AVAPAG
Avatrombopag 20 mg tablets

Everest

COMPOSITION

AVAPAG tablet: Each film coated tablet contains Avatrombopag Maleate INN equivalent to Avatrombopag 20 mg.

PHARMACOLOGY

Mechanism of Action

Avatrombopag is an orally bioavailable, small molecule TPO receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an 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.

Pharmacodynamics

Platelet Response

Avatrombopag resulted in dose- and exposure-dependent elevations in platelet counts in adults. The onset of the platelet count increase was observed within 3 to 5 days of the start of a 5-day treatment course, with peak effect observed after 10 to 13 days. Subsequently, platelet counts decreased gradually, returning to near baseline values after 35 days.

Cardiac Electrophysiology

At exposures similar to that achieved at the 40 mg and 60 mg dose, Avatrombopag 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.

Pharmacokinetics

Avatrombopag demonstrated dose-proportional pharmacokinetics after single doses from 10 mg (0.25-times the lowest approved dosage) to 80 mg (1.3-times the highest recommended dosage). Healthy subjects administered 40 mg of Avatrombopag had a geometric mean (%CV) maximal concentration (C_{max}) of 166 (84%) ng/mL and area under the time-concentration curve extrapolated to infinity ($AUC_{0\text{-}inf}$) of 4198 (83%) ng.hr/mL. The pharmacokinetics of Avatrombopag were similar in both healthy subjects and the chronic liver disease population.

Absorption

The median time to maximal concentration (T_{max}) occurred at 5 to 6 hours post-dose.

Effect of Food

Avatrombopag $AUC_{0\text{-}inf}$ and C_{max} were not affected when Avatrombopag was co-administered with a low fat meal (approximately 500 calories, 3 g fat) or a high fat meal (approximately 918 calories, 59 g fat). The variability of Avatrombopag exposure was reduced by 40% to 60% with food. The T_{max} of Avatrombopag was delayed by 0 to 2 hours when Avapag was administered with a low-fat or high-fat meal.

Distribution

Avatrombopag has an estimated mean volume of distribution (%CV) of 180 L (25%). Avatrombopag is greater than 96% bound to human plasma proteins.

Elimination

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%).

Metabolism

Avatrombopag is primarily metabolized by cytochrome P450 CYP2C9 and CYP3A4.

Excretion

Fecal excretion accounted for 88% of the administered dose, with 34% of the dose excreted as unchanged Avatrombopag. Only 6% of the administered dose was found in urine.

Specific Populations

Age (18-86 years), body weight (39-175 kg), sex, race [Whites, African-Americans, and East Asians (i.e., Japanese, Chinese and Koreans)], and any hepatic impairment (Child-Turcotte-Pugh (CTP) grade A, B, and C, or Model for End-Stage Liver Disease (MELD) score 4-23) and mild to moderate renal impairment (CLcr ≥30 mL/min) did not have clinically meaningful effects on the pharmacokinetics of Avatrombopag.

INDICATIONS

- Avatrombopag is indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

- Avatrombopag is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

DOSAGE AND ADMINISTRATION

Recommended Dosage for patients with Chronic Liver Disease

- Begin Avatrombopag dosing 10-13 days prior to the scheduled procedure. Patients should undergo their procedure 5 to 8 days after the last dose of Avatrombopag.

- Avatrombopag should be taken orally once daily for 5 consecutive days with food.

- The recommended daily dose of Avatrombopag is based on the patient's platelet count prior to the scheduled procedure (Refer to Table 1).

- In the case of a missed dose, patients should take the next 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 at the usual time the next day; all five days of dosing should be completed.

Table 1: Recommended Dose and Duration

Platelet Count ($x10^9$/L)	Once Daily Dose	Duration
Less than 40	60 mg (3 tablets)	5 days
40 to less than 50	40 mg (2 tablets)	5 days

Recommended Dosage for Patients with Chronic Immune Thrombocytopenia

- Use the lowest dose of Avatrombopag needed to achieve and maintain a platelet count greater than or equal to 50 $x10^9$ /L as necessary to reduce the risk for bleeding.

- Dose adjustments are based on platelet count response.

- Do not use Avatrombopag to normalize platelet counts.

Initial Dose Regimen:

Begin Avatrombopag at a starting dose of 20 mg (1 tablet) once daily with food.

Discontinuation:

Discontinue Avatrombopag if the platelet count does not increase to greater than or equal to 50 $x10^9$ /L after 4 weeks of dosing at the maximum dose of 40 mg once daily. Discontinue Avatrombopag if the platelet count is greater than 400 $x10^9$ /L after 2 weeks of dosing at 20 mg once weekly.

CONTRAINDICATIONS

None.

WARNING AND PRECAUTIONS

Thrombotic/Thromboembolic Complications

Avatrombopag is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In the ADAPT-1 and ADAPT-2 clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (n=1/430) with chronic liver disease and thrombocytopenia treated with Avatrombopag. Consider the potential increased thrombotic risk when administering Avatrombopag to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency).

