SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

TAVLESSE 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TAVLESSE 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).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

TAVLESSE 100 mg film-coated tablets

Approximately 9.0 mm round, biconvex, dark orange film-coated tablet debossed “100” on one side and “R” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TAVLESSE is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).

4.2 Posology and method of administration

Fostamatinib treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Posology

Fostamatinib dosing requirements must be individualised based on the patient's platelet counts. The lowest dose of fostamatinib to achieve and maintain a platelet count of at least 50,000/µL should be used. Dose adjustments are based upon the platelet count response and tolerability (see table 2).

The recommended starting dose of fostamatinib is 100 mg twice daily.

After initiating fostamatinib, the dose can be increased to 150 mg twice daily after 4 weeks based on platelet count and tolerability. A daily dose of 300 mg daily must not be exceeded.

Missed dose

In the case of a missed dose of fostamatinib, patients should take their next dose at its regularly scheduled time.

Discontinuation

Treatment with fostamatinib should be discontinued after 12 weeks of fostamatinib therapy if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.

Monitoring and dose modifications

Fostamatinib dose modification is recommended based on tolerability and platelet counts. Management of some adverse reactions may require dose interruption, reduction, or discontinuation (see table 1 and table 2).

Clinical haematology, blood pressure and liver function tests should be monitored regularly throughout therapy with fostamatinib (see section 4.4.) and the dosing should be adjusted as outlined in table 1. 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[1]	---
100 mg/day[2]	100 mg[1]	---

[1] Once daily fostamatinib should be taken in the morning.
[2] If further dose reduction below 100 mg/day is required, discontinue fostamatinib.

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

Table 2: Recommended dose modifications for adverse reactions

Adverse reaction	Recommended action
Hypertension	
Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg	Initiate or increase dose of antihypertensive medication for patients with increased cardiovascular risk, and adjust as needed until blood pressure (BP) is controlled. If the BP target is not met after 8 weeks, reduce fostamatinib to next lower daily dose (refer to table 1).
Stage 2: systolic at least 140 or diastolic at least 90 mmHg	Initiate or increase dose 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 fostamatinib 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 fostamatinib.
Hypertensive crisis: systolic over 180 and/or diastolic over 120 mmHg	Interrupt or discontinue fostamatinib. Initiate or increase dose of antihypertensive medication, and adjust as needed until BP is controlled. If BP returns to less than the target BP, resume fostamatinib at same daily dose. If repeat BP is 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive treatment, discontinue fostamatinib.
Hepatotoxicity	
AST/ALT is 3 x ULN or higher and less than 5 x ULN	If patient is symptomatic (e.g., nausea, vomiting, abdominal pain): Interrupt fostamatinib. 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 fostamatinib 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 x ULN) and total BL remains less than 2 x ULN. Consider interruption or dose reduction of fostamatinib 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 fostamatinib at next lower daily dose (refer to table 1) when ALT/AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN.

Adverse reaction	Recommended action
AST/ALT is 5 x ULN or higher and total BL is less than 2 x ULN	Interrupt fostamatinib. 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 fostamatinib at next lower daily dose (refer to table 1). If AST/ALT persist at 5 x ULN or higher for 2 weeks or more, discontinue fostamatinib.
AST/ALT is 3 x ULN or higher and total BL is greater than 2 x ULN	Discontinue fostamatinib.
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities	Continue fostamatinib with frequent monitoring since isolated increase in unconjugated (indirect) BL may be due to UGT1A1 inhibition.
Diarrhoea	
Diarrhoea	Manage diarrhoea using supportive measures (e.g., dietary changes, hydration and/or antidiarrhoeal medication) early after the onset until symptom(s) have resolved. If symptom(s) become severe (Grade 3 or above), temporarily interrupt fostamatinib. If diarrhoea improves to mild (Grade 1), resume fostamatinib at the next lower daily dose (refer to table 1).
Neutropenia	
Neutropenia	If absolute neutrophil count decreases (ANC less than 1.0 x 10^9/L) and remains low after 72 hours, temporarily interrupt fostamatinib until resolved (ANC greater than 1.5 x 10^9/L). Resume fostamatinib 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; ANC = absolute neutrophil count

Special populations

Renal impairment

No dose adjustment is necessary in patients with renal impairment.

