopenia

Reduce the starting dosage of avatrombopag when used concomitantly with a moderate or strong dual inhibitor of CYP2C9 and CYP3A4/5 (see Table 4 and «Dosage/Administration» section). 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 «Dosage/Administration» section).

Combinations of medicinal products for the 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.

Pregnancy, lactation

Pregnancy

Insufficient data available on use in pregnant women. Animal studies have shown reproductive toxicity (see "Preclinical data"). The potential risk for humans is not known. Doptelet is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation

There are no clinical 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 «Preclinical data» section. A risk to the breast-feeding child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/suspend 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 risks cannot be ruled out. In animal studies, avatrombopag had no effect on male and female fertility (see "Preclinical data").

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

Chronic liver disease

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

Chronic immune thrombocytopenia

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

Tabulated list of adverse reactions

The 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
Blood and lymphatic system disorders		Anaemia
Immune system disorders		Hypersensitivity
Vascular disorders		Portal vein thrombosis
Musculoskeletal and connective tissue disorders		Bone pain, myalgia
General disorders and administration site conditions	Fatigue (> 3 %)	Pyrexia

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

Chronic immune thrombocytopenia study population

System Organ Class (MedDRA terminology*)	Frequency	Adverse reaction
Infections and infestations	uncommon	Furuncle, septic thrombophlebitis, upper respiratory tract infection
Benign, malignant and unspecified neoplasms (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
Nervous system disorders	very common	Headache (> 10 %)
	common	Dizziness, headache, migraine, paraesthesia
	uncommon	Cerebrovascular accident, Cognitive disorder, dysgeusia, hypoesthesia, sensory disturbance, reversible ischaemia
Eye disorders	uncommon	Abnormal sensation in eye, eye irritation, pruritus and swelling of the eyes, increased lacrimation, ocular discomfort, photophobia, retinal artery occlusion, blurred vision, vision impairment

Ear and labyrinth disorders	uncommon	Ear pain, hyperacusis (increased sensitivity to sound)
Cardiac disorders	uncommon	Myocardial infarction
Vascular disorders	common	Hypertension
	uncommon	Deep vein thrombosis, jugular vein thrombosis, vasoconstriction
Respiratory, thoracic and mediastinal disorders	common	Epistaxis (nose bleeds), dyspnoea
	uncommon	Haemoptysis, nasal congestion, pulmonary embolism
Gastrointestinal disorders	common	Nausea, diarrhoea, vomiting, upper abdominal pain, flatulence
	uncommon	Abdominal discomfort, bloating, lower abdominal pain, anorectal varices, constipation, eructation, gastroesophageal reflux disease, glossodynia, haemorrhoids, oral paraesthesia, swollen tongue, tongue disorder
Hepatobiliary disorders	uncommon	Portal vein thrombosis
Skin and subcutaneous tissue disorders	common	Rash, acne, petechiae, pruritus
	uncommon	Alopecia, dry skin, ecchymosis, hyperhidrosis, pigmentation disorder, pruritic rash, skin haemorrhage, skin irritation
Musculoskeletal and connective tissue disorders	common	Arthralgia, back pain, pain in the extremities, myalgia, musculoskeletal pain
	uncommon	Arthropathy, limb discomfort, muscle spasms, muscle weakness, 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
Investigations	common	Increased blood glucose, increased platelet count, decreased blood glucose, increased blood triglycerides, increased blood lactate dehydrogenase, decreased platelet count, increased alanine aminotransferase, increased blood gastrin
	uncommon	Increased aspartate aminotransferase, increased blood pressure, irregular heart rate, increased hepatic enzymes

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

Description of selected undesirable effects

Thromboembolic Events

In the two clinical trials with patients with chronic liver disease and thrombocytopenia, there was one treatment-emergent event of portal vein thrombosis in one patient (n = 1/274) 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 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 patient was cerebrovascular accident in 1.6 % (2/128).

Thrombocytopenia and bleeding 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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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. An increase in platelet count was observed within 3 to 5 days after the start of treatment. The peak effect was observed after 10 to 13 days. After the treatment, platelet counts gradually decreased and returned to near baseline values.