Avatrombopag should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

SIDE EFFECTS

Most common adverse reactions are: pyrexia, abdominal pain, nausea, headache, fatigue, and edema peripheral.

DRUG INTERACTIONS

Effect of Other Drugs on Avatrombopag in Patients with Chronic Immune Thrombocytopenia.

Moderate or Strong Dual Inhibitors of CYP2C9 and CYP3A4

Concomitant use with a moderate or strong dual inhibitor of CYP2C9 and CYP3A4 increases Avatrombopag AUC, which may increase the risk of Avatrombopag toxicities. Reduce the starting dosage of Avatrombopag when used concomitantly with a moderate or strong dual inhibitor of CYP2C9 and CYP3A4.

Moderate or Strong Dual Inducers of CYP2C9 and CYP3A4

Concomitant use with a moderate or strong dual inducer of CYP2C9 and CYP3A4 decreases Avatrombopag AUC, which may reduce Avatrombopag efficacy. Increase the recommended starting dosage of Avatrombopag when used concomitantly with a moderate or strong dual inducer of CYP2C9 and CYP3A4.

CLINICAL TRIALS EXEPRIENCE

Patients with Chronic Liver Disease

The safety of Avatrombopag was evaluated in two international, identically designed, randomized, 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) daily for 5 days prior to a scheduled procedure, and had 1 post-dose safety assessment. Patients were divided into two groups based on their mean platelet count at baseline:

• Low Baseline Platelet Count Cohort (less than 40 $x10^9$ /L) who received Avatrombopag 60 mg once daily for 5 days

• High Baseline Platelet Count Cohort (40 to less than 50 $x10^9$ /L) who received Avatrombopag 40 mg once daily for 5 days

For the Low Baseline Platelet Count Cohort, the incidence of serious adverse reactions was 7% (11/159) in the 60 mg Avatrombopag treatment group. For the High Baseline Platelet Count Cohort, the incidence of serious adverse reactions was 8% (9/115) in the 40 mg Avatrombopag treatment group. The most common serious adverse reaction reported with Avatrombopag was hyponatremia. Two Avatrombopag-treated patients (0.7%) developed hyponatremia

Patients with Chronic Immune Thrombocytopenia

The safety of Avatrombopag was evaluated in four clinical trials in patients with chronic immune thrombocytopenia: two Phase 3 trials (one randomized, double-blind, placebo-controlled trial, and one randomized, double-blind, active-controlled trial) and two Phase 2 trials (one randomized, double-blind, placebo-controlled, dose-ranging, trial, and one open-label extension trial) in 161 patients with chronic immune thrombocytopenia in both the double-blind and open-label extension phases.

The pooled safety data from these four clinical trials includes 128 patients who received 2.5 to 40 mg of Avatrombopag once daily for a median duration of exposure of 29.1 weeks and had 1 post-dose safety assessment. The incidence of serious adverse reactions was 9% (12/128) in the Avatrombopag treatment group. Serious adverse reactions reported in more than 1 individual Avatrombopag-treated patient included headache, occurring in 1.6% (2/128).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal reproduction studies, Avatrombopag may cause fetal harm when administered to a pregnant woman. The available data on Avatrombopag in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise pregnant women of the potential risk to a fetus.

Lactation

Risk Summary

There are no information regarding the presence of Avatrombopag in human milk, the effects on the breastfed child, or the effects on milk production. Due to the potential for serious adverse reactions in a breastfed child from Avatrombopag, breastfeeding is not recommended during treatment with Avatrombopag and for at least 2 weeks after the last dose

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Reported clinical experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

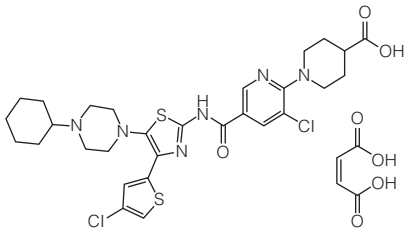
In the event of overdose, platelet count may increase excessively and result in thrombotic or thromboembolic complications. Closely monitor the patient and platelet count. Treat thrombotic complications in accordance with standard of care.

No antidote for Avatrombopag overdose is known.

Hemodialysis is not expected to enhance the elimination of Avatrombopag because Avatrombopag is only approximately 6% renally excreted and is highly bound to plasma proteins.

DESCRIPTION

The active ingredient in AVAPAG is Avatrombopag Maleate, a thrombopoietin receptor agonist. The chemical name of Avatrombopag Maleate is 4-piperidin-ecarboxylic acid, 1-[3-chloro-5- [[[4-(4-chloro-2 thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl] amino]carbonyl]-2-pyridinyl]-, (2Z)-2-butenedioate (1:1). The structural formula is:



The aqueous solubility of Avatrombopag Maleate at various pH levels indicates that the drug substance is practically insoluble at pH 1 to 11.

AVAPAG is provided as an immediate-release tablet. Each AVAPAG tablet contains 20 mg Avatrombopag (equivalent to 23.6 mg of Avatrombopag Maleate).

STORAGE CONDITION

Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED

AVAPAG tablet: Each HDPE container contains 28 film coated tablets, a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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