Hepatic impairment

Fostamatinib should not be used in patients with severe hepatic impairment. In patients with mild or moderate hepatic impairment, monitoring of liver function throughout therapy with fostamatinib should be done. Dose regimen adjustment according to platelet counts and tolerability may be required (see table 1 and table 2, and section 4.4).

Elderly

No dose adjustment is necessary in elderly patients.

Paediatric population

Fostamatinib should not be used in children and adolescents less than 18 years of age because of adverse reactions on actively growing bones observed in nonclinical studies (see section 5.3).

Method of administration

Fostamatinib is for oral use.

The tablets should be taken twice daily, whole with or without food (see section 5.2). In the event of gastric upset, tablets may be taken with food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Information is based on ITP placebo-controlled population unless specified.

Excipients:

TAVLESSE 100 mg film-coated tablets contains 23 mg sodium per tablet, equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Hypertension

Over the range of doses studied in healthy volunteers, the effect of R406 (the major active metabolite of fostamatinib) on BP appears to be dose-dependent and varies among subjects. In the ITP placebo-controlled population, increased blood pressure, including the development of hypertension, was reported in patients treated with fostamatinib. Hypertensive crisis occurred in 1 (1%) patient. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects of fostamatinib. In clinical studies, the blood pressure effects resolved within a week of discontinuing treatment.

The patient's blood pressure should be monitored every two weeks until stable, then monthly, and adjust or initiate antihypertensive therapy to ensure maintenance of blood pressure control during fostamatinib therapy. If increased blood pressure persists despite appropriate therapy, the physician should consider fostamatinib dose interruption, reduction or discontinuation (see section 4.2).

Liver function test abnormalities and risk of hepatotoxicity

In the placebo-controlled studies, laboratory testing showed maximum ALT/AST levels more than 3 x the upper limit of normal (ULN) in 9% of patients receiving fostamatinib and no patients receiving placebo.

Sparse data suggest an increase risk of hyperbilirubinemia in patients with genetic polymorphisms of UGT1A1, e.g. Gilbert, the physician should monitor these patients frequently (see section 4.2).

For all patients, transaminases recovered generally to baseline levels within 2 to 6 weeks of dose-modification. The physician should monitor liver function tests monthly during treatment. If ALT or AST increase more than 3 x ULN, the physician should manage hepatotoxicity by treatment interruption, reduction or discontinuation. Concomitant total bilirubin increases greater than 2 X ULN should lead to treatment discontinuation (see section 4.2).

Complete blood counts (CBCs)

The physician should monitor CBCs, including platelet counts, monthly until a stable platelet count (of at least 50,000/µL) is achieved. Thereafter, the physician should continue to monitor CBCs, including neutrophils, regularly.

Diarrhoea

Diarrhoea is the most common adverse reaction with fostamatinib treatment, but severe diarrhoea occurred in 1% of patients. Patients should be monitored for the development of diarrhoea and managed by using supportive care measures (e.g., dietary changes, hydration and/or antidiarrhoeal medication) early after the onset of symptoms. If diarrhoea becomes severe (Grade 3 or above), administration of fostamatinib should be interrupted, reduced, or discontinued (see section 4.2).

Neutropenia

Neutropenia occurred in 7% of patients treated with fostamatinib; febrile neutropenia occurred in 1% of patients. Patients with neutropenia may be more susceptible to infections.

The physician should monitor the absolute neutrophil count monthly. The physician should manage toxicity with fostamatinib interruption, reduction or discontinuation (see section 4.2).

Infections

Infections, including pneumonia and respiratory tract infections, have been reported during clinical trials (see section 4.8).

The patient should be monitored for infection during treatment. The benefit risk of continuing therapy during an infection should be evaluated by the physician.

Bone remodeling

Since fostamatinib was shown *in vitro* to not only target SYK but also other tyrosine kinases that are involved in the bone metabolism (e.g., VEGFR, RET), any potential

untargeted effects on bone remodelling or formation remain undetermined, especially in patients with osteoporosis, patients with fractures or young adults where epiphyseal fusion has not yet occurred. Closer monitoring in these patients is therefore recommended. The benefit risk of continuing therapy during the healing of a bone fracture should be thoroughly evaluated by the physician.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on fostamatinib

Concomitant use of rifampicin, a strong CYP3A4 inducer (600 mg once daily for 8 days) with a single dose of 150 mg fostamatinib decreased R406 AUC by 75% and C_{max} by 59%.