Pharmacodynamics

Clinical efficacy

Studies on chronic liver disease

The efficacy and safety of avatrombopag for the treatment of adult patients with chronic liver disease and a platelet count < 50 x 10^9/L who were scheduled to undergo a procedure, were studied in two identically-designed multicentre, randomised, double-blind, placebo-controlled Phase 3 studies (Study 1 and Study 2). In each study, patients were assigned to the low baseline platelet count cohort (< 40 x 10^9/L) or the high baseline platelet count cohort (≥ 40 to < 50 x 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 Study-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 x 10^9/L and for placebo-treated patients was 30.7 x 10^9/L. In the low baseline platelet count cohort, the mean baseline platelet count for the avatrombopag-treated group was 44.3 x 10^9/L and for placebo-treated patients was 44.9 x 10^9/L.

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

In the cohort with the low baseline platelet count (< 49 x 10^9/L) the proportion of patients not requiring platelet transfusion or rescue procedures for bleeding was higher at 65.6 % (59/90) in the group treated with 60 mg avatrombopag than in the group receiving placebo with only 22.9 % (11/48). The treatment difference (60 mg avatrombopag minus placebo) was 42.6 % (95 % CI [27.2, 58.1]) and was statistically significant; P < 0.0001 as per Cochran-Mantel-Haenszel test (adjusted for bleeding risk).

Similarly, in the cohort with the higher baseline platelet count (≥ 40 to < 50 x 10^9/L) the proportion of patients not requiring platelet transfusion or rescue procedures for bleeding was higher at 88.1 % (52/59) in the group treated with 40 mg avatrombopag than in the group receiving placebo with only 38.2 % (13/34). The treatment difference (40 mg avatrombopag minus placebo) was 49.9 % (95 % CI [31.6, 68.2]) and was statistically significant; P < 0.0001 as per Cochran-Mantel-Haenszel test (adjusted for bleeding risk).

The first secondary efficacy endpoint was the proportion of patients whose platelet count achieved the target of 50 × 10^9/l or more on the day of the procedure (Day 10 to Tag 13). In the cohort with the low baseline platelet count (< 40 x 10^9/L), the proportion of patients whose platelet count was 50 x 10^9/L or more on the day of the procedure, was higher at 68.9 % (62/90) in the group treated with 60 mg avatrombopag than in the group receiving placebo with only 4.2 % (2/48) responders. The treatment difference (60 mg avatrombopag minus placebo) was 64.7 % (95 % CI [53.6, 75.8]) and was statistically significant with P < 0.0001 as per Cochran-Mantel-Haenszel test (adjusted for the bleeding risk).

Similarly, in the cohort with the higher baseline platelet count (≥ 40 to < 50 x 10^9/L), the proportion of responders in the group treated with 40 mg avatrombopag was higher at 88.1 % (52/59) than in the group receiving placebo with only 20.6 % (7/34) responders. The treatment difference (40 mg avatrombopag minus placebo) was 67.5 % (95 % CI [51.6, 83.4]) and was statistically significant with P < 0.0001 as per Cochran-Mantel-Haenszel test (adjusted for the bleeding risk).

The secondary efficacy endpoint was the change in platelet count from baseline on the day of the procedure (Day 10 to Day 13). In the cohort with the lower baseline platelet count (< 40 x 10^9/L), the mean (SD) change in baseline platelet count until the count on the day of the procedure, was greater at 32.0 x 10^9/L (25,53) in the group treated with 60 mg avatrombopag than in the group receiving

placebo with only 0.8 x 10^9/L (6.36). The treatment difference (60 mg avatrombopag minus placebo) was 27.5 × 10^9/L (95 % CI [22.5, 32.5]) and was statistically significant with P < 0.0001 as per Wilcoxon rank sum test.

In the cohort with the higher baseline platelet count (≥ 40 to < 50 x 10^9/L), the mean change from baseline in the avatrombopag-treated group was 37.1 × 10^9/L (27.41) and 1.0 x 10^9/L (9.30) in the group receiving placebo. The treatment difference (40 mg avatrombopag minus placebo) was 33.0 × 10^9/L (95 % CI [25.5, 41.5]) and was statistically significant with P < 0.0001 as per 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. Mean platelet count remained greater than or equal to 50 x 10^9/L on Day 17 (Visit 5).

The efficacy of avatrombopag was similar across various subgroups for the pooled Phase 3 study population (Study-1 and Study-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 (incl. corticosteroids, Danazol, Dapson and intravenous immunoglobulin) and had an average of screening and baseline platelet counts < 30 x 10^9/L. Patients were centrally stratified by splenectomy status, baseline platelet count (≤ 15 or > 15 x 10^9/L), and use of concomitant chronic immune thrombocytopenia medication, 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.

