Tavalisse®
(fostamatinib disodium hexahydrate) tablets

DOSING AND ADMINISTRATION GUIDE

INDICATION

TAVALISSE is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

SELECT IMPORTANT SAFETY INFORMATION

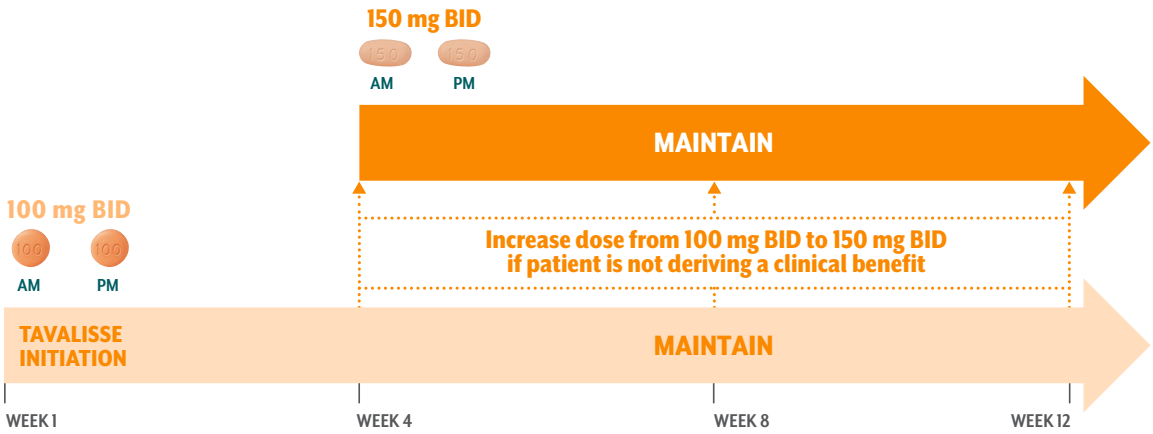
Warnings and Precautions

- Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during therapy. If increased blood pressure persists, TAVALISSE interruption, reduction, or discontinuation may be required.

Please see Important Safety Information on pages 7 and 8 and accompanying full Prescribing Information.

TAVALISSE OFFERS THE CONVENIENCE OF ORAL DOSING WITHOUT FOOD RESTRICTIONS

When starting TAVALISSE, a 12-week evaluation period is recommended—evaluate the clinical benefit at weeks 4, 8, and 12*,†



After 12 weeks: Continue treatment at therapeutic dose
OR if patient has not derived a clinical benefit, discontinue treatment‡

- Initiate TAVALISSE at 100 mg orally twice daily with or without food. If a dose is missed, the next dose should be taken at its regularly scheduled time
- Use the lowest dose of TAVALISSE to achieve and maintain a platelet count of at least 50 x 10^9/L to reduce the risk of bleeding
- After 1 month, if platelet count has not increased to at least 50 x 10^9/L, increase TAVALISSE dose to 150 mg twice daily
- Discontinue TAVALISSE after 12 weeks of treatment if platelet count does not increase to a level sufficient to avoid clinically important bleeding
- In clinical trials, stable concurrent ITP therapy was allowed and rescue therapy was permitted if needed

*12-week evaluation period recommended per product labeling.

†Clinical benefit: platelet count increase to a level sufficient to avoid clinically important bleeding.

‡Discontinue TAVALISSE after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.

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TREATMENT WITH TAVALISSE SHOULD BE ACCOMPANIED BY REGULAR PATIENT MONITORING

As part of chronic ITP care, patient monitoring is recommended with TAVALISSE

Complete blood counts, including platelet counts and neutrophils	Baseline plus monthly monitoring until a stable platelet count (≥50 x 10^9/L) is achieved, then regular monitoring
Liver function tests (LFTs) (eg, ALT, AST, and bilirubin)	Baseline plus monthly monitoring
Blood pressure	Baseline plus monitoring every 2 weeks until a stable dose is reached, then monthly thereafter

TAVALISSE is available in 2 dose strengths

- **100 mg tablets:** orange, film-coated, round, biconvex tablets debossed with "100" on 1 side and "R" on the reverse side
- **150 mg tablets:** orange, film-coated, oval, biconvex tablets debossed with "150" on 1 side and "R" on the reverse side

88% of patients in the phase 3 clinical studies were maintained at the 150 mg BID dose

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MODIFICATION OF THE TAVALISSE DOSE CAN HELP IN THE MANAGEMENT OF ADVERSE REACTIONS

TAVALISSE dose modification guidance

- TAVALISSE dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose interruption, reduction, or discontinuation
  - See the tables in this dosing guide, or section 2.3 of the full Prescribing Information, for specific guidance on dose modification and recommendations for treatment discontinuation

DAILY DOSE	ADMINISTERED AS:	
	AM	PM
300 mg/day		
200 mg/day		
150 mg/day	 *	---
100 mg/day†	 *	---

*Once-daily TAVALISSE should be taken in the morning.

