PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

TAVALISSE 100 mg
TAVALISSE 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAVALISSE 100 mg film-coated tablets
Each film-coated tablet contains 126.2 mg of fostamatinib disodium hexahydrate equivalent to 100 mg fostamatinib

Excipient(s) with known effect
Each 100 mg tablet contains 23 mg sodium (from excipients and fostamatinib disodium hexahydrate).

TAVALISSE 150 mg film-coated tablets
Each film-coated tablet contains 189.3 mg of fostamatinib disodium hexahydrate equivalent to 150 mg fostamatinib.

Excipient(s) with known effect
Each 150 mg tablet contains 34 mg sodium (from excipients and fostamatinib disodium hexahydrate). For the full list of excipients, see section 11

3. Therapeutic indications

TAVALISSE is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dosage

Initiate TAVALISSE at a dose of 100 mg taken orally twice daily. After a month, if platelet count has not increased to at least 50×10^9/L, increase TAVALISSE dose to 150 mg twice daily.

Use the lowest dose of TAVALISSE to achieve and maintain a platelet count at least 50×10^9/L as necessary to reduce the risk of bleeding.

TAVALISSE may be taken with or without food. In the case of a missed dose of TAVALISSE, instruct patients to take their next dose at its regularly scheduled time.

4.2 Monitoring

After obtaining baseline assessments:

- Monitor CBCs, including platelet counts, monthly until a stable platelet count (at least 50×10^9/L) is achieved. Thereafter, continue to monitor CBCs, including neutrophils, regularly.
- Monitor liver function tests (LFTs) (e.g., ALT, AST, and bilirubin) monthly.
- Monitor blood pressure every 2 weeks until establishment of a stable dose, then monthly thereafter.

4.3 Dose Modification for Adverse Reactions

TAVALISSE dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose-interruption, reduction, or discontinuation.

A dose reduction schedule is provided in Table 1, based on daily dose. For example, if a patient is on

the maximum dose at the time of an adverse reaction, the first dose reduction would be from 300 mg/day to 200 mg/day.

Table 1: Dose Reduction Schedule

Daily Dose	Administered as:	
	AM	**PM**
300 mg/day	150 mg	150 mg
200 mg/day	100 mg	100 mg
150 mg/day	150 mg*	---
100 mg/day†	100 mg*	---

* Once daily TAVALISSE should be taken in the morning.

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

The recommended dose modifications for adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications and Management for Specific Adverse Reactions

Adverse Reaction	Recommended Action
Hypertension	
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 Table 1).
	Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled.

Stage 2: systolic at least 140 or diastolic at least 90 mmHg	• If BP remains 140/90 mmHg or higher for more than 8 weeks, reduce TAVALISSE to next lower daily dose (refer to Table 1). • 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.
Hepatotoxicity	
AST/ALT is 3 × ULN or higher and less than 5 × ULN	If patient is symptomatic (e.g., nausea, vomiting, abdominal pain): • Interrupt TAVALISSE. • Recheck LFTs every 72 hours until ALT/AST values are no longer elevated (below 1.5 × ULN) and total BL remains less than 2 × ULN. Resume • TAVALISSE at next lower daily dose (refer to Table 1).
	If patient is asymptomatic: • Recheck LFTs every 72 hours until ALT/AST are below 1.5 × ULN) and total BL remains less than 2 × ULN. • Consider interruption or dose reduction of TAVALISSE if ALT/AST and TBL remain in this category (AST/ALT is 3 to 5 × ULN; and total BL remains less than 2 × ULN) • If interrupted, resume TAVALISSE at next lower daily dose (refer to Table 1) when ALT/AST are no longer elevated (below 1.5 × ULN) and total BL remains less than 2 × ULN.

AST/ALT is 5 × ULN or higher and total BL is less than 2 × 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 × ULN) and total BL remains less than 2 × ULN; resume TAVALISSE at next lower daily dose (refer to Table 1).
	  • If AST/ALT persist at 5 × ULN or higher for 2 weeks or more, discontinue TAVALISSE.