Concomitant use of fostamatinib with strong CYP3A4 inducers decreases exposure to R406, which may result in reduced efficacy. Therefore, concomitant use of fostamatinib with strong CYP3A4 inducers is not recommended.

Concomitant use of fostamatinib with strong CYP3A4 inhibitors increases exposure to R406 (the major active metabolite), which may increase the risk of adverse reactions. The patient should be monitored for toxicities of fostamatinib that may require dose reduction (see table 2) when given concurrently with strong CYP3A4 inhibitors. For treatment with strong CYP3A4 inhibitor of shorter periods, e.g. antifungals or antibacterial treatment, dose reductions could be warranted from the beginning of the additional treatment. A two-fold reduction in dose frequency (i.e. from 150 mg twice daily to 150 mg once daily or 100 mg twice daily to 100 mg once daily) of fostamatinib in the presence of a strong CYP3A4 inhibitor is warranted. The physician should consider resuming the fostamatinib dose that was used prior to concomitant use of a strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the inhibitor.

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

Other medicinal products with strong CYP3A4 inhibition potential when coadministered with fostamatinib are:

boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir

Concomitant use of verapamil, a moderate CYP3A4 inhibitor (80 mg three times daily for 4 days) with a single dose of 150 mg fostamatinib increased R406 (the major active metabolite) AUC by 39% and C_{max} by 6%.

Increase in gastric pH does not affect exposure of R406

Coadministration of fostamatinib with 150 mg ranitidine, an H2-blocker that increases gastric pH did not have clinically relevant impact on R406 exposure.

Effects of fostamatinib on other medicinal products

CYP3A4 substrate

Concomitant use of fostamatinib may increase systemic exposure of some CYP3A4 substrate medicinal products. Patients should be monitored for toxicities of CYP3A4 substrate medicinal products, that may require dose reduction when given concurrently with fostamatinib.

Concomitant use of simvastatin (single dose 40 mg) with fostamatinib 100 mg administered twice daily increased simvastatin AUC by 64% and C_{max} by 113% and simvastatin acid AUC by 66% and C_{max} by 83%.

Concomitant use of midazolam (single dose 7.5 mg) with fostamatinib 100 mg administered twice daily increased midazolam AUC by 23% and C_{max} by 9%.

Concomitant use of a combined hormonal contraceptive containing 0.03 mg ethinylestradiol with fostamatinib 100 mg administered twice daily increased AUC by 28% and C_{max} by 34%.

BCRP and P-gp substrate

Concomitant use of fostamatinib may increase concentrations of P-gp substrates (e.g. digoxin) and BCRP substrates (e.g. rosuvastatin). The toxicities of these drugs should be monitored as a dose reduction may be required when given concurrently with fostamatinib. For rosuvastatin, shift to another treatment should be considered and for digoxin, additional therapeutic drug monitoring could be necessary.

Concomitant use of rosuvastatin (single dose 20 mg) with fostamatinib 100 mg administered twice daily increased rosuvastatin AUC by 95% and C_{max} by 88%.

Concomitant use of digoxin (0.25 mg once daily) fostamatinib 100 mg administered twice daily increased digoxin AUC by 37% and C_{max} by 70%.

CYP2C8 substrate

Concomitant use of fostamatinib does not affect the exposure of CYP2C8 substrate drugs. No dose adjustment of CYP2C8 substrate drug is necessary.

Concomitant use of pioglitazone (single dose 30 mg) with fostamatinib 100 mg administered twice daily increased pioglitazone AUC by 18% and decreased C_{max} by 17%. Hydroxyl-pioglitazone AUC and C_{max} decreased by 10% and by 9%, respectively.

Effect on warfarin

Since SYK-inhibition may have potential effects on platelet aggregation, anticoagulant activity (e.g. INR) where relevant should be monitored when anticoagulants with narrow therapeutic index such as warfarin, are co-administered with fostamatinib.

Co-administration with JAK-inhibitor, TPO-RAs, rituximab and other immune-modulating agents has not been investigated.

In vitro studies

Fostamatinib 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 not an inhibitor of CYP2C8 and UGT2B7.

R406 is an inhibitor of UGT1A1. Inhibition of UGT1A1 may result in increased unconjugated bilirubin in the absence of other LFT abnormalities. Patients should be monitored for toxicity for drugs that are metabolised extensively by UGT1A1.