†If further dose reduction below 100 mg/day is required, discontinue TAVALISSE.

Effect of TAVALISSE on other drugs

CYP3A4 substrates: Concomitant use of TAVALISSE may increase concentrations of some CYP3A4 substrate drugs. Monitor for toxicities of CYP3A4 substrate drugs that may require dosage reduction when given concurrently with TAVALISSE.

BCRP substrates: Concomitant use of TAVALISSE may increase concentrations of BCRP substrate drugs (eg, rosuvastatin). Monitor for toxicities of BCRP substrate drugs that may require dosage reduction when given concurrently with TAVALISSE.

P-Glycoprotein (P-gp) substrates: Concomitant use of TAVALISSE may increase concentrations of P-gp substrates (eg, digoxin). Monitor for toxicities of the P-gp substrate drugs that may require dosage reduction when given concurrently with TAVALISSE.

Please see Important Safety Information on pages 7 and 8 and accompanying full Prescribing Information.

DOSING MODIFICATION AND SUPPORTIVE CARE RECOMMENDATIONS—DIARRHEA AND NEUTROPENIA

Diarrhea management

	Recommended action
Diarrhea	• Manage diarrhea using supportive measures (eg, dietary changes, hydration, and/or antidiarrheal medication) early after the onset until symptom(s) have resolved • If symptom(s) become severe (grade 3 or above), temporarily interrupt TAVALISSE • If diarrhea improves to mild (grade 1), resume TAVALISSE at the next lower daily dose (refer to dose reduction schedule)

Neutropenia management

	Recommended action
Neutropenia	• If absolute neutrophil count decreases (ANC less than 1.0 x 10^9/L) and remains low after 72 hours, temporarily interrupt TAVALISSE until resolved (ANC greater than 1.5 x 10^9/L) • Resume TAVALISSE at the next lower daily dose (refer to dose reduction schedule)

Effect of other drugs on TAVALISSE

Strong CYP3A4 inhibitors: Concomitant use with strong CYP3A4 inhibitors increases exposure to R406 (the major active metabolite), which may increase the risk of adverse reactions. Monitor for toxicities of TAVALISSE that may require dose reduction when given concurrently with a strong CYP3A4 inhibitor.

Strong CYP3A4 inducers: Concomitant use with a strong CYP3A4 inducer reduces exposure to R406. Concomitant use of TAVALISSE with strong CYP3A4 inducers is not recommended.

Please see section 12.3, Clinical Pharmacology, in the full Prescribing Information.

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DOSING MODIFICATION AND SUPPORTIVE CARE RECOMMENDATIONS—HEPATOTOXICITY

Hepatotoxicity management

	Recommended action
AST/ALT is 3 x ULN or higher and less than 5 x ULN	If patient is symptomatic (eg, nausea, vomiting, abdominal pain): • Interrupt TAVALISSE • Recheck LFTs every 72 hours until ALT/AST values are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN • Resume TAVALISSE at next lower daily dose (refer to dose reduction schedule)
	If patient is asymptomatic: • Recheck LFTs every 72 hours until ALT/AST are below 1.5 x ULN and total BL remains less than 2 x ULN • Consider interruption or dose reduction of TAVALISSE if ALT/AST and total BL remain in this category (AST/ALT is 3 to 5 x ULN; and total BL remains less than 2 x ULN) • If interrupted, resume TAVALISSE at next lower daily dose (refer to dose reduction schedule) when ALT/AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN
AST/ALT is 5 x ULN or higher and total BL is less than 2 x ULN	• Interrupt TAVALISSE • Recheck LFTs every 72 hours: – If AST and ALT decrease, recheck until ALT and AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN; resume TAVALISSE at next lower daily dose (refer to dose reduction schedule) – If AST/ALT persist at 5 x ULN or higher for 2 weeks or more, discontinue TAVALISSE
AST/ALT is 3 x ULN or higher and total BL is greater than 2 x ULN	• Discontinue TAVALISSE
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities	• Continue TAVALISSE with frequent monitoring since isolated increase in unconjugated (indirect) BL may be due to UGTIA1 inhibition

ALT=alanine aminotransferase; AST=aspartate aminotransferase; AST/ALT=AST or ALT; BL=bilirubin; LFT=liver function test (AST, ALT, total BL with fractionation if elevated, alkaline phosphatase); ULN=upper limit of normal.

