# PDL DRUG REVIEW

**Proprietary Name: Tavalisse®**
**Common Name: fostamatinib**
**PDL Category: Hematopoietics Chronic ITP**

## Summary


**Pharmacology/Usage:** Fostamatinib, the active ingredient of Tavalisse®, is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major metabolite of fostamatinib is R406, and this reduces antibody-mediated destruction of platelets.

**Indication:** For the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and the mechanism of action, Tavalisse® can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Pregnancy status should be verified before starting treatment. The safety and efficacy of use in the pediatric population have not been established.

**Dosage Forms:** Film-Coated Tablets: 100mg, 150mg

**Recommended Dosage:** Start at 100mg PO BID. After a month, if the platelet count has not increased to at least 50 X $10^9$/L, increase the dose to 150mg PO BID. Use the lowest dose to achieve and maintain a platelet count at least 50 X $10^9$/L as necessary to reduce the risk of bleeding. Treatment should be discontinued after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.

After obtaining baseline assessments:

- Monitor CBCs (including platelet counts), monthly until a stable platelet count is achieved. Thereafter, continue to monitor CBCs, including neutrophils, regularly
- Monitor liver function tests monthly (e.g. ALT, AST, and bilirubin)
- Monitor blood pressure every 2 weeks until establishment of a stable dose, then monthly thereafter.

Dose modifications for the management of specific adverse reactions, such as hypertension, hepatotoxicity, diarrhea, and neutropenia, may be required. Refer to the prescribing information for additional information.

**Drug Interactions:** The concomitant use of Tavalisse® with strong CYP3A4 inducers is not recommended. It is recommended to monitor for toxicities of Tavalisse® that may require dose reduction when given concurrently with a strong CYP3A4 inhibitor. Monitor for toxicities of CYP3A4 substrates, of BCRP substrates, and of P-gp substrates that may require dose reduction when given concurrently with Tavalisse®.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tavalisse®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included diarrhea (16%), hypertension (15%), nausea (11%), dizziness (3%), ALT increased (11%), AST increased (9%), respiratory infection (5%), rash (7%), abdominal pain (4%), fatigue (4%), chest pain (4%), and neutropenia (6%). The following elevations in hepatic transaminases were reported with ALT and/or AST: >3 and ≤5 X ULN (3%), >5 and ≤10 X ULN (5%), and ≥10 X ULN (1%).

Hypertension can occur with Tavalisse®. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects of Tavalisse®. It is recommended to monitor blood pressure every 2 weeks until stable, then monthly and adjust or start antihypertensive therapy to ensure maintenance of blood pressure control during Tavalisse® therapy.

Elevated liver function tests, mainly ALT and AST, can occur with Tavalisse®. It is recommended to monitor liver function tests monthly during treatment. If ALT or AST increase more than 3 times the upper limit of normal, manage hepatotoxicity using Tavalisse® interruption, reduction, or discontinuation.

As neutropenia occurred in 6% of patients treated with Tavalisse®, it is recommended to monitor ANC monthly and for infection during treatment. Manage toxicity with Tavalisse® interruption, reduction, or discontinuation.

**Contraindications:** There are no contraindications listed with this product.

**Manufacturer:** Rigel Pharmaceuticals

**Analysis:** The safety and efficacy of Tavalisse® were assessed in 2 placebo-controlled studies and one open-label extension study. FIT-1 and FIT-2 were identical, double-blind, placebo-controlled studies that included patients with persistent or chronic ITP, who had an insufficient response to previous treatment (which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonist). Stable concurrent ITP therapy (glucocorticoids, azathioprine, or danazol) was allowed, and rescue therapy was permitted if needed. Patients who did not respond to treatment after 12 weeks, as well as patients who completed the 24-week double blind study, were eligible to enroll in the open-label extension study (FIT-3). Patients enrolled had a median age of 54 years and a majority were female (61%) and were white (93%). At baseline, the median platelet count was 16 X $10^9$/L and 47% were on stable ITP therapy.

