

ANNEX I
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

TAVLESSE 150 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).

TAVLESSE 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 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.

TAVLESSE 150 mg film-coated tablets

Approximately 7.25 mm x 14.5 mm oval, biconvex, light orange film-coated tablet debossed “150” 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/ μ L 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.
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.

Adverse reaction	Recommended action
	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 $1.0 \times 10^9/L$) and remains low after 72 hours, temporarily interrupt fostamatinib until resolved (ANC greater than $1.5 \times 10^9/L$). 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.

TAVLESSE 150 mg film-coated tablets contains 34 mg sodium per tablet, equivalent to 1.7% 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/ μ L) 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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
	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 abnormalities, 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 $< 1.0 \times 10^9/L$. Seven patients receiving fostamatinib and 1 patient receiving placebo had neutrophil counts decrease to between ≥ 1.0 and $< 1.5 \times 10^9/L$. No patient had a decrease in neutrophils to $< 0.5 \times 10^9/L$.

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 national reporting system listed in [Appendix V](#).

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/ μ L (with almost half [45%] less than 15,000/ μ L) 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/ μ L 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/ μ L 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 \geq 50,000/ μ L) 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/ μ L across post-baseline visits with a maximum of 150,000/ μ L. 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 (\geq 50000/ μ L) at Week 12, n (%)		
Yes	23 (22.8%)	14 (19.4%)
No	78 (77.2%)	58 (80.6%)
Change From Baseline in Platelet Count (/ μ L) 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 (\pm standard deviation [SD]) exposure estimates of R406 are 550 (\pm 270) ng/mL for C_{max} and 7080 (\pm 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 (\pm SD) volume of distribution at steady-state of R406 is 256 (\pm 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 (\pm SD) terminal half-life of R406 is approximately 15 (\pm 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 [CL_{cr}] = 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

5 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
EU/1/19/1405/001

TAVLESSE 150 mg film-coated tablets
EU/1/19/1405/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 january 2020

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAVLESSE 100 mg film-coated tablets
fostamatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Do not remove desiccants.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1405/001 (100 mg film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TAVLESSE 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

TAVLESSE 100 mg film-coated tablets
fostamatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Do not remove desiccants.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1405/001 (100 mg film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAVLESSE 150 mg film-coated tablets
fostamatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Do not remove desiccants.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1405/002 (150 mg film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TAVLESSE 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

TAVLESSE 150 mg film-coated tablets
fostamatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Do not remove desiccants.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1405/002 (150 mg film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

TAVLESSE 100 mg film-coated tablets

TAVLESSE 150 mg film-coated tablets

fostamatinib disodium hexahydrate

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TAVLESSE is and what it is used for
2. What you need to know before you take TAVLESSE
3. How to take TAVLESSE
4. Possible side effects
5. How to store TAVLESSE
6. Contents of the pack and other information

1. What TAVLESSE is and what it is used for

What TAVLESSE is

TAVLESSE contains the active substance fostamatinib. It specifically targets an enzyme called spleen tyrosine kinase, that plays an important part in the destruction of platelets. In this way TAVLESSE limits platelet destruction by the immune system and increases platelet count in the body. This helps reduce the risk of severe bleeding.

What TAVLESSE is used for

TAVLESSE is used to treat adults with low platelet counts due to chronic immune thrombocytopenia (ITP) when an earlier treatment for ITP has not worked well enough. ITP is an autoimmune disease, in which the body's own immune system attacks and destroys platelets in the blood. Platelets are needed to help create clots and stop bleeding.

2. What you need to know before you take TAVLESSE

Do not take TAVLESSE

- if you are allergic to fostamatinib or any of the other ingredients in this medicine (listed in section 6).
- if you are pregnant.

Warnings and precautions

Talk to your doctor or pharmacist before taking TAVLESSE, about all of your medical conditions, particularly if you:

- have high blood pressure,
- have liver problems,
- are pregnant or plan to become pregnant,
- are breastfeeding or plan to breastfeed.