Although R406 shows no inhibitory activity against UGT2B7 *in vitro* and is considered as a weak UGT1A1 inhibitor *in vivo*, the effect on other UGTs has not been determined. The potential of PK DDI for co-administration with acetaminophen therefore remains undetermined.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Women of childbearing potential must use effective contraception during treatment and at least one month after the last dose.

Pregnancy

Based on findings from animal studies and its mechanism of action, fostamatinib can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised about the potential risk to a foetus.

Pregnancies occurring during clinical trials resulted in healthy newborns as well as stillbirths/spontaneous abortions and miscarriages (see sections 4.3 and 5.3).

If a patient becomes pregnant while taking fostamatinib, therapy should be discontinued. Fostamatinib is contraindicated during pregnancy (see sections 4.3 and 5.3).

Breast-feeding

It is unknown whether fostamatinib/metabolites are excreted in human milk.

Available pharmacodynamic/toxicological data in animals have shown excretion of fostamatinib metabolites in milk (see section 5.3) A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with fostamatinib and for at least one month after the last dose.

Fertility

There are no data on the effect of fostamatinib on human fertility. Based on the finding of reduced pregnancy rates in animal studies, fostamatinib may affect female fertility (see section 5.3).

Studies in animals have shown no adverse effect on male fertility. Given there is no evidence for mutagenic or clastogenic potential, there is no concern for male-mediated birth defects.

4.7 Effects on ability to drive and use machines

Fostamatinib is not expected to influence the ability to drive or to use machines. The patient should avoid driving cars or using machines if feeling dizzy.

4.8 Undesirable effects

Summary of the safety profile

In the ITP placebo-controlled studies, serious adverse drug reactions were febrile neutropenia, diarrhoea, pneumonia, and hypertensive crisis, which each occurred in 1% of patients receiving fostamatinib. In addition, severe adverse reactions observed in patients receiving fostamatinib included dyspnea and hypertension (both 2%); and neutropenia, arthralgia, chest pain, diarrhoea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope and hypoxia (all 1%).

Tabulated list of adverse reactions

The adverse reactions are presented from the placebo-controlled clinical trials and organised according to primary system organ class (SOC) for each preferred term in MedDRA. The adverse reactions are ranked by frequency within each SOC, and presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 3: Tabulated list of the adverse reactions

MedDRA SOC	Frequency	Adverse reactions
Infections and infestations	Uncommon	Pneumonia
	Common	Upper respiratory tract infection, respiratory tract infection, bronchitis, lower respiratory tract infection, viral upper respiratory tract infection
Blood and lymphatic disorders	Common	Neutropenia, febrile neutropenia
Nervous system disorders	Very common	Dizziness
	Common	Dysgeusia, headache
Vascular disorders	Very Common	Hypertension

MedDRA SOC	Frequency	Adverse reactions
	Uncommon	Hypertensive crisis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, frequent bowel movement
	Common	Abdominal pain upper, abdominal pain
Skin and subcutaneous tissue disorders	Common	Rash, rash erythematous, rash macular
General disorders and administration site conditions	Common	Chest pain, fatigue, influenza like illness
Investigations	Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood pressure (BP) increased, BP diastolic abnormal, BP diastolic increased, BP systolic increased, hepatic enzyme increased, liver function test abnormal
	Common	Neutrophil count decreased

Description of selected adverse reactions

The most commonly reported adverse reactions associated with fostamatinib were hypertension, liver function test abnormaltities, diarrhoea, neutropenia and infections.

Hypertension

Increases in blood pressure were dose dependent in early studies with fostamatinib in healthy subjects (see section 4.4). Hypertension events were reversible within days after dose discontinuation in these subjects.

In the ITP placebo-controlled population, hypertension-related adverse reactions were reported for 27.5% of patients receiving fostamatinib and 12.5% of patients receiving placebo in the placebo-controlled studies. Hypertension-related adverse reactions were mostly mild or moderate in severity, with 2 patients receiving fostamatinib and 1 subject receiving placebo experiencing severe hypertension. Hypertensive crises was reported as a serious adverse reaction and occurred in 1 (1%) patient receiving fostamatinib. Dose modification (reduction or interruption) was required for 4 patients receiving fostamatinib and no placebo patients. Study drug was withdrawn due to a hypertension-related adverse reaction in 1 patient receiving placebo and no patients receiving fostamatinib.

Approximately 20% of patients receiving fostamatinib required at least 1 intervention for hypertension-related events: increase in antihypertensive medications and/or a new antihypertensive medication.

