## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use DOPTELET safely and effectively. See full prescribing information for DOPTELET.**

**DOPTELET® (avatrombopag) tablets, for oral use**

**Initial U.S. Approval: 2018**

### INDICATIONS AND USAGE

DOPTELET (avatrombopag) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. (1)

### DOSAGE AND ADMINISTRATION

- Begin dosing DOPTELET 10 to 13 days prior to a scheduled procedure. (2.1)
- Patients should undergo their procedure within 5 to 8 days after the last dose. (2.1)
- DOPTELET should be taken orally with food once daily for 5 consecutive days. (2.1)
- The recommended dose of DOPTELET is based on a patient's platelet count prior to a scheduled procedure. (2.1)
- Recommended Dose and Duration: (2.1)

| 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 |

### DOSAGE FORMS AND STRENGTHS

Tablet: 20 mg (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

Thrombotic/Thromboembolic Complications: DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Monitor platelet counts and for thromboembolic events and institute treatment promptly. (5.1)

### ADVERSE REACTIONS

Most common adverse reactions (≥ 3%) are: pyrexia, abdominal pain, nausea, headache, fatigue, and edema peripheral. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Dova Pharmaceuticals at 1-844-506-3682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm (8.1)
- Lactation: Breastfeeding not recommended during treatment (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 3/2019**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



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

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

DOPTELET (avatrombopag) is indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

Begin DOPTELET dosing 10-13 days prior to the scheduled procedure. The recommended daily dose of DOPTELET is based on the patient's platelet count prior to the scheduled procedure (Refer to Table 1). Patients should undergo their procedure 5 to 8 days after the last dose of DOPTELET.

DOPTELET should be taken orally once daily for 5 consecutive days with food. In the case of a missed dose, patients should take the next dose of DOPTELET 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 |

DOPTELET has been investigated only as a single 5-day once daily dosing regimen in clinical trials in patients with chronic liver disease *[see Clinical Studies (14)]*. DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

### 2.2 Monitoring

Obtain a platelet count prior to administration of DOPTELET therapy and on the day of a procedure to ensure an adequate increase in platelet count.

## 3 DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg avatrombopag as round, biconvex, yellow, film-coated tablets debossed with "AVA" on one side and "20" on the other side.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombotic/Thromboembolic Complications

DOPTELET 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 DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET 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).

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

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in detail in other sections of the labeling:

- Thrombotic/Thromboembolic Complications [*see Warnings and Precautions (5.1)*]

### 6.1 Clinical Trials Experience

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

The safety of DOPTELET 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 DOPTELET (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 DOPTELET 60 mg once daily for 5 days
- **High Baseline Platelet Count Cohort** (40 to less than 50 $x10^9$/ L) who received DOPTELET 40 mg once daily for 5 days

The majority of patients were males (65%) and median subject age was 58 years (ranging from 19-86 years of age). The racial and ethnic distribution was White (60%), Asian (33%), Black (3%), and Other (3%).

The most common adverse reactions (those occurring in ≥3% of patients) in the DOPTELET-treated groups (60 mg or 40 mg) across the pooled data from the two trials are summarized in Table 2.

**Table 2: Adverse Reactions with a Frequency ≥3% in Patients treated with DOPTELET - Pooled Data ADAPT-1 and ADAPT-2**

| | **Low Baseline Platelet Count Cohort (<40 $x10^9$/L)** | | **High Baseline Platelet Count Cohort (≥40 to <50 $x10^9$/L)** | | **Combined Baseline Platelet Count Cohorts (<50 $x10^9$/L)** | |
|---|---|---|---|---|---|---|
| Adverse Reactions[a] | DOPTELET 60 mg (N=159) % | Placebo (N=91) % | DOPTELET 40 mg (N=115) % | Placebo (N=65) % | Total DOPTELET (N=274) % | Total Placebo (N=156) % |
| Pyrexia | 11 | 9 | 8 | 9 | 10 | 9 |
| Abdominal Pain | 6 | 7 | 7 | 6 | 7 | 6 |
| Nausea | 6 | 8 | 7 | 6 | 7 | 7 |
| Headache | 4 | 8 | 7 | 5 | 6 | 6 |
| Fatigue | 4 | 4 | 3 | 2 | 4 | 3 |
| Edema Peripheral | 3 | 2 | 4 | 2 | 3 | 2 |

[a]Treatment emergent adverse reactions are sorted in descending order by Total DOPTELET-treated patients (N=274)

For the **Low Baseline Platelet Count Cohort**, the incidence of serious adverse reactions was 7% (11/159) in the 60 mg DOPTELET treatment group and 13% (12/91) in the matching placebo treatment group. For the **High Baseline Platelet Count Cohort**, the incidence of serious adverse reactions was 8% (9/115) in the 40 mg

DOPTELET treatment group and 3% (2/65) in the matching placebo treatment group. The most common serious adverse reaction reported with DOPTELET was hyponatremia. Two DOPTELET-treated patients (0.7%) developed hyponatremia as compared to no patients in the combined placebo group.

