



Tavalisse™

(fostamatinib disodium hexahydrate) tablets

DOSING AND ADMINISTRATION GUIDE

Indication

TAVALISSE is a kinase inhibitor 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

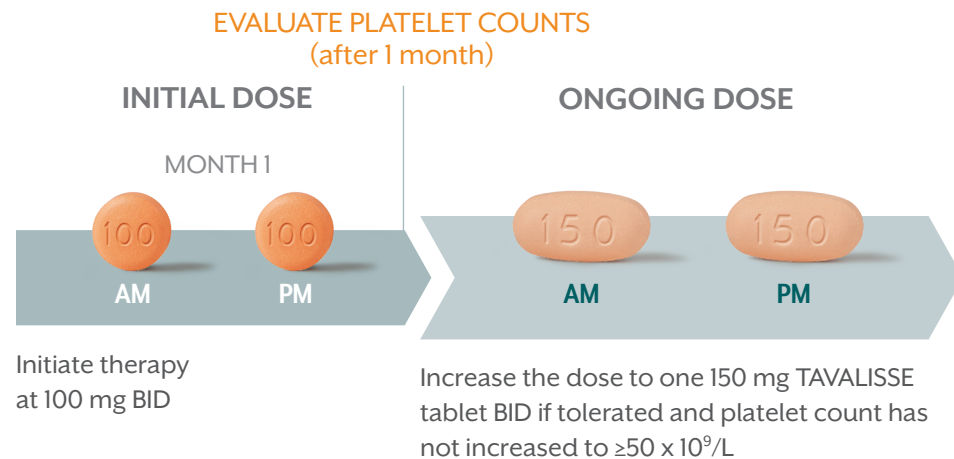
- Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during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

Dosage and administration—one tablet BID*

Dosing schedule



- Use the lowest dose of TAVALISSE to achieve and maintain a platelet count of at least $50 \times 10^9/L$ to reduce the risk of bleeding
- 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
- After 1 month, if platelet count has not increased to at least $50 \times 10^9/L$, 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

*Please see following pages for details on dose modification as necessary.

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

TREATMENT WITH TAVALISSE SHOULD BE ACCOMPANIED BY REGULAR PATIENT MONITORING

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

Complete blood counts (CBCs), including platelet counts and neutrophils	Baseline plus monthly monitoring until a stable platelet count ($\geq 50 \times 10^9/L$) 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 two dose strengths



Tablets: 100 mg, 150 mg

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

- In addition to supportive care measures, 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
- Starting with the current dose, gradually reduce the dose following the steps provided below until the adverse reaction resolves

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

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

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

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 drug 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 drug 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 drug 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

Diarrhea

Recommended action

Diarrhea	<ul style="list-style-type: none"> 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 modification table)
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Neutropenia management

Neutropenia

Recommended action

Neutropenia	<ul style="list-style-type: none"> If absolute neutrophil count decreases (ANC less than $1.0 \times 10^9/L$) and remains low after 72 hours, temporarily interrupt TAVALISSE until resolved (ANC greater than $1.5 \times 10^9/L$) Resume TAVALISSE at the next lower daily dose (refer to dose modification table)
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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

Hepatotoxicity	Recommended action
AST/ALT is 3 x ULN or higher and less than 5 x ULN	<p>If patient is symptomatic (eg, nausea, vomiting, abdominal pain):</p> <ul style="list-style-type: none"> • 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 modification table) <p>If patient is asymptomatic:</p> <ul style="list-style-type: none"> • 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 TBL 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 modification table) 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	<ul style="list-style-type: none"> • Interrupt TAVALISSE • Recheck LFTs every 72 hours: <ul style="list-style-type: none"> – 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 modification table) – 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	<ul style="list-style-type: none"> • Discontinue TAVALISSE
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities	<ul style="list-style-type: none"> • Continue TAVALISSE with frequent monitoring since isolated increase in unconjugated (indirect) BL may be due to UGT1A1 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

Hypertension	Recommended action
<p>Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg</p>	<ul style="list-style-type: none"> • 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 modification table)
<p>Stage 2: systolic at least 140 or diastolic at least 90 mmHg</p>	<ul style="list-style-type: none"> • 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 modification table) • If BP remains 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive therapy, interrupt or discontinue TAVALISSE
<p>Hypertensive crisis: systolic over 180 and/or diastolic over 120 mmHg</p>	<ul style="list-style-type: none"> • 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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INDICATION AND IMPORTANT SAFETY INFORMATION

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.

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 (\geq 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.

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 (\geq 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).

LEARN MORE AT [TAVALISSEhcp.com](https://www.TAVALISSEhcp.com)



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