Liver function test abnormalities and risk of hepatotoxicity

Mild to moderate increases in liver enzymes (ALT and AST) were observed in fostamatinib treated subjects in phase 1 studies in healthy volunteers, occurring more frequently at the higher doses tested (250 mg oral twice daily). These changes were mild and all were reversible (see section 4.4).

In the ITP placebo-controlled population, transaminase elevation adverse reactions (ALT increased and AST increased) were reported in 11% and 9% of patients

receiving fostamatinib. All transaminase elevations were mild or moderate in severity and dose modification (dose reduction or dose interruption) was required in 8 patients. One patient discontinued fostamatinib due to a transaminase elevation (ALT increased); this event resolved after discontinuation of treatment.

In the ITP placebo-controlled population, laboratory testing showed maximum ALT/AST levels more than 3 x the upper limit of normal (ULN) in 9% of patients receiving fostamatinib and no patients receiving placebo. Maximum ALT and/or AST levels were > 10 x ULN in 1 patient receiving fostamatinib. Transaminase elevations recovered to baseline levels within 2 to 4 weeks of dose modification. The median (range) time to onset of transaminase elevation was 58 days (43 to 127), and the median (range) duration of each event was 14.5 days (6 to 28 days).

Diarrhoea

Gastrointestinal complaints, specifically noninfectious diarrhoea events, were among the most common adverse reactions reported in patients treated with fostamatinib throughout the clinical development program. Non-infectious diarrhoea events are considered definitely related to fostamatinib treatment (see section 4.4).

In the placebo-controlled ITP population, noninfectious diarrhoea was the most commonly reported GI complaint, occurring in 31% of subjects receiving fostamatinib. Noninfectious diarrhoea events were most frequently mild-to-moderate in severity. The majority of subjects with moderate diarrhoea received antidiarrhoeal agents (loperamide) to mitigate their symptoms. Severe diarrhoea was reported in 1% of patients receiving fostamatinib during the placebo-controlled period. Dose modification (interruption or reduction) was reported for approximately 5% of subjects receiving fostamatinib; however study drug was discontinued because of adverse events (AEs) of diarrhoea in a single fostamatinib subject during the placebo-controlled period.

Approximately 25% of patients receiving fostamatinib experienced noninfectious diarrhoea during the first 12 weeks of treatment during the placebo-controlled period. Among the patients receiving fostamatinib who had moderate or severe diarrhoea, the median time to the first occurrence of moderate or severe diarrhoea was 57 days and the median duration of the events was approximately 15 days.

Neutropenia

In the initial Phase 1 human subject study, it was observed that at higher fostamatinib doses (up to 300 mg twice daily), the biologically active component of fostamatinib produced significant reductions in neutrophils, which were rapidly reversible upon discontinuation of therapy (see section 4.4). The rapidity of the recovery suggested a compartment effect more than an effect on progenitors. This effect on neutrophils was observed in all clinical programs.

In the placebo-controlled ITP population, neutropenia adverse reactions were reported for 7% of patients in the fostamatinib group and no patients in the placebo group. Most neutropenia adverse reactions were not associated with an infection and were mild or moderate in severity. Severe neutropenia was reported in 2 patients; 1 of these was a serious adverse reaction of febrile neutropenia that was attributed to an unknown infection. Three patients required dose modification for neutropenia per protocol, and study drug was discontinued due to neutropenia in 1 patient. All neutropenia adverse reactions except 1 resolved by the end of the study.

In the placebo-controlled ITP population, 2 patients receiving fostamatinib and no patients receiving placebo had a decrease in neutrophils to between ≥ 0.5 and < 1.0 × 10^9/L. Seven patients receiving fostamatinib and 1 patient receiving placebo had neutrophil counts decrease to between ≥ 1.0 and < 1.5 × 10^9/L. No patient had a decrease in neutrophils to < 0.5 × 10^9/L.

Infections

In the placebo-controlled ITP population, infection adverse reactions were reported in 30% of patients receiving fostamatinib and 20% of patients receiving placebo (see section 4.4). Infections involving the respiratory tract accounted for 60% of the adverse events in the fostamatinib group and 40% of the events in the placebo group. No systemic opportunistic infections were reported in the fostamatinib program. Serious adverse reactions for infection were uncommon. Severe infection events included pneumonia and influenza-like illness (1 patient each in the fostamatinib group) and sepsis (1 patient in the placebo group). One patient in the fostamatinib group discontinued study treatment due to an infection (pneumonia). Neutropenia was rarely associated with infection.