Adverse reactions resulting in discontinuation of DOPTELET were anemia, pyrexia, and myalgia; each was reported in a single (0.4%) patient in the DOPTELET (60 mg) treatment group.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 PREGNANCY

Risk Summary

Based on findings from animal reproduction studies, DOPTELET may cause fetal harm when administered to a pregnant woman *(see Data)*. The available data on DOPTELET in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, oral administration of avatrombopag resulted in adverse developmental outcomes when administered during organogenesis in rabbits and during organogenesis and the lactation period in rats. However, these findings were observed at exposures based on AUC substantially higher than the AUC observed in patients at the recommended dose of 60 mg once daily. Advise pregnant women of the potential risk to a fetus.

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

Data

*Animal Data*

In embryo-fetal development studies, avatrombopag was administered during organogenesis at doses of 100, 300, and 1000 mg/kg/day in rats and doses of 100, 300, and 600 mg/kg/day in rabbits. Minimal decreases in fetal weights were observed in rats at the maternally toxic dose of 1000 mg/kg/day with exposures 190-times the human exposure based on AUC. Spontaneous abortions were observed at all doses tested in rabbits and were associated with decreased body weights and food consumption at 300 and 600 mg/kg/day; exposures at the lowest dose of 100 mg/kg/day were 10-times the AUC in patients at the recommended dose of 60 mg once daily. There were no embryo-fetal effects in rats administered avatrombopag at doses up to 100 mg/kg/day (53-times the human exposure based on AUC) or rabbits administered avatrombopag at doses up to 600 mg/kg (35-times the human exposure based on AUC).

In pre- and postnatal development studies in rats, avatrombopag was administered during both the organogenesis and lactation periods at doses ranging from 5 to 600 mg/kg/day. Doses of 100, 300, and 600 mg/kg/day caused maternal toxicity leading to total litter losses, decreased body weight in pups, and increased pup mortality, with the majority of the pup mortality occurring between postnatal days 14 to 21. At a dose of 50 mg/kg/day that did not produce clear maternal toxicity, avatrombopag caused increased pup mortality from postnatal days 4 to 21, and mortality continued through postnatal day 25. The 50 mg/kg/day dose also decreased body weight gain in the pups, resulting in a delay in sexual maturation. There were no effects on behavioral or reproductive functions in the offspring. The 50 mg/kg/day dose resulted in maternal exposures 43-times and pup exposures approximately 3-times the AUC observed in patients at the recommended dose of 60 mg once daily.

### 8.2 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. Avatrombopag was present in the milk of lactating rats. When a drug is present in animal milk, it is likely the drug will be present in human milk. Due to the potential for serious adverse reactions in a breastfed child from DOPTELET, breastfeeding is not recommended during treatment with DOPTELET and for at least 2 weeks after the last dose *(see Clinical Considerations).*

Clinical Considerations

*Minimizing Exposure*

A lactating woman should interrupt breastfeeding and pump and discard breastmilk during treatment and for two weeks after the last dose of DOPTELET in order to minimize exposure to a breastfed child.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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 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).

### 8.5 Geriatric Use

Clinical studies of DOPTELET did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

## 10 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.

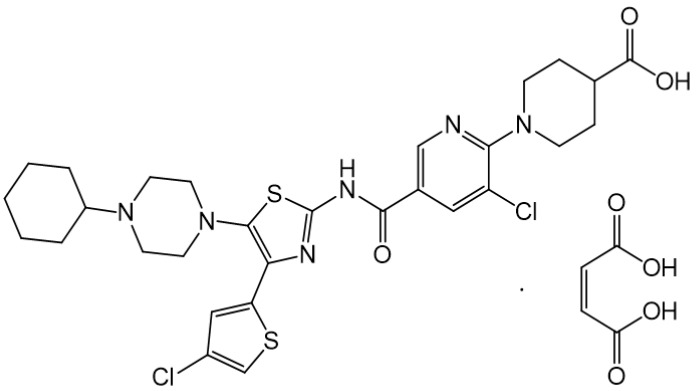
No antidote for DOPTELET overdose is known.