AST/ALT is 3 × ULN or higher and total BL is greater than 2 × 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 UGT1A1 inhibition
Diarrhea	
Diarrhea	• Manage diarrhea using supportive measures (e.g., 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 Table 1).
Neutropenia	
Neutropenia	• If absolute neutrophil count decreases (ANC less than 1.0×10^9/L) and remains low after 72 hours, temporarily interrupt TAVALISSE until resolved (ANC greater than 1.5×10^9/L). • Resume TAVALISSE at the next lower daily dose (refer to Table 1).

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

4.4 Dose Modification for Drug Interactions

Concomitant use with a strong CYP3A4 inhibitor increases exposure to R406 (the major active metabolite). Monitor for toxicities of TAVALISSE that may require TAVALISSE dose modifications (see Table 1) when given concurrently with a strong CYP3A4 inhibitor *[see Drug Interactions (9.1)]*.

4.5 Discontinuation

Discontinue TAVALISSE after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding *[see Clinical Studies (14)]*.

5 CONTRAINDICATIONS

Hypersensitvity to the active substance or to any of the excipients listed in section 11

6 WARNINGS AND PRECAUTIONS

6.1 Hypertension

Hypertension can occur with TAVALISSE treatment; hypertensive crisis occurred in 1% of patients. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects of TAVALISSE.

Monitor blood pressure every 2 weeks until stable, then monthly and adjust or initiate antihypertensive therapy to ensure maintenance of blood pressure control during TAVALISSE therapy. If increased blood pressure persists despite appropriate therapy, TAVALISSE interruption, reduction or discontinuation may be necessary *[see Dosage and Administration (4.3)]*.

6.2 Hepatotoxicity

Elevated liver function tests (LFTs), mainly ALT and AST, can occur with TAVALISSE.

In the placebo-controlled studies, laboratory testing showed maximum ALT/AST levels more than 3 × the upper limit of normal (ULN) in 9% of patients receiving TAVALISSE *[see Adverse Reactions (6.1)]*. For most patients, transaminases recovered to baseline levels within 2 to 6 weeks of dose-modification.

Monitor liver function tests monthly during treatment. If ALT or AST increase more than 3 × ULN, manage hepatotoxicity using TAVALISSE interruption, reduction, or discontinuation *[see Dosage and Administration (4.3)]*.

6.3 Diarrhea

Diarrhea occurred in 31% of patients treated with TAVALISSE. Severe diarrhea occurred in 1% of patients treated with TAVALISSE. Monitor patients for the development of diarrhea. Manage diarrhea using supportive care measures, including dietary changes, hydration and/or antidiarrheal medication, early after the onset of symptoms. Interrupt, dose reduce, or discontinue TAVALISSE if diarrhea becomes severe (Grade 3 or above) *[see Dosage and Administration (4.3)]*.

6.4 Neutropenia

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 *[see Dosage and Administration (4.3)]*.

6.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TAVALISSE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fostamatinib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-fetal mortality (post-implantation loss), alterations to growth (lower fetal weights), and structural abnormalities (variations and malformations) at maternal exposures (AUCs) approximately 0.3 and 10 times the human exposure at the maximum recommended human dose (MRHD), respectively.
Advise pregnant women of 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. *[see Use in Specific Populations (10.1) and Clinical Pharmacology (12.1)]*.

7 ADVERSE REACTIONS

The following clinically important adverse reactions, that can become serious are described elsewhere

in the labeling:

- Hypertension [*see Warnings and Precautions (7.1)*]
- Hepatotoxicity [*see Warnings and Precautions (7.2)*]
- Diarrhea [*see Warnings and Precautions (7.3)*]
- Neutropenia [*see Warnings and Precautions (7.4)*]

7.1 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.

