SUMMARY OF THE RISK MANAGEMENT PLAN FOR TAVLESSE (FOSTAMATINIB)

Summary of risk management plan for fostamatinib

This is a summary of the risk management plan (RMP) for fostamatinib. The RMP details important risks of fostamatinib, how these risks can be minimised, and how more information will be obtained about fostamatinib's risks and uncertainties.

Fostamatinib's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how fostamatinib should be used.

This summary of the RMP for fostamatinib should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of fostamatinib's RMP.

1.1 The Medicine and What it is Used For

Fostamatinib is authorised for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see SmPC). It contains fostamatinib as the active substance and it is given orally in a film coated tablet.

Further information about the evaluation of fostamatinib's benefits can be found in fostamatinib's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/tavlesse

1.2 Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of fostamatinib, together with measures to minimise such risks and the proposed studies for learning more about fostamatinib's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

1.2.1 List of important risks and missing information

Important risks of fostamatinib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of fostamatinib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

The important risks and missing information for fostamatinib are listed in Table 1:

Table 1: Summary of important risks and missing information for fostamatinib

Important identified risks	• Diarrhoea • Hypertension • Hepatotoxicity • Neutropenia • Infections
Important potential risk	• Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development) • Use in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred (effect of fostamatinib during bone formation and regrowth during development)
Missing information	• Long term safety information

1.2.2 Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Summaries of the important risks and missing information for fostamatinib are provided in the following tables.

Table 2: Important identified risk of fostamatinib: Diarrhoea

Diarrhoea	
Evidence for linking the risk to the medicine	The events of diarrhoea in the placebo-controlled period in the ITP studies were reported with a higher incidence in fostamatinib patients (31.4%) than placebo patients (14.6%). Most of the events of diarrhoea were treatment-related (87.5% of fostamatinib patients, 85.7% of placebo patients) .
Risk factors and risk groups	None identified
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where advice is given on monitoring for diarrhoea, dose modification and interruption of fostamatinib treatment in case of a severe event. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 3: Important identified risk of fostamatinib: Hypertension

Hypertension	
Evidence for linking the risk to the medicine	Most of the Hypertension AEs during the fostamatinib exposure period were treatment-related (in 18.5%; 27/146 patients). Changes in blood pressure are shown by shift analysis showed 44 subjects (43.1%) receiving fostamatinib and 28 subjects (58.3%) receiving placebo retained their baseline blood pressure status throughout the Placebo-Controlled Period. A one category increase in blood pressure was observed in 45 subjects (44.1%) receiving fostamatinib and 18 subjects (37.5%) receiving placebo. Two category increases were observed in 9 subjects (8.8%) receiving fostamatinib and 1 subject receiving placebo (2.1%). One subject receiving fostamatinib and no subjects receiving placebo had a 3 category increase in blood pressure.
Risk factors and risk groups	Patients with pre-existing hypertension may be more susceptible to the fostamatinib blood pressure effects.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where advice is given on monitoring for changes in blood pressure and administration of anti-hypertensive treatment (and interruption of fostamatinib) in case blood pressure remains 160/100 mmHg or higher for more than 4 weeks. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 4: Important identified risk of fostamatinib: Hepatotoxicity

