Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2300

fostamatinib 100mg and 150mg film-coated tablets (Tavlesse®)

Instituto Grifols, S.A.

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan equivalent process:

fostamatinib (Tavlesse®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

SMC restriction: for the treatment of patients with severe symptomatic ITP or with a high risk of bleeding who have not had a suitable response to other therapies, including a thrombopoietin receptor-agonist (TPO-RA), or where use of a TPO-RA is not appropriate.

Fostamatinib has been shown to be significantly more effective than placebo in raising and maintaining platelet counts at (or above) a minimum target level in previously-treated patients with ITP.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.[1]

Dosing Information

The recommended starting dose of fostamatinib is 100mg taken orally twice daily, with or without food. [1]

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

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/microlitre should be used. These and dose adjustments based on tolerability are detailed in the Summary of product characteristics (SPC).

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.

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

Please refer to the SPC for further details.[1]

Product availability date

July 2020

Fostamatinib meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Fostamatinib is a prodrug of a spleen tyrosine kinase (SYK) inhibitor that inhibits signal transduction of B-cell receptors and Fc-activating receptors, which play a key role in antibody-mediated cellular responses. Fostamatinib reduces antibody-mediated destruction of platelets.[1]

The submitting company has requested that SMC consider fostamatinib when positioned for use for the treatment of patients with severe symptomatic ITP or patients with a high risk of bleeding who have not had a suitable response to other therapies, including a thrombopoietin receptor-agonist (TPO-RA), or where use of a TPO-RA is not appropriate.

The key evidence supporting the efficacy and safety of fostamatinib in the indication under review comes from FIT1 and FIT2, which were two replicate international, multicentre, randomised, double-blind, placebo-controlled, parallel group, phase III studies. These studies recruited adult patients (≥18 years) with a diagnosis of ITP for at least 3 months (persistent or chronic) and no known aetiology for thrombocytopenia, who had an average platelet count <30,000/microlitre

(and none >35,000/microlitre unless as the result of rescue therapy) from at least three qualifying counts within the preceding 3 months. Patients were included if they had received at least one typical regimen for the treatment of ITP (such as a TPO-RA [romiplostim, eltrombopag], corticosteroids with or without splenectomy or immunoglobulin). Patients were required to have a Karnofsky Performance Status (KPS) score ≥70. All therapeutic agents for ITP, other than those allowed as concomitant therapy (glucocorticoids <20 mg prednisone equivalent per day, azathioprine or danazol), were discontinued in accordance with the protocol-defined washout periods.[2, 3]

Patients were randomised in a 2:1 ratio to receive fostamatinib 100mg orally twice daily or placebo orally twice daily. Fostamatinib could be increased to 150mg orally twice daily after 4 weeks or later, depending on platelet count, or could be reduced to 100mg or 150mg once daily if a dose-limiting adverse event occurred. Treatment was to continue until week 24. Patients assessed at week 12 as being non-responders could discontinue the studies and enter the open-label extension study, FIT3.[2, 3] Concomitant use of ITP medication (as detailed above) were permitted during the studies, without change, if patients were on a stable dose for 14 days prior to baseline. The use of rescue therapy was also allowed in both studies. [2]

The primary outcome was stable response by week 24 and was defined as a platelet count ≥50,000/microlitre on at least four of the six clinic visits that occurred every 2 weeks between weeks 14 to 24 of the treatment period. The primary outcome was assessed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation. Results for FIT1, FIT2 and the pooled analysis of both studies are reported in Table 1.[2, 3]

Table 1: Proportion of patients achieving a stable platelet response in the FIT1 and FIT2 studies and pooled analysis[2, 3]

	FIT1		**FIT2 [a]**		**Pooled analysis (FIT1 and FIT2)**	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Fostamatinib (n=101)**	**Placebo (n=49)**
Database lock	16 August 2016		4 October 2016		-	
Stable response						
Patients with event, % (n)	16% (8)	0	18% (9)	4.2% (1)	17% (17)	2% (1)
Absolute difference	16%		14%		15%	
95% CI	5.7% to 25.7%		-6.1% to 27.9%		6.5% to 23.1%	
p-value	<0.05		0.15		<0.05	

CI = confidence interval. a) In FIT2, one patient randomised to placebo achieved a stable response. It was reported that fluctuating platelet counts were observed during the study for this patient. The EMA suggested that this patient likely had cyclic thrombocytopenia and should have been ineligible for inclusion in the study.