Elderly population

Of the total number of patients in clinical studies of fostamatinib, 16.4% were 65 years of age and older, while 2.4% were 75 years of age and older. In general, incidences of adverse reactions were higher in the older population.

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 fostamatinib, 11 (39%) patients experienced hypertension versus 2 (18%) placebo compared to 17 (23%) in patients under 65 years of age versus 4 (11%) placebo.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific antidote for overdose with fostamatinib, and the amount of R406 cleared by dialysis is negligible. There has not been any experience of overdose in the clinical development program. In the event of an overdose, the physician should monitor the patient closely for signs and symptoms of adverse reactions as described in section 4.2, and treat the reactions with supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic haemostatics. ATC code: B02BX09

Mechanism of action

Fostamatinib mediates its activity effectively through its major metabolite, R406, which is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). R406 inhibits signal transduction of B-cell receptors and Fc-activating receptors, which play a key role in antibody-mediated cellular responses. The fostamatinib metabolite R406 reduces antibody-mediated destruction of platelets.

Clinical efficacy and safety

The efficacy and safety of fostamatinib has been demonstrated in two Phase III, randomised, double-blind, placebo-controlled studies (C788-047 and C788-048) in adult patients with previously treated persistent (3-12 months since diagnosis) or chronic (greater than 12 months since diagnosis) ITP.

Randomised, 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 randomised 2:1 to fostamatinib or placebo for 24 weeks; randomisation was stratified with respect to prior splenectomy and severity of thrombocytopenia. Stable concurrent ITP therapy (glucocorticoids [less than 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 86% of patients at Week 4 or later.

Patients enrolled in the placebo-controlled studies had a median age of 54 years old (range: 20 to 88 years; median age in C788-047 was 57.0 and in C788-048 was 49.5 years), and the majority were female (61%) and were white (93%). Prior ITP treatments were varied (median of 3, range of 1-14), 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 8.5 years, and 35% had undergone splenectomy. At baseline, the median platelet count was 16,000/µL (with almost half [45%] less than 15,000/µL)

and 47% were on stable ITP therapy. Of the 102 patients with ITP who received fostamatinib, 28 (27%) were 65 years of age and older while 11 (11%) were 75 years of age and older.

In Study C788-047, 76 patients were randomised; 51 to the fostamatinib group and 25 to the placebo group. In Study C788-048, 74 patients were randomised; 50 to the fostamatinib group and 24 to the placebo group. The efficacy of fostamatinib was based on the primary endpoint of stable platelet response (at least 50,000/μL on at least 4 of the 6 visits between Weeks 14 to 24). Study outcomes for C788-047 and C788-048 are shown in table 4.

Table 4: Study outcomes from placebo-controlled clinical studies

Study Outcomes	Statistical Parameters	Study C788-047		Study C788-048		Pooled studies		Refractory population[6]	
		Fosta (N=51)	PBO (N=25)	Fosta (N=50)	PBO (N=24)	Fosta (N=101)	PBO (N=49)	Fosta (N= 72)	PBO (N=33)
Stable platelet response[1,2]	n (%)	8 (16)	0 (0)	9 (18)	1 (4)	17 (17)	1 (2)	10 (14)	0 (0)
	CI 95%	(5.7, 25.7)	(0, 0)	(7.4, 28.7)	(0, 12.2)	(9.5, 24.1)	(0, 6.0)	(5.9, 21.9)	(0.0, 0.0)
	p-value	$p^3 = 0.0471$		NS		$p^3=0.0071$		$P^3=0.0287$	
Eligible for C788-049[4] at Week 12[5]	n (%)	28 (55)	22 (88)	33 (66)	19 (79)	61 (60)	41 (84)	43 (60)	29 (88)
Completed study (Week 24)	n (%)	12 (24)	1 (4)	13 (26)	2 (8)	25 (25)	3 (6)	16 (22)	1 (3)

[1] Includes all patients with platelet counts and excludes patients whose platelet counts were measured following rescue therapy after Week 10.

[2] Stable platelet response was prospectively defined as a platelet count of at least 50,000/μL on at least 4 of the 6 visits between Weeks 14 and 24.

[3] p-value from Fisher Exact test

[4] C788-049: open label extension study

[5] Patients who did not respond to treatment after 12 weeks were eligible to enrol in open-label extension study.