TAVALISSE was studied in two randomized, double-blind, placebo-controlled trials that were identical in design. The data described below reflect exposure to TAVALISSE in 102 patients with chronic ITP who had received one or more prior ITP treatment(s). Groups were stratified with respect to splenectomy and severity of thrombocytopenia. Patients randomized to the TAVALISSE arm received 100 mg orally twice daily. Based upon platelet count and tolerability, if a patient's platelet count did not increase to at least 50×10^9/L, the TAVALISSE dose could be increased to 150 mg twice daily after one month. In the placebo controlled studies, the median duration of TAVALISSE exposure in these studies was 86 days (range 8 to 183) *[see Clinical Studies (14)* for additional details for patients on TAVALISSE*]*.

In the ITP double-blind studies, serious adverse drug reactions were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which each occurred in 1% of patients receiving TAVALISSE. In addition, severe adverse reactions observed in patients receiving TAVALISSE included dyspnea and hypertension (both 2%); and neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope and hypoxia (all 1%) *[see Warnings and Precautions (7.1)]*. Table 3 presents the common adverse reactions from these studies.

Table 3: Incidence of Common (≥ 5%) Adverse Reactions from Double-Blind Clinical Studies (FIT 1 and FIT 2)

	TAVALISSE (N=102)				**Placebo (N=48)**			
Adverse Reaction	**Mild %**	**Moderate %**	**Severe %**	**TOTAL %**	**Mild %**	**Moderate %**	**Severe %**	**TOTAL %**
Diarrhea*	21	10	1	31	13	2	0	15
Hypertension†	17	9	2	28	10	0	2	13
Nausea	16	3	0	19	8	0	0	8
Dizziness	8	2	1	11	6	2	0	8
ALT increased	5	6	0	11	0	0	0	0
AST increased	5	4	0	9	0	0	0	0
Respiratory infection‡	7	4	0	11	6	0	0	6
Rash§	8	1	0	9	2	0	0	2
Abdominal pain¶	5	1	0	6	2	0	0	2
Fatigue	4	2	0	6	0	2	0	2
Chest pain	2	3	1	6	2	0	0	2
Neutropenia#	3	2	1	6	0	0	0	0

ALT = Alanine aminotransferase
AST = Aspartate aminotransferase
Note: Common adverse reactions defined as all adverse reactions occurring at a rate of ≥ 5% of patients in the TAVALISSE group and greater than placebo rate.

* Includes diarrhea and frequent bowel movement.

† Includes hypertension, blood pressure (BP) increased, BP diastolic abnormal, and BP diastolic increased.

‡ Includes upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, and viral upper respiratory tract infection.

§ Includes rash, rash erythematous and rash macular.

¶ Includes abdominal pain, and abdominal pain upper.

Includes neutropenia and neutrophil count decreased.

Table 4: Elevations in Hepatic Transaminases During Placebo-Controlled Clinical Studies

Enzyme	Maximum Level of Elevation	Number of Patients (%)	
		TAVALISSE (N=102)	Placebo (N=48)
Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST)	>3 and ≤5 × ULN	3 (3)	0
	>5 and ≤10 × ULN	5 (5)	0
	≥10 × ULN	1 (1)	0

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

8 DRUG INTERACTIONS

8.1 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 (see Table 1) when given concurrently with a strong CYP3A4 inhibitor *[see Dosage and Administration (.4) and Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

8.2 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 *[see Clinical Pharmacology (12.3)]*.

BCRP Substrates

Concomitant use of TAVALISSE may increase concentrations of BCRP substrate drugs (e.g., rosuvastatin). Monitor for toxicities of BCRP substrate drug that may require dosage reduction when given concurrently with TAVALISSE *[see Clinical Pharmacology (12.3)]*.

P-Glycoprotein (P-gp) Substrates

Concomitant use of TAVALISSE may increase concentrations of P-gp substrates (e.g., digoxin). Monitor for toxicities of the P-gp substrate drug that may require dosage reduction when given concurrently with TAVALISSE *[see Clinical Pharmacology (12.3)]*.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, TAVALISSE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*.