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

## 11 DESCRIPTION

The active ingredient in DOPTELET is avatrombopag maleate, a thrombopoietin receptor agonist. The chemical name of avatrombopag maleate is 4-piperidinecarboxylic acid, 1-[3-chloro-5-[[[4-(4-chloro-2-thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]-, (2*Z*)-2-butenedioate (1:1). It has the molecular formula $C_{29}H_{34}Cl_2N_6O_3S_2 \cdot C_4H_4O_4$. The molecular weight is 765.73.

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.

DOPTELET is provided as an immediate-release tablet. Each DOPTELET tablet contains 20 mg avatrombopag (equivalent to 23.6 mg of avatrombopag maleate) and the following inactive ingredients: lactose monohydrate, colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Coating film: polyvinyl alcohol, talc, polyethylene glycol, titanium dioxide and ferric oxide yellow.

## 12 CLINICAL PHARMACOLOGY

### 12.1 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.

### 12.2 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, DOPTELET does 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.

### 12.3 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 DOPTELET was co-administered with a low-fat meal (500 calories, 3 g fat, 15 g proteins, and 108 g carbohydrates) or a high-fat meal (918 calories, 59 g fat, 39 g proteins, and 59 g carbohydrates). 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 DOPTELET was administered with a low-fat or high-fat meal (median $T_{max}$ range 5 to 8 hours) compared to the fasted state.

*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 (CYP) 2C9 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.

The effect of age (< 18 years) and severe renal impairment (CLcr < 30 mL/min, Cockcroft-Gault) including patients requiring hemodialysis on avatrombopag pharmacokinetics is unknown.

*Drug Interactions*
Drug interaction studies were performed in healthy subjects with single 20 mg DOPTELET dose and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions (see Table 3).

**Table 3: Drug Interactions: Changes in Pharmacokinetics of Avatrombopag in the Presence of Co-administered Drug**

| Co-administered Drug* | 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) 3 and breast cancer resistance protein (BCRP) but not organic anion transporter polypeptide (OATP) 1B1 and 1B3, organic cation transporter (OCT) 2, and OAT1 in vitro.

Effect of Transporters

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In two-year carcinogenicity studies, avatrombopag was administered orally at doses of 20, 60, 160 mg/kg/day in mice and doses of 20, 50, 160 mg/kg/day in rats. Avatrombopag induced a statistically significant increase in neuroendocrine cell (enterochromaffin-like cell, ECL cell) gastric tumors (carcinoids) in the stomach at 160 mg/kg in female rats. The 160 mg/kg/day dose resulted in exposures 117-times the AUC observed in patients at the recommended dose of 60 mg once daily. 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.

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.

## 14 CLINICAL STUDIES

The efficacy of DOPTELET for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was established in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 (NCT01972529) and ADAPT-2 (NCT01976104)). 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** ($\geq 40$ to $<50 \times 10^9$ L) based on their platelet count at Baseline. Patients were then randomized in a 2:1 ratio to either DOPTELET or placebo. Patients were stratified according to hepatocellular cancer (HCC) status and risk of bleeding associated with the elective procedure (low, moderate, or high). Patients undergoing neurosurgical interventions, thoracotomy, laparotomy or organ resection were not eligible for enrollment.

Patients in the **Low Baseline Platelet Count Cohort** received 60 mg DOPTELET or matching placebo once daily for 5 days, and patients in the **High Baseline Platelet Count Cohort** received 40 mg DOPTELET or matching placebo once daily for 5 days. Eligible patients were scheduled to undergo their procedure (low, moderate, or high bleeding risk) 5 to 8 days after their last dose of treatment. Patient populations were similar between the pooled **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.

In ADAPT-1, a total of 231 patients were randomized, 149 patients were treated with DOPTELET and 82 patients were treated with placebo. In the **Low Baseline Platelet Count Cohort**, the mean Baseline platelet count for the DOPTELET-treated group was 31.1 $\times 10^9$/L and for placebo-treated patients was 30.7 $\times 10^9$/L. In the **High Baseline Platelet Count Cohort**, the mean Baseline platelet count for the DOPTELET-treated patients was 44.3 $\times 10^9$/L and for placebo-treated patients was 44.9 $\times 10^9$/L.