Hepatotoxicity	
Evidence for linking the risk to the medicine	Fostamatinib administration can result in blood transaminase (ALT and/or AST) elevations that may necessitate drug dose reduction or discontinuation (m2.5). During the placebo-controlled period, 16 patients (15.7%) treated with fostamatinib and 1 placebo patient (2.1%) had an AE coded under the standardised MedDRA Query (SMQ) Drug-related hepatic disorder. Review of liver function laboratory testing showed that maximum ALT levels were > 3 x the ULN in 9 subjects (8.8%) receiving fostamatinib and no subjects receiving placebo. Of the 9 fostamatinib subjects with ALT levels > 3 x ULN, 3 subjects had ALT levels between > 3 and ≤ 5 x ULN, 5 subjects (4.9%) had ALT levels > 5 and ≤ 10 x ULN, and 1 subject (1.0%) had an ALT level > 10 x ULN. Maximum AST levels among subjects receiving fostamatinib were > 3 x ULN in 2 subjects (2.0%), including 1 subject (1.0%) with AST > 5 x ULN; no subjects receiving placebo had an AST increase ≥ 3 x ULN. Transaminases recovered to baseline levels within 2 to 4 weeks of dose modification.
Risk factors and risk groups	Patients receiving concomitant medications known to frequently produce transaminase elevations. Patients with a history of hepatic impairment or hepatotoxicity.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where advice is given on monitoring liver function tests monthly and considering interruption, dose reduction or discontinuation if ALT/ AST increase more than 3 x upper limit of normal (ULN). *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 5: Important identified risk of fostamatinib: Neutropenia

Neutropenia	
Evidence for linking the risk to the medicine	Early in clinical development, fostamatinib was recognised to produce reductions in neutrophils that were rapidly reversible upon discontinuation of therapy. During Placebo-Controlled Period, neutropenia was considered to be treatment-related in 6 patients (5.9%).
Risk factors and risk groups	Patients with a history of bone marrow depression; combination therapy with myelotoxic agents; low white blood cell at the onset of the treatment.
Risk minimisation measures	*Routine risk minimisation measures:*

Neutropenia	
	SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where advice is given on monitoring the absolute neutrophil count (Maison-Blanche et al.) monthly and interrupt, reduce or discontinue fostamatinib if ANC decreases to less than 1.0 x 10^9/L for at least 72 hours. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 6: Important identified risk of fostamatinib: Infections

Infections	
Evidence for linking the risk to the medicine	Fostamatinib administration has been associated with a slightly increased risk of routine/local infections (but not opportunistic infections) although the effect may deserve further analysis. The infections do not appear to be associated with neutropenia, with some exceptions. Most of the Infection events were assessed by the investigator as unrelated to treatment; 2.9% of fostamatinib subjects and no placebo subjects experienced treatment-related Infection events.
Risk factors and risk groups	Patients with conditions causing alterations in immune functions. Patients with poor performance status.
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.4 and Section 4.8. Patient Information Leaflet Section 2 *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 7: Important potential risk of fostamatinib: Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)

Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	
Evidence for linking the risk to the medicine	Based on findings from several Good Laboratory Practice (GLP) toxicology studies in rodents and a GLP juvenile toxicology study in rabbits with fostamatinib there is potential for adverse bone development changes in paediatric populations. These changes may occur at dose levels below those promoting maternal toxicity and at unity or below calculated margin of safety.
Risk factors and risk groups	Patients under 18 years old.

Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.2 where warning is given not to use fostamatinib in children. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* None

Table 8: Important potential risk of fostamatinib: Patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred (effect of fostamatinib during bone formation and regrowth during development)

Important potential risk of fostamatinib: Patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred (effect of fostamatinib during bone formation and regrowth during development)	
Evidence for linking the risk to the medicine	Fostamatinib has shown in vitro to target SYK and other tyrosine kinases that are involved in the bone metabolism (e.g. VEGFR, RET), so 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. There was a low incidence of young adults enrolled in clinical studies and no data was collected on the development of growth plates in these patients.
Risk factors and risk groups	Patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred
Risk minimisation measures	*Routine risk minimisation measures:* SmPC Section 4.4 where warning is given not to use fostamatinib in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* None

1.2.3 Post-authorisation Development Plan

1.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of fostamatinib.

1.2.3.2 Other studies in post-authorisation development plan

A non-interventional post-authorisation study (PASS) will be conducted with the objective to collect information on the long-term safety/tolerability of fostamatinib in clinical practice, for the treatment of chronic ITP in adult patients who are refractory to other treatments.