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of fostamatinib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes that were directly attributed to exposure in utero to the major fostamatinib metabolite (R406) at maternal exposures (AUC) as low as 0.3 and 10 times the exposure in patients at the maximum recommended human dose (MRHD), respectively (see Data). Advise pregnant women of the potential risk to a fetus.

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 miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. An estimated background risk of major birth defects and miscarriage for the chronic ITP population is 8% and 4-11%, respectively.

Data

Animal Data

In a fertility and early embryonic development study in female rats, fostamatinib was administered orally for 15 days before mating to Day 7 of pregnancy, which caused a slight decrease in pregnancy rates and an increase in post-implantation loss were seen at maternal doses approximately 4.2 times the dose in patients at the MRHD.

In embryo-fetal development studies, pregnant animals were orally administered fostamatinib during the period of organogenesis at doses up to 25 and 50 mg/kg/day in rats and rabbits, respectively. The adverse developmental outcomes included an increase in embryo-fetal mortality (post-implantation loss), alterations to growth (lower fetal weights), and structural abnormalities (variations and malformations). These effects occurred at maternal exposures (AUCs) of 3,763 ng.h/mL in rats and 111,105 ng.h/mL in rabbits that were approximately 0.3 and 10 times the human exposure at the MRHD in rats and rabbits, respectively.

In a peri and postnatal development study in rats, fostamatinib was orally administered at doses of 2.5, 12.5, and 25 mg/kg/day from gestation day 7 until lactation day 20. The dose of 25 mg/kg/day was associated with maternal toxicity, including decreased body weights, body weight gains, and food consumption. At doses as low as 12.5 mg/kg/day fostamatinib caused increases in newborn mortality (neonatal mortality), alterations in growth and/or development (lower neonatal weights into post-weaning and structural abnormalities [malformations]). Functional impairment (delayed sexual maturation) was observed at 25 mg/kg/day. There was no evidence of neurobehavioral defects (maze learning and shuttle box avoidance) or immunological compromise (influenza host resistance challenge) in the F1 generation or latent untoward effects in the F2 generation. The maternal doses were approximately 2.1 and 4.2 times the MHRD in patients.

9.2 Lactation

Risk Summary

There are no data on the presence of fostamatinib and/or its metabolites in human milk, the effects on the breastfed child, or on milk production. In rodents, R406 (the major active metabolite) was detected in maternal milk in concentrations 5- to 10-fold higher than in maternal plasma. Because of the potential for serious adverse reactions in a breastfed child from TAVALISSE, advise a lactating woman not to breastfeed during treatment with TAVALISSE and for at least 1 month after the last dose.

9.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, TAVALISSE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)]*. For females of reproductive potential, verify pregnancy status prior to initiating TAVALISSE.

Contraception

Females

Based on animal studies, TAVALISSE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TAVALISSE and for at least 1 month after the last dose.

Infertility

There are no data on the effect of TAVALISSE on human fertility. Based on the finding of reduced pregnancy rates in animal studies, TAVALISSE may affect female fertility *[see Use in Specific Populations (10.1)]*.

9.4 Pediatric Use

TAVALISSE is not indicated for children and adolescents under 18

9.5 Safety and effectiveness in pediatric patients have not been established. Geriatric Use

Of the 102 patients with ITP who received TAVALISSE, 28 (27%) were 65 years of age and older, while 11 (11%) were 75 years of age and older. In patients 65 years of age and older, 6 (21%) patients experienced serious adverse events and 5 (18%) experienced adverse events leading to treatment withdrawal while in patients under 65 years of age, 7 (9%) and 5 (7%) experienced serious adverse events and adverse events leading to treatment withdrawal, respectively. In patients 65 years of age and older who received TAVALISSE, 11 (39%) patients experienced hypertension versus 2 (18%) placebo compared to 17 (23%) in patients under 65 of age versus 4 (11%) placebo. No overall differences in effectiveness were observed in these patients compared to younger patients.