Tell your doctor, pharmacist or nurse immediately if you get any of the following symptoms while you are taking this medicine:

- if you have high blood pressure (hypertension). New or worsening high blood pressure is common in people treated with TAVLESSE and can be severe. Your doctor will check your blood pressure regularly during treatment with this medicine. If needed, your doctor may start you on blood pressure medicine or change your current medicine to treat your blood pressure. Tell your doctor or pharmacist if you get headaches, confusion, dizziness, chest pain or shortness of breath.
- if your skin and eyes appear yellowish (jaundice) or if you get abdominal pain and swelling, swelling in your legs and ankles, itchy skin, abnormal dark urine, pale stool colour or bloody or tar-coloured stool, chronic fatigue, feeling or being sick in the stomach, and loss of appetite. Changes in liver function blood tests are common with this medicine. These may be symptoms of liver problems. Liver problems may occur and can be severe. Your doctor will regularly carry out blood tests to check how well your liver is working during treatment with this medicine.
- if you get diarrhoea. This is common in people treated with this medicine and can be severe. Tell your doctor or pharmacist if you get diarrhoea during treatment with this medicine. Your doctor may recommend changes in your diet, drinking more water, or give an antidiarrhoeal medicine to limit your symptoms.
- if you get a high fever (a sign of serious infection), chills, feel sick, or have a general feeling of being unwell. Your doctor will regularly do blood tests to check your white blood cell counts, and you may be told about a decrease in your white blood cell counts (neutropenia). Decreases in your white blood cell count are common with this medicine and can be severe. This may increase your risk of infection, including serious infections.

Children and adolescents

TAVLESSE should not be used in patients less than 18 years of age. This medicine has not been studied in this age group.

Other medicines and TAVLESSE

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Taking TAVLESSE with certain other medicines may affect how the other medicines work and other medicines may affect how TAVLESSE works.

In particular, tell your doctor if you are taking anything in this list:

- Ketoconazole, this medicine is typically used to treat fungal infections.
- Rifampicin, this medicine is typically used to treated bacterial infections.
- Simvastatin and rosuvastatin, these medicines are typically used to treat high cholesterol.
- Digoxin, this medicine is typically used to treat various heart conditions such as atrial fibrillation, atrial flutter and heart failure.
- Midazolam, this medicine is typically used for sedation or to treat anxiety.
- Anticoagulants, this medicine is typically used to prevent blood clotting.
- Nelfinavir, this medicine is typically used to treat HIV infection.
- Verapamil, this medicine it typically used to treat various heart conditions such as high blood pressure.
- Ranitidine, this medicine is typically used to treat heart burn.
- Ethinylestradiol, this medicine is typically used for birth control.
- Pioglitazone, this medicine is typically used to treat type 2 diabetes.

Pregnancy, breast-feeding and fertility

Pregnancy

TAVLESSE should not be used during pregnancy. It can cause harm or birth defects to your unborn baby.

If you are pregnant, if think you may be pregnant or if you are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are a woman who could become pregnant, you must use reliable contraception while you are taking TAVLESSE, and you must continue to use reliable contraception for at least 1 month after taking your last dose.

Contact your doctor straight away if you become pregnant while taking this medicine.

Breast-feeding

TAVLESSE is not recommended while breast-feeding. You should not breastfeed during treatment with TAVLESSE and for at least 1 month after your last dose.

If you are breast-feeding, or are planning to breast-feed, ask your doctor or pharmacist for advice before taking this medicine.

Fertility

TAVLESSE may affect the ability of a woman to get pregnant and have a child. Talk to your doctor if this is a concern for you. There is no impact on males.

TAVLESSE contains sodium

TAVLESSE 100 mg film-coated tablets contains 23 mg sodium (main component of cooking/table salt) per tablet. This is equivalent to 1.2% of the recommended maximum daily dietary intake of sodium for an adult.

TAVLESSE 150 mg film-coated tablets contains 34 mg sodium (main component of cooking/table salt) per tablet. This is equivalent to 1.7% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take TAVLESSE

How much to take

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will measure your platelet count.