49 patients were randomised (32 to avatrombopag and 17 to placebo). The mean [SD] baseline platelet counts in the two treatment groups were similar (14.1 [8.6] x 10^9/L and 12.7 [7.8 x 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 x 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 x 10^9/L in the absence of rescue therapy than those who received placebo (median 12.4 [0.25] vs 0 [0.2] weeks, p < 0.0001). In addition, a greater proportion of patients in the avatrombopag group showed a platelet count of ≥ 50 × 10^9/L (21/32; 66 % versus 0/17; 0.0 %; p < 0.0001) compared to the placebo group on Day 8.

Even though only few subjects received concomitant ITP medications at the start of the study, the proportion of patients in the avatrombopag treatment group compared to placebo was lower with placebo (5/15; 33 % versus 0/7; 0.0 %), respectively 95 % CI (12, 62); p = 0.1348).

Pharmacokinetics

Absorption

The plasma concentration-time profiles following the oral administration of avatrombopag were characterised by a short lag time (0.5 to 0.75 hours) with peak exposure at 6 to 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 «Dosage/Administration» and «Interactions» sections).

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, it is recommended to take avatrombopag with food (see «Dosage/Administration» section).

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 in patients with chronic immune thrombocytopenia is approximately 235 L, suggesting that avatrombopag is extensively distributed.

Metabolism

The oxidative metabolism of avatrombopag is mainly mediated by CYP2C9 and CYP3A4. 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.

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/non-linearity

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

Kinetics in specific patient groups

Age (18-86 years), body weight (39-175 kg), gender, and ethnicity [White, African American and East Asian (i.e., Japanese, Chinese, and Koreans)] had no clinically significant effects on the pharmacokinetics of avatrombopag.

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.

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 «Dosage/Administration» and «Undesirable effects» sections).

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.

Elderly patients

Population pharmacokinetic analysis of avatrombopag plasma concentrations from clinical studies 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 «Dosage/Administration» section).

Paediatric patients

Pharmacokinetic effects of avatrombopag on children and adolescents aged less than 18 years are not known.

Racial or ethnic groups

Population pharmacokinetic analysis of avatrombopag plasma concentrations from the clinical studies with healthy subjects and patients with thrombocytopenia due to chronic liver disease indicated that avatrombopag exposures were similar across the different races studied (White, African American, East Asian).

Genetic polymorphisms

The loss-of-function polymorphisms CYP2C9 * 2 and CYP2C9 * 3 leads to a decrease in enzymatic activity of CYP2C9. A pooled pharmacogenomic analysis of avatrombopag studies showed that subjects heterozygous for CYP2C9 loss-of-function polymorphisms (mean metabolisers [n = 24]) had an approximate 1.4-times higher exposure, and subjects homozygous for CYP2C9 loss-of-function polymorphisms (poor metabolisers [n = 2]) had an approximate 2-times higher exposure compared to the wildtype subjects for CYP2C9 (normal metabolisers [n = 94]).

Preclinical data

Repeated-dose toxicity

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 33-fold higher in mice, 9-fold higher in rats, and 3-fold higher in Javan monkeys than the exposures in humans at the maximum recommended human dose (MRHD). indicating little relevance to clinical use.

Mutagenicity

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.

Carcinogenicity

In two-year carcinogenicity studies in mice (20, 60, 160 mg/kg/day) and rats (20, 50, 160 mg/kg/day), neuroendocrine cell (enterochromaffin-like cell, ECL cell) gastric tumours (carcinoids) occurred in the stomach at high doses. Exposure of 160 mg/kg/day corresponded to 117-fold exposure in humans based on AUC for the maximum daily dose of 60 mg. 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.

Reproductive 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. The oral administration of avatrombopag during organogenesis in rabbits (100, 300, and 600 mg/kg) and during organogenesis and lactation period in rats (5 to 600 mg/kg) did not lead to adverse development results in this dose range (maternal and foetal toxicity).

Excretion in milk

Avatrombopag was present in milk of lactating rats after oral administration of radioactive-labelled 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 pivotal toxicology study in juvenile rats, avatrombopag was administered at doses ranging from 20 to 300 mg/kg/day. There were no mortality or clinical signs associated with the investigational medicinal product 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. 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). The NOAEL of 20 mg/kg/day was 7 times the maximum daily dose, similar to adults.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging.
Keep out of the reach of children.

Marketing authorisation number

67893 (Swissmedic)

Packs

10 film-coated tablets at 20 mg (A)
15 film-coated tablets at 20 mg (A)
30 film-coated tablets at 20 mg (A)

Marketing authorisation holder

Swedish Orphan Biovitrum AG, Basel

Date of revision of the text

January 2022