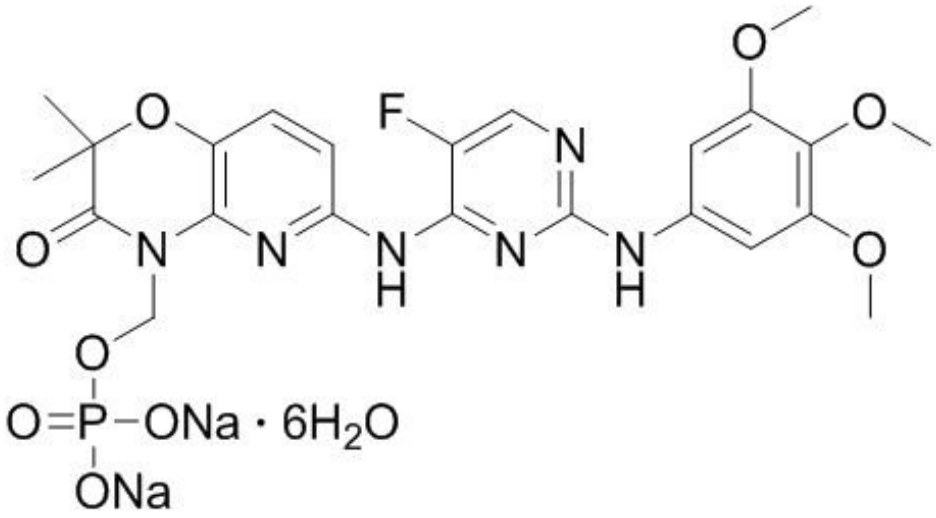
10 OVERDOSAGE

There is no specific antidote for overdose with TAVALISSE, and the amount of R406 (the pharmacologically active metabolite of fostamatinib) cleared by dialysis is negligible. In the event of an overdose, monitor patient closely for signs and symptoms of adverse reactions, and treat the reactions with supportive care *[see Warnings and Precautions (7)]*.

11 DESCRIPTION

Fostamatinib is a tyrosine kinase inhibitor. TAVALISSE is formulated with the disodium hexahydrate salt of fostamatinib, a phosphate prodrug that converts to its pharmacologically active metabolite, R406, *in vivo*.

The chemical name for fostamatinib disodium hexahydrate is disodium (6-[[5-fluoro-2-(3,4,5-trimethoxyanilino) pyrimidin-4-yl]amino]-2,2-dimethyl-3-oxo-pyrido[3,2-b][1,4]oxazin-4-yl)methyl phosphate hexahydrate. The molecular formula is $C_{23}H_{24}FN_6Na_2O_9P \cdot 6H_2O$, and the molecular weight is 732.52. The structural formula is:



Fostamatinib disodium is a white to off-white powder that is practically insoluble in pH 1.2 aqueous buffer, slightly soluble in water, and soluble in methanol.

Each TAVALISSE oral tablet contains 100 mg or 150 mg fostamatinib, equivalent to 126.2 mg or 189.3 mg fostamatinib disodium hexahydrate, respectively.

The inactive ingredients in the tablet core are mannitol, sodium bicarbonate, sodium starch glycolate, povidone, and magnesium stearate. The inactive ingredients in the film coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fostamatinib is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major metabolite of fostamatinib, R406, inhibits signal transduction of Fc-activating receptors and B-cell receptor. The fostamatinib metabolite R406 reduces antibody-mediated destruction of platelets.

12.2 Pharmacodynamics

Mean treatment-related increases of 2.93 mmHg in systolic blood pressure and 3.53 mmHg in diastolic blood pressure over placebo were observed following TAVALISSE doses of 100 mg twice daily for 28 days. About 31% of patients in the TAVALISSE group experienced blood pressures ≥140/90 mmHg compared to 15% of patients in the placebo group. Blood pressure returned to baseline within 1 week following TAVALISSE discontinuation in 58% (11 of 19) of patients in the TAVALISSE group who had blood pressures ≥140/90 mmHg.

Cardiac Electrophysiology

At 2 times the maximum recommended dose, TAVALISSE did not prolong the QT interval to a clinically relevant extent.