The recommended dose of TAVLESSE is 100 mg twice daily (one tablet of 100 mg).

However, your doctor will check your platelet counts during your treatment with TAVLESSE and may change your dose as needed.

After starting treatment with TAVLESSE, the dose can be increased to 150 mg twice daily (one tablet of 150 mg) based on platelet count and tolerability. A daily dose of 300 mg (two tablets of 150 mg) daily must not be exceeded.

If you do not respond to treatment with fostamatinib, your doctor will stop treatment

If you have liver problems or high blood pressure, your doctor may start you on a lower dose. If you get serious side effects (such as high blood pressure, liver problems, diarrhoea or a decrease in white blood cell counts), your doctor may lower your dose or stop your treatment temporarily or permanently.

How to take TAVLESSE

Swallow the tablets whole with water.

TAVLESSE can be taken with food or between meals.

In case of stomach upset, take the tablets with food.

If you are sick

If you are sick at any time after taking TAVLESSE, do not take an additional tablet. Take your next dose at its regularly scheduled time.

If you take more TAVLESSE than you should

If you take too much TAVLESSE, call your doctor or pharmacist right away or go to the nearest hospital emergency room.

If you forget to take TAVLESSE

Do not take a double dose to make up for a forgotten tablet. Take your next dose at its regularly scheduled time.

If you stop taking TAVLESSE

It is important to take TAVLESSE for as long as your doctor prescribes it. Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

TAVLESSE may cause serious side effects. Tell your doctor immediately if you have any of the following serious side effects, either for the first time or if they get worse (see also section 2):

- high fever. Fever has been associated with low levels of white blood cells (febrile neutropenia) or infection
- diarrhoea
- infection and inflammation of the lungs (pneumonia). Symptoms include feeling short of breath, chest pain and producing discoloured mucus
- jaundice, abdominal pain and swelling, swelling in your legs and ankles, itchy skin, abnormal dark urine, pale stool colour or bloody or tar-coloured stool, chronic fatigue, feeling or being sick in the stomach, loss of appetite. These may be symptoms of liver problems.
- severe increase of blood pressure that can lead to a stroke (hypertensive crisis). Symptoms are headache, confusion, dizziness.

Other side effects

Besides the serious side effects mentioned above, you may also get other side effects.

Very common (may affect more than 1 in 10 people):

- gastrointestinal disorders such as diarrhoea, feeling or being sick in the stomach, and frequent bowel movement
- high blood pressure
- abnormal blood test results showing how your liver is working
- dizziness

Common (may affect up to 1 in 10 people):

- low white blood cell count or neutropenia
- stomach pain
- chest pain
- tiredness (fatigue)
- flu-like symptoms
- infections of the nose and throat, such as sore throat and the common cold
- infection of the windpipe, such as bronchitis

- taste changes
- rash
- headache

Reporting of side effects

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store TAVLESSE

Keep this medicine out of the sight and reach of children.

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.

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TAVLESSE contains

- The active substance is fostamatinib disodium hexahydrate.
TAVLESSE 100 mg film-coated tablets
TAVLESSE 150 mg film-coated tablets
- The other ingredients are:
 - 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

What TAVLESSE looks like and contents of the pack

TAVLESSE 100 mg film-coated tablets

The tablet is round, curved on both sides with a dark orange film coat. The commercial tablets are debossed with “R” on one side and “100” on the reverse side.

Available in bottle of 30 and 60 film-coated tablets. Each bottle has 2 desiccants.

Not all pack sizes may be marketed.

TAVLESSE 150 mg film-coated tablets

The tablet is oval, curved on both sides, with a light orange film coat. The commercial tablets are debossed with “R” on one side and “150” on the reverse side.

Available in bottle of 30 and 60 film-coated tablets. Each bottle has 2 desiccants.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Instituto Grifols, S.A.

Can Guasc, 2 - Parets del Vallès

08150 Barcelona - Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**AT/BE/BG/CY/EE/EL/ES/HR/HU/IE/LV/
LT/LU/MT/NL/RO/SI/SK/UK(NI)**

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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu/en>