In ADAPT-2, a total of 204 patients were randomized, 128 patients were treated with DOPTELET and 76 patients were treated with placebo. In the **Low Baseline Platelet Count Cohort**, the mean Baseline platelet count for the DOPTELET-treated group was 32.7 $\times 10^9$/L and for placebo-treated patients was 32.5 $\times 10^9$/L. In the **High Baseline Platelet Count Cohort**, the mean Baseline platelet count for the DOPTELET-treated patients was 44.3 $\times 10^9$/L and for placebo-treated patients was 44.5 $\times 10^9$/L.

Across both baseline platelet count cohorts and the avatrombopag and placebo treatment groups, patients underwent a broad spectrum of types of scheduled procedures that ranged from low to high bleeding risk. Overall, the majority of patients (60.8% [248/430] subjects) in all treatment groups underwent low bleeding risk procedures, 17.2% [70/430] of patients underwent procedures associated with moderate bleeding risk, and 22.1% [90/430] of subjects underwent procedures associated with high bleeding risk. The proportions of patients undergoing low, moderate, and high-risk procedures were similar between the avatrombopag and placebo treatment groups.

The major efficacy outcome was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Additional secondary efficacy outcomes were the proportion of patients who achieved platelet counts of $>50 \times 10^9$/L on the day of procedure and the change in platelet count from baseline to procedure day.

Responders were defined as patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure. The following were considered rescue therapies to manage risk of bleeding associated with a procedure: whole blood transfusion, packed red blood cell (RBC) transfusion, platelet transfusion, fresh frozen plasma (FFP) or cryoprecipitate administration, Vitamin K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, or surgical or interventional radiology procedures performed to achieve hemostasis and control blood loss. In both baseline platelet count cohorts, patients in the DOPTELET treatment groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant as detailed in Table 4.

**Table 4: Proportion of Subjects Not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Baseline Platelet Count Cohort and Treatment Group – ADAPT-1 and ADAPT-2**

| **Low Baseline Platelet Count Cohort (<40 x10$^9$/L)** | | | | |
|---|---|---|---|---|
| **Category** | **ADAPT-1** | | **ADAPT-2** | |
| | **DOPTELET 60 mg (n=90)** | **Placebo (n=48)** | **DOPTELET 60 mg (n=70)** | **Placebo (n=43)** |
| **Responders** *95% CI*[a] | **66%** *(56, 75)* | **23%** *(11, 35)* | **69%** *(58, 79)* | **35%** *(21, 49)* |
| **Difference of Proportion vs. Placebo**[b] *95% CI*[c] | **43%** *(27, 58)* | | **34%** (16, 52) | |
| **p-value**[d] | **<0.0001** | | **0.0006** | |
| **High Baseline Platelet Count Cohort (≥40 to <50 x10$^9$/L)** | | | | |
| **Category** | **ADAPT-1** | | **ADAPT-2** | |
| | **DOPTELET 40 mg (n=59)** | **Placebo (n= 34)** | **DOPTELET 40 mg (n=58)** | **Placebo (n=33)** |
| **Responders** *95% CI*[a] | **88%** *(80, 96)* | **38%** *(22, 55)* | **88%** *(80, 96)* | **33%** *(17, 49)* |
| **Difference of Proportion vs. Placebo**[b] *95% CI*[c] | **50%** *(32, 68)* | | **55%** *(37, 73)* | |
| **p-value**[d] | **<0.0001** | | **<0.0001** | |

a Two-sided 95% confidence interval based on normal approximation.

b Difference of proportion vs. placebo = proportion of Responders for DOPTELET – proportion of Responders for placebo

c 95% confidence interval calculated based on normal approximation.

d By Cochran-Mantel-Haenszel Testing stratified by bleeding risk for the procedure.

In addition, both trials demonstrated a higher proportion of patients who achieved the target platelet count of ≥ 50 x10$^9$/L on the day of the procedure, a secondary efficacy endpoint, in both DOPTELET-treated groups versus the placebo-treated groups for both cohorts (**Low Baseline Platelet Count Cohort**-ADAPT-1: 69% vs 4%, respectively; P <0.0001; ADAPT-2: 67% vs 7%, respectively; P <0.0001; **High Baseline Platelet Count Cohort**- ADAPT-1: 88% vs 21%, respectively; P <0.0001; ADAPT-2: 93% vs 39%, respectively; P <0.0001).