12.3 Pharmacokinetics

TAVALISSE is a prodrug that is converted in the gut to the major active metabolite, R406. Mean (± standard deviation [SD]) exposure estimates of R406 are 550 (± 270) ng/mL for C_{max} and 7080 (± 2670) ng·h/mL for AUC. R406 exposure is approximately dose proportional up to 200 mg twice daily (1.3 times the 150 mg dosage). R406 accumulates approximately 2- to 3-fold upon twice daily dosing at

100–160 mg (0.67 to 1.06 times the 150 mg dosage).

Absorption

After oral administration of TAVALISSE, the absolute bioavailability of R406 was 55%. The median t_{max} of R406 is approximately 1.5 hours (range: 1 to 4 hours). Negligible levels of fostamatinib were found in plasma.

Effect of Food

Administration of TAVALISSE with a high-calorie, high-fat meal (deriving approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively) increased R406 AUC by 23% and C_{max} by 15% *[see Dosage and Administration (4.1)]*.

Distribution

In *in vitro* studies, the R406 is 98.3% protein bound in human plasma. The red blood cell to plasma concentration ratio is approximately 2.6. The mean (± SD) volume of distribution at steady-state of R406 is 256 (± 92) L.

Elimination

The mean (± SD) terminal half-life of R406 is approximately 15 (± 4.3) hours.

Metabolism

TAVALISSE is metabolized in the gut by alkaline phosphatase to the major active metabolite, R406. R406 is extensively metabolized, primarily through pathways of CYP450-mediated oxidation (by CYP3A4) and glucuronidation (by UDP glucuronosyltransferase [UGT]1A9). R406 is the predominant moiety in the systemic circulation, and there was minimal exposure to any R406 metabolites.

Excretion

Following an oral dose of TAVALISSE, approximately 80% of the R406 metabolite is excreted in feces with approximately 20% excreted in the urine. The major component excreted in urine was R406 N-glucuronide. The major components excreted in feces were R406, *O*-desmethyl R406 and a metabolite produced by gut bacteria from the *O*-desmethyl metabolite of R406.

Specific Populations

Population pharmacokinetics analyses indicate TAVALISSE is not altered based on age, sex, race/ethnicity. In addition, the pharmacokinetics of TAVALISSE is not altered in patients with renal impairment (creatinine clearance [CLcr] $\geq$ 30 to < 50 mL/min, estimated by Cockcroft Gault equation and end stage renal disease requiring dialysis), or hepatic impairment (Child-Pugh Class A, B and C).

Drug Interaction Studies

Clinical Pharmacology Studies

No significant interactions were seen with concomitant use of TAVALISSE with the following drugs: methotrexate (OAT1/3 transporters), midazolam (CYP3A4 substrate), microgynon (ethinyl estradiol and levonorgestrel), warfarin, pioglitazone (CYP2C8 substrate) and ranitidine (H2-antagonist that increases gastric pH).

Effect of Other Drugs on TAVALISSE

Strong CYP3A4 inhibitor: Concomitant use of ketoconazole (200 mg twice daily for 3.5 days) with a single dose of 80 mg TAVALISSE (0.53 times the 150 mg dosage) increased R406 AUC by 102% and C_{max} by 37%.

Moderate CYP3A4 Inhibitor: Concomitant use of verapamil (80 mg three times daily for 4 days) with a single dose of 150 mg TAVALISSE increased R406 AUC by 39% and C_{max} by 6% .

CYP3A4 inducer: Concomitant use of rifampicin (600 mg once daily for 8 days) with a single dose of

150 mg TAVALISSE decreased R406 AUC by 75% and C_{max} by 59% .

Effect of TAVALISSE on Other Drugs

CYP3A4 substrate: Concomitant use of simvastatin (single dose 40 mg) with 100 mg twice daily TAVALISSE increased simvastatin AUC by 64% and C_{max} by 113% and simvastatin acid AUC by 64% and C_{max} by 83%.