The efficacy of Tavalisse® was based on stable platelet response (at least 50 X$10^9$/L on at least 4 of the 6 visits between weeks 14 to 24). The table below includes the results, which was adapted from the prescribing information.

| Treatment | Study FIT-1 | | Study FIT-2 | |
|---|---|---|---|---|
| | Tavalisse® (N=51) | Placebo (N=25) | Tavalisse® (N=50) | Placebo (N=24) |
| Stable platelet response | 9 (18%) | 0 | 8 (16%) | 1 (4%) |
| | p=0.03 | | Not statistically different | |
| Rolled-over into FIT-3 at week 12 | 28 (55%) | 22 (88%) | 33 (66%) | 19 (79%) |
| Completed study (week 24) | 12 (24%) | 1 (4%) | 13 (26%) | 2 (8%) |

In the FIT-1 and FIT-2 studies, there were 47 in the Tavalisse® arm that had received a prior thrombopoietin receptor agonists (TPO-RA) treatment. Of these, 8 patients (17%) achieved a stable response to Tavalisse®. All 8 patients had previously discontinued TPO-RA due to loss of effect. Rescue medication was required by 30% of the Tavalisse® group and 45% of the placebo group.

During the placebo-controlled studies, the incidence of bleeding occurred in 29% of the Tavalisse® group vs 37% of the placebo group. Moderate, severe, and serious bleeding events can be seen in the table below, which was adapted from the prescribing information. All severe events led to hospitalizations.

| Treatment | Tavalisse® (N=101) | Placebo (N=49) |
|---|---|---|
| Incidence of moderate bleeding-related adverse events | 9 (9%) | 5 (10%) |
| Incidence of severe bleeding-related adverse events | 1 (1%) | 3 (6%) |
| Incidence of serious bleeding-related adverse events | 4 (4%) | 5 (10%) |

FIT-3 was the open-label extension study that included patients from FIT-1 and FIT-2 who completed 24 weeks of treatment, or who did not respond to treatment any time after 12 weeks. Patients remained blinded to their treatment assignment from the previous study, so the starting dose in this study was based on the final platelet count. Patients labeled as responders at the time of the roll-over continued in the extension study at the current trial dose and regimen, but patients who entered the extension study as non-responders received Tavalisse® 100mg BID regardless of the dose and regimen in the prior study.

There were 123 enrolled in FIT-3, with 44 previously randomized to placebo and 79 previously randomized to Tavalisse®. Stable response was prospectively defined as no 2 visits, at least 4 weeks apart, with a platelet count $<50 \times 10^9$/L, without an intervening visit with a platelet count of at least $50 \times 10^9$/L (unrelated to rescue therapy), within a period of 12 weeks after initial achievement of the target platelet count. Of the 123 patients, 61 (50%) discontinued from the study early. In the prospectively defined analysis, the 44 treated with placebo in the prior study were assessed for stable response for Tavalisse®; 10 of these subjects (23%) met the criteria for stable response. Of the subjects who achieved stable response in all 3 studies, 18 subjects maintained the platelet count of at least $50 \times 10^9$/L for ≥12 months.

**Place in Therapy:** Tavalisse® is an oral tablet indicated for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous first line therapy treatment. While in one study a significantly larger number of subjects treated with Tavalisse® achieved a stable platelet response as compared with placebo, statistical significance was not seen in the second study.

Tavalisse® is indicated for adults who have had an insufficient response to a previous first line therapy treatment. It is an alternative to rituximab for patients at risk of bleeding who have failed a first line therapy (steroids, IVIG, splenectomy). It is therefore recommended that Tavalisse® remain non-preferred to ensure it is used in clinically appropriate situations.

**PDL Placement:**
☐ **Preferred**
☒ **Non-Preferred with Conditions**

## References

[1] Tavalisse [package insert]. South San Francisco, CA: Rigel Pharmaceuticals; 2018.