DOSING MODIFICATION AND SUPPORTIVE CARE RECOMMENDATIONS—HYPERTENSION

Hypertension management

	Recommended action
Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg	• Initiate or increase dosage of antihypertensive medication for patients with increased cardiovascular risk, and adjust as needed until BP is controlled • If the BP target is not met after 8 weeks, reduce TAVALISSE to next lower daily dose (refer to dose reduction schedule)
Stage 2: systolic at least 140 or diastolic at least 90 mmHg	• Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled • If BP remains 140/90 mmHg or higher for more than 8 weeks, reduce TAVALISSE to next lower daily dose (refer to dose reduction schedule) • If BP remains 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive therapy, interrupt or discontinue TAVALISSE
Hypertensive crisis: systolic over 180 and/or diastolic over 120 mmHg	• Interrupt or discontinue TAVALISSE • Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled. If BP returns to less than the target BP, resume TAVALISSE at same daily dose • If repeat BP is 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive treatment, discontinue TAVALISSE

BP=blood pressure.

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during therapy. If increased blood pressure persists, TAVALISSE interruption, reduction, or discontinuation may be required.
- Elevated liver function tests (LFTs), mainly ALT and AST, can occur with TAVALISSE. Monitor LFTs monthly during treatment. If ALT or AST increase to ≥3 x upper limit of normal, manage hepatotoxicity using TAVALISSE interruption, reduction, or discontinuation.
- Diarrhea occurred in 31% of patients and severe diarrhea occurred in 1% of patients treated with TAVALISSE. Monitor patients for the development of diarrhea and manage using supportive care measures early after the onset of symptoms. If diarrhea becomes severe (≥Grade 3), interrupt, reduce dose or discontinue TAVALISSE.
- Neutropenia occurred in 6% of patients treated with TAVALISSE; febrile neutropenia occurred in 1% of patients. Monitor the ANC monthly and for infection during treatment. Manage toxicity with TAVALISSE interruption, reduction, or discontinuation.
- TAVALISSE can cause fetal harm when administered to pregnant women. Advise pregnant women the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Verify pregnancy status prior to initiating TAVALISSE. It is unknown if TAVALISSE or its metabolite is present in human milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during TAVALISSE treatment and for at least 1 month after the last dose.

Please see accompanying full Prescribing Information.

Drug Interactions

- Concomitant use of TAVALISSE with strong CYP3A4 inhibitors increases exposure to the major active metabolite of TAVALISSE (R406), which may increase the risk of adverse reactions. Monitor for toxicities that may require a reduction in TAVALISSE dose.
- It is not recommended to use TAVALISSE with strong CYP3A4 inducers, as concomitant use reduces exposure to R406.
- Concomitant use of TAVALISSE may increase concentrations of some CYP3A4 substrate drugs and may require a dose reduction of the CYP3A4 substrate drug.
- Concomitant use of TAVALISSE may increase concentrations of BCRP substrate drugs (eg, rosuvastatin) and P-Glycoprotein (P-gp) substrate drugs (eg, digoxin), which may require a dose reduction of the BCRP and P-gp substrate drug.

Adverse Reactions

- Serious adverse drug reactions in the ITP double-blind studies were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which occurred in 1% of TAVALISSE patients. In addition, severe adverse reactions occurred including dyspnea and hypertension (both 2%), neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope, and hypoxia (all 1%).
- Common adverse reactions (≥5% and more common than placebo) from FIT-1 and FIT-2 included: diarrhea, hypertension, nausea, dizziness, ALT and AST increased, respiratory infection, rash, abdominal pain, fatigue, chest pain, and neutropenia.

To report side effects of prescription drugs to the FDA, visit www.fda.gov/medwatch or call 1-800-FDA-1088 (1-800-332-1088).

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Learn more at **TAVALISSEhcp.com**

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