BCRP substrate*:* Concomitant use of rosuvastatin (single dose 20 mg) with 100 mg twice daily TAVALISSE increased rosuvastatin AUC by 95% and C_{max} by 88%.

P-gp substrate*:* Concomitant use of digoxin (0.25 mg once daily) with 100 mg twice daily TAVALISSE increased digoxin AUC by 37% and C_{max} by 70% .

In Vitro Studies

TAVALISSE is an inhibitor of the human P-gp efflux transporter in vitro.

CYP3A4 and UGT1A9 are involved in the metabolism of R406. R406 is a substrate of P-gp but not of other major transporters (OAT1/3, OCT2, OATP1B1/3, MRP2, and BCRP). R406 can inhibit CYP3A4 and BCRP, and can induce CYP2C8 activity.

R406 is an inhibitor of UGT1A1. Inhibition of UGT1A1 may result in increased unconjugated bilirubin in the absence of other LFT abnormalities.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fostamatinib was not carcinogenic in a 2-year study in mice when administered daily by oral gavage at doses up to 500/250 mg/kg/day, and was not carcinogenic in rats when administered by oral gavage at 45 mg/kg/day.

Fostamatinib and its major active metabolite (R406) were not mutagenic in an in vitro bacterial reverse mutation (Ames) assay or clastogenic in an in vitro human lymphocyte chromosomal aberration assay or an in vivo mouse bone marrow micronucleus assay.

In a fertility study with oral fostamatinib, all mating (e.g., time to mating, breeding proficiency), sperm assessments (e.g., number and motility), and organ weight (e.g., paired testis weight) parameters in male rats were unaffected by dosages as high as 40 mg/kg/day, which is 6.7 times the MRHD. All mating and fertility parameters in female rats were unaffected by dosages as high as 11 mg/kg/day (which is 1.8 times the MRHD), but a slight decrease in pregnancy rates and an increase in post-implantation loss were seen at 25 mg/kg/day, which is 4.2 times the MRHD.

14 CLINICAL STUDIES

TAVALISSE was studied in two placebo-controlled efficacy and safety studies (referred to as FIT-1 [NCT02076399] and FIT-2 [NCT02076412]), and in an open-label extension study referred to as FIT-3 (NCT 02077192).

Randomized, Placebo-Controlled Studies

A total of 150 patients with persistent or chronic ITP, who had an insufficient response to previous treatment (which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonists) were enrolled in two identical, double-blind, placebo-controlled studies that were conducted in different countries. For each study, patients were randomized 2:1 to TAVALISSE or placebo for 24 weeks; randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia. Stable concurrent ITP therapy (glucocorticoids [< 20 mg prednisone equivalent per day], azathioprine, or danazol) was allowed, and rescue therapy was permitted, if needed. All patients initially received study drug at 100 mg twice daily (or matching placebo). Based on platelet count and

tolerability, dose escalation to 150 mg twice daily (or matching placebo) was undertaken in 88% of patients at Week 4 or later. 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 open-label extension study (FIT-3).

Patients enrolled in the placebo-controlled studies had a median age of 54 years (range: 20 to 88), and the majority were female (61%) and were White (93%). Prior ITP treatments were varied, with the most common including corticosteroids (94%), immunoglobulins (53%), and thrombopoietin receptor agonists (TPO-RA) (48%). Most patients had chronic ITP (93%), with a median time since ITP diagnosis of 8.45 years, and 35% had undergone splenectomy. At baseline, the median platelet count was 16×10^9/L (with almost half [45]%) less than 15×10^9/L) and 47% were on stable ITP therapy.

In Study FIT-1, 76 patients were randomized; 51 to the TAVALISSE group and 25 to the placebo group. In Study FIT-2, 74 patients were randomized; 50 to the TAVALISSE group and 24 to the placebo group. The efficacy of TAVALISSE was based on stable platelet response (at least 50×10^9/L on at least 4 of the 6 visits between Weeks 14 to 24). Study outcomes for FIT-1 and FIT-2 are shown in Table 5.