Further, both trials demonstrated a greater mean change in platelet counts from baseline to the day of the procedure, a secondary efficacy endpoint, in both DOPTELET-treated groups versus the placebo-treated groups

for both cohorts (**Low Baseline Platelet Count Cohort-**ADAPT-1: 32 $x10^9$/L vs 0.8 $x10^9$/L, respectively; P <0.0001; ADAPT-2: 31.3 $x10^9$/L vs 3.0 $x10^9$/L, respectively; P <0.0001; **High Baseline Platelet Count Cohort**-ADAPT-1: 37.1 $x10^9$/L vs 1.0 $x10^9$/L, respectively; P <0.0001;ADAPT-2: 44.9 $x10^9$/L vs 5.9 $x10^9$/L, respectively; P <0.0001).

A measured increase in platelet counts was observed in both DOPTELET treatment groups over time beginning on Day 4 post-dose, that peaked on Day 10-13, decreased 7 days post-procedure, and then returned to near baseline values by Day 35.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

DOPTELET 20 mg tablets are supplied as round, biconvex, yellow, film-coated tablets, and debossed with "AVA" on one side and "20" on the other side.

NDC 71369-020-10: carton with one blister card of ten 20 mg tablets
NDC 71369-020-11: one blister card with ten 20 mg tablets
NDC 71369-020-15: carton with one blister card of fifteen 20 mg tablets
NDC 71369-020-16: one blister card of fifteen 20 mg tablets

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store tablets in original package.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information).

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

*Risks*

*Thrombotic/Thromboembolic Complications*
DOPTELET 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.

*Pregnancy*

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

*Lactation*

Advise women not to breastfeed during treatment with DOPTELET and for at least 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured for: AkaRx, Inc., Durham, North Carolina 27707

Marketed by Dova Pharmaceuticals, Inc., Durham, North Carolina 27707

 PI0001 R3

**PATIENT INFORMATION**
**DOPTELET® (dop-TEL-et)**
**(avatrombopag)**
**tablets**

**What is DOPTELET?**

DOPTELET is a prescription medicine used to treat low blood platelet counts in adults with long-lasting (chronic) liver disease who are scheduled to have a medical or dental procedure.

DOPTELET is not used to make platelet counts normal in adults with chronic liver disease.

It is not known if DOPTELET is safe and effective in children.

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

- have ever had a blood clot.
- are pregnant or plan to become pregnant. DOPTELET may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with DOPTELET.
- are breastfeeding or plan to breastfeed. It is not known if DOPTELET passes into your breast milk. Do not breastfeed during your treatment with DOPTELET and for at least 2 weeks after the last dose. Talk to your healthcare provider about the best way to feed your baby during this time.

**Tell your healthcare provider about all of the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**How should I take DOPTELET?**

- Take DOPTELET exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much DOPTELET to take and when to start taking it.
- Take your prescribed dose of DOPTELET 1 time per day for five days in a row as instructed by your healthcare provider.
- Take DOPTELET with food.
- Your healthcare provider will check your platelet count before treatment with DOPTELET and on the day of your scheduled procedure.
- If you forget to take a dose of DOPTELET, take it as soon as you remember. Do not take two doses at one time to make up for a missed dose. Take your next dose at your usual time the next day and complete all five days of dosing.
- If you take too much DOPTELET, call your healthcare provider or go to the nearest hospital emergency room right away.

**What are the possible side effects of DOPTELET?**

**DOPTELET may cause serious side effects, including:**

- **Blood clots.** People with chronic liver disease and people with certain blood clotting conditions may have an increased risk of developing blood clots. Tell your healthcare provider right away if you have signs and symptoms of a blood clot, including:
  - ○ swelling, pain, or tenderness in your leg
  - ○ shortness of breath
  - ○ chest pain
  - ○ fast heartbeat
  - ○ stomach (abdominal) pain or tenderness

**The most common side effects of DOPTELET are:**

- fever
- stomach (abdominal) pain
- nausea
- headache
- tiredness
- swelling of the hands or feet

These are not all the possible side effects of DOPTELET.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store DOPTELET?**

- Store DOPTELET at room temperature between 68°F to 77°F (20°C to 25°C).
- Store DOPTELET tablets in the original package.

**Keep DOPTELET and all medicines out of the reach of children.**

**General information about the safe and effective use of DOPTELET.**

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information. Do not use DOPTELET for a condition for which it was not prescribed. Do not give DOPTELET to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about DOPTELET that is written for health professionals.

**What are the ingredients in DOPTELET?**

**Active ingredient:** avatrombopag

**Inactive ingredients:** lactose monohydrate, colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Tablet coating film: polyvinyl alcohol, talc, polyethylene glycol, titanium dioxide and ferric oxide yellow.



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This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 5/2018

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