[6] Refractory patient population defined as the subgroup of patients who had received three or more prior other ITP therapies

Fosta = fostamatinib; PBO = placebo; NS = Did not demonstrate a statistically significant difference between treatment arms

An initial therapeutic response (platelet count ≥ 50,000/μL) was observed within 6 weeks for most responders (11 of 17 responders) and within 12 weeks for all stable responders.

Among patients who were stable responders, the median platelet count increased to 95,000/μL across post-baseline visits with a maximum of 150,000/μL. Rescue medication was required by 30% and 45% of patients receiving fostamatinib or placebo, respectively.

During the placebo-controlled studies, the incidence of bleeding occurred in 29% and 37% of patients in the fostamatinib and placebo arms, respectively. The incidence of moderate or severe bleeding-related adverse events (AEs) (16.3% vs. 9.9%) and serious adverse events (SAEs) (10.2% vs 5.0%) was about twice as high in the placebo group compared with the fostamatinib group. Only one subject treated with fostamatinib experienced a severe bleeding-related event (contusion), while three subjects treated with placebo experienced severe events (gastrointestinal haemorrhage, menorrhagia and petechiae). In sum, there were trends for reduced bleeding-related AEs with fostamatinib compared to placebo; differences between the groups were not statistically significant.

Subset analyses

Platelet count responses for patients treated with TAVLESSE were further analysed as shown in table 5. Results are shown for both the pooled population (from Studies C788-047 and C788-048) and a refractory patient population defined as the subgroup of patients who had received three or more prior other ITP therapies. For all platelet count parameters, the results for the pooled population are comparable to the refractory patient population.

Table 5: Summary of platelet count parameters by subgroup – pooled patient population (C788-047 and C788-048) and refractory patient population

Parameters	Pooled Population Fostamatinib N=101	Refractory Patient Population Fostamatinib N=72
Subject With Platelet Response (≥50000/µL) at Week 12, n (%)		
Yes	23 (22.8%)	14 (19.4%)
No	78 (77.2%)	58 (80.6%)
Change From Baseline in Platelet Count (/µL) at Week 12		
Median	4000	3000
Range	(-15000, 220000)	(-5000, 159000)
Median Platelet Count (/µL) Over Time		
Median	22000	16750
Range	(1000, 254500)	(1000, 105500)

Extension Study

The C788-049 trial is an open label extension study. Patients from C788-047 and C788-048 who completed 24 weeks of treatment, or who did not respond to treatment after 12 weeks, were eligible to enrol in this study. Patients remained blinded to their treatment assignment from the previous study (fostamatinib or placebo), so their starting dose in this study was based on their final platelet count.

For the C788-049 trial, 123 patients were enrolled, 44 patients previously randomised to placebo and 79 patients previously randomised to fostamatinib.

Placebo Crossover: In a prospectively defined analysis, the 44 subjects treated with placebo in the prior study were evaluated for stable response for fostamatinib (from the first 24 weeks of the study) with their placebo data as the comparator for this objective measure. Ten of these subjects (22.7%) (including a single subject who was classified as a placebo responder in the prior study) met the criteria for stable response. Thus, the difference in response from fostamatinib compared with placebo was 20.5% (95% CI = 8.5-32.4).

Extension: Among the patients who achieved stable response in C788-047, C788-048 and C788-049 trials, 18 subjects maintained the platelet count of at least 50,000/µL for 12 months or longer.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with fostamatinib in all subsets of the paediatric population for the treatment of thrombocytopenia for patients with chronic immune thrombocytopenia (ITP), who have had an insufficient response to a previous treatment (e.g., corticosteroids), (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, the prodrug fostamatinib is rapidly converted to its active metabolite R406, presumably via enzymes in the gut.

After oral administration of fostamatinib, the mean absolute bioavailability of R406 was 55% with high variability (range 30 – 85 %). The median T_{max} of R406 is approximately 1.5 hours (range: 1 to 4 hours). Negligible levels of fostamatinib were found in plasma.

After a single 150 mg oral dose of fostamatinib, mean (± standard deviation [SD]) exposure estimates of R406 are 550 (± 270) ng/mL for C_{max} and 7080 (± 2670) ng/mL for AUC. R406 exposure is approximately dose proportional up to 200 mg twice daily (1.3 times the 150 mg dose). R406 accumulates approximately 2- to 3-fold upon twice daily dosing at 100–160 mg (0.67 to 1.06 times the 150 mg dose).