Table 5: Study Outcomes from Placebo-Controlled Clinical Studies

	Study FIT-1			
	TAVALISSE (N=51)	**Placebo (N=25)**	**TA**	
Study Outcomes	**n (%)**	**n (%)**		
Stable platelet response*,†	9 (18)	0 (0)	8 (16)	1 (4)
	p‡ = 0.03		NS	

NS = Did not demonstrate a stastistically significant difference between treatment arms

* Includes all patients with platelet counts and excludes patients whose platelet counts were measured following rescue therapy after Week 10

† Stable platelet response was prospectively defined as a platelet count of at least 50×10^9/L on at least 4 of the 6 visits between Weeks 14 and 24

‡ p- value from Fisher Exact test

§ Patients who did not respond to treatment after 12 weeks were eligible to enroll in open- label extension study.

In the FIT-1 and FIT-2 studies a total of 47 patients in the TAVALISSE arm had received a prior TPO-RA treatment; among these patients, 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% and 45% of patients receiving TAVALISSE or placebo, respectively.

During the placebo-controlled studies, the incidence of bleeding occurred in 29% and 37% of patients in the TAVALISSE and placebo arms, respectively. Moderate, severe and serious bleeding events are described in Table 6. All severe events led to hospitalizations.

Table 6: Incidence of Moderate, Severe and Serious Bleeding-Related Events (Placebo-Controlled Efficacy Population)

Parameter	**TAVALISSE Total N=101 n (%)**	**Placebo Total N=49 n (%)**
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)

Extension Study

The FIT-3 trial is an open label extension study. 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, were eligible to enroll in this study. Patients remained blinded to their treatment assignment from the previous study (TAVALISSE or placebo), so their starting dose in this study was based on their final platelet count. Patients designated as responders (defined as achievement of platelet count of at least 50×10^9/L) at the time of roll over continued in the extension study at their current trial dose and regimen. Patients who entered the extension study as non-responders (defined as platelet count less than 50×10^9/L) received TAVALISSE 100 mg twice daily regardless of their dose and regimen in the prior study.

For the FIT-3 trial, 123 patients were enrolled, 44 patients previously randomized to placebo and 79 patients previously randomized to TAVALISSE. Stable response in this study was prospectively defined as no 2 visits, at least 4 weeks apart, with a platelet count less than 50×10^9/L, without an intervening visit with a platelet count of at least 50×10^9/L (unrelated to rescue therapy), within a period of 12 weeks following initial achievement of the target platelet count. Sixty-one of the 123 subjects (50%) have discontinued from the study early.

In a prospectively defined analysis, the 44 subjects treated with placebo in the prior study were evaluated for stable response for TAVALISSE. Ten of these subjects (23%) (including a single subject who was classified as a placebo responder in the prior study) met the criteria for stable response.

Among the subjects who achieved stable response in FIT-1, FIT-2 and FIT-3 trials, 18 subjects maintained the platelet count of at least 50×10^9/L for 12 months or longer.

16 HOW SUPPLIED/STORAGE AND HANDLING

- 100 mg tablet: orange, film-coated, round with a diameter of 9 mm, biconvex tablets debossed with "100" on one side and "R" on the reverse side.
- 150 mg tablet: orange, film-coated, oval measuring 7.25 mmx 14.5 mm, biconvex tablets debossed with "150" on one side and "R" on the reverse side.

100 mg tablets: Available in bottle of 60 with 2 desiccant canisters

150 mg tablets: Available in bottle of 60 with 2 desiccant canisters

Store at room temperature below 25°C /60% RH (Do not remove desiccants).

MANUFACTURER

Rigel Pharmaceuticals, Inc.
1180 Veterans Blvd. South San Francisco,
CA 94080 USA

LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St., POB 7090 Petach Tikva Israel

Registration Numbers:
Tavalisse 100 mg : 168-04-36449-99
Tavalisse 150 mg : 168-05-36450-99

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