Distribution

Fostamatinib is highly bound to plasma proteins (98.3% in human plasma) and distributes reversibly into blood cells. The mean (± SD) volume of distribution at steady-state of R406 is 256 (± 92) L.

Metabolism

Fostamatinib is metabolised in the gut by alkaline phosphatase to the major active metabolite, R406. R406 is extensively metabolised, 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.

Elimination/Excretion

In humans, the mean (± SD) terminal half-life of R406 is approximately 15 (± 4.3) hours. Approximately 20% of the administered radioactivity was recovered in the urine, primarily in the form of an N-glucuronide of R406. Renal elimination of parent drug was low. The remaining radioactivity (~80%) was recovered in the faeces, mainly represented by 2 major metabolites of R406.

Linearity/non-linearity

R406 pharmacokinetics is linear and exposure is approximately dose-proportional up to 200 mg twice daily (1.3 times the 150 mg dose). R406 accumulates approximately 2- to 3-fold upon twice daily dosing at 100-160 mg (0.67 to 1.06 times the 150 mg dose).

Food interaction

Administration of fostamatinib 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%, indicating fostamatinib can be administered with or without food.

Special populations

Population pharmacokinetics analyses indicate fostamatinib is not altered based on age, sex, race/ethnicity.

The pharmacokinetics of fostamatinib is not altered in subjects with renal impairment (creatinine clearance [CLcr] = 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).

5.3 Preclinical safety data

In two fostamatinib 4-week rat studies (with the calcium and sodium salts), chondrodystrophy of the femoral head was observed in some animals in the highest dose groups (that were still juvenile/young during the treatment interval) and was not fully reversible by the end of the recovery period.

In a 1-month study in juvenile rabbits, fostamatinib produced growth plate dysplasia in the proximal femur and femoro-tibial joint and reduced bone marrow cellularity in the femur and sternum at 30 and 60 mg/kg/day. Increased degenerate/necrotic ovarian follicles occurred in females at all fostamatinib dose levels (including 10 mg/kg/day). The changes noted in the growth plates and ovaries are consistent with an anti-angiogenic effect.

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.

Studies in animals have shown no adverse effect on male fertility. Given there is no evidence for mutagenic or clastogenic potential, there is no concern for male-mediated birth defects. 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 doses as high as 40 mg/kg/day. This dose yields an AUC of R406 approximately 3.8 times that of the MRHD. All mating and fertility parameters in female rats were unaffected by doses as high as 11 mg/kg/day. This dose would yield an AUC of R406 similar to that of the MRHD. A slight decrease in pregnancy rates and an increase in post-implantation loss were seen at 25 mg/kg/day. This dose would yield an AUC of R406 2.6 times that of the MRHD.

In animal reproduction studies, administration of fostamatinib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-foetal mortality (post-implantation loss), alterations to growth (lower foetal 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.

A slight decrease in pregnancy rates and an increase in post-implantation loss in female rats was observed. Nonclinical studies have established that the administration of fostamatinib during pregnancy can increase the risk of embryonic loss, retard growth, and promote specific malformations of the kidney (including agenesis) and associated urogenital (e.g. ureter) tissues, as well as variations/malformations in major vessel and skeletal development. These effects are consistent with known targets of fostamatinib, including Syk (target), VEGFR-2 (off target) and Ret-kinase (off target). Based on nonclinical studies, any latent issues with female fertility is not expected after fostamatinib is withdrawn.

In pregnant rats and rabbits, R406 was found to cross the placenta. In general, the maternal plasma R406 concentrations were greater than the foetal plasma R406 concentrations.

In rodents, R406 was detected in maternal milk in concentrations 5- to 10-fold higher than in maternal plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol

Sodium hydrogen carbonate

Sodium starch glycolate, (type A)

Povidone (K30)

Magnesium stearate

Film-coating

Poly(vinyl alcohol)

Titanium dioxide

Macrogol (3350)

Talc

Iron oxide yellow

Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

White high density polyethylene (HDPE) bottle with an aluminium foil tamper evident seal and a white polypropylene (PP) child-resistant cap, together with two white opaque HDPE desiccant canisters containing silica gel.

Pack sizes of 30 and 60 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

8 MARKETING AUTHORISATION NUMBER(S)

TAVLESSE 100 mg film-coated tablets
PLGB 12930/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021