A hierarchical statistical testing strategy was planned for the secondary outcomes, however, it was not employed. The secondary outcome results are therefore only descriptive and are non-

inferential (no p-values reported). See Table 2 for key platelet-related secondary outcome results of the pooled analysis of FIT1 and FIT2. Measurements of frequency and severity of bleeding were similar across the groups.[3]

Table 2: Key platelet-related secondary outcome results from the pooled analysis of FIT1 and FIT2[3]

	Fostamatinib	Placebo
Proportion of patients with a platelet count ≥ 50,000/microlitre		
Week 12	23% (23/101)	6.1% (3/49)
Absolute difference (95% CI)	17% (6.1% to 27%)	
Week 24	16% (16/101)	2% (1/49)
Absolute difference (95% CI)	14% (5.7% to 22%)	
Proportion of patients with a baseline platelet count <15,000/microlitre achieving a platelet count of ≥30,000/microlitre and ≥20,000/microlitre above baseline		
Week 12	21% (10/47)	4.8% (1/21)
Absolute difference (95% CI)	16% (1.7% to 31%)	
Week 24	15% (7/47)	0 (0/21)
Absolute difference (95% CI)	15% (4.7% to 25%)	

CI = confidence interval. All 95% CI are descriptive only.

Quality of Life (QoL) was assessed using short form-36 (SF-36) health survey. This instrument was used at baseline on day 1, and on weeks 4, 12 and 24. Descriptive statistics for the SF-36 generally did not suggest differences between the fostamatinib and placebo groups.[4]

Non-responders, from FIT1 and FIT2, and responders who completed the 24-week treatment could enrol in an open-label extension study (FIT3) with fostamatinib 100 or 150mg twice daily. At the latest data cut-off 8 March 2018, it was reported that 15% (19/123) (95% confidence interval (CI): 9.6%, 23%) of patients achieved platelet response within 12 weeks and maintained stable platelet response for at least 12 months.[3] Among the patients randomised to placebo in FIT1 and FIT2, 23% (10/44) (95% CI: 12% to 38%) achieved a stable platelet response for at least 12 weeks, including one patient who had achieved a stable platelet response during treatment with placebo in FIT2. These results are supportive of the primary outcomes in FIT1 and FIT2.

Summary of evidence on comparative safety

In the FIT1 (data cut-off August 2016) and FIT2 studies (data cut-off October 2016), the median duration of treatment in the pooled fostamatinib group was 86 days (range 8 to 183 days) and in the pooled placebo group was 85 days (range 16 to 173 days). During the placebo controlled periods, any treatment-emergent adverse event (AE) was reported by 83% (85/102) of patients in the pooled fostamatinib group and 75% (36/48) in the pooled placebo group and these were considered treatment-related in 59% and 27% respectively. In the pooled fostamatinib and placebo groups respectively, patients reporting a severe AE (grade 3 to 4) during the placebo controlled periods, were 16% versus 15%; patients with a reported serious AE were 13% versus

21%; patients with a dose reduction due to treatment emergent AEs were 8.8% versus 2.1%; the proportion of AEs that led to dose interruptions were 18% versus 10%; and patients discontinuing therapy due to an AE was 9.8% versus 8.3%. The most frequently reported treatment-related AEs of any grade with an incidence ≥5% in the pooled fostamatinib group versus the pooled placebo group were: diarrhoea (26% versus 12%), nausea (15% versus 6.3%), hypertension (16% versus 4.2%), dizziness (8.8% versus 4.2%), increased ALT (9.8% versus 0%), and increased AST (6.7% versus 0%).[2, 3]

Summary of clinical effectiveness issues

ITP is an acquired immune mediated disorder characterised by isolated thrombocytopenia (peripheral blood platelet count <100,000/microlitre), platelet production impairment, variable bleeding tendency and absence of any underlying cause. It is classified as newly diagnosed, persistent (3 to 12 months) or chronic (≥ 12 months). Symptoms are variable (from bruising to serious bleeding such as intracranial haemorrhage).[3] First-line treatment options for adult patients with ITP include corticosteroids, intravenous immunoglobulin (IVIg), and intravenous anti-D immunoglobulin (IV anti-D Ig). Subsequent therapies include TPO-RAs (eltrombopag, avatrombopag and romiplostim) and rituximab. Current ITP treatments in the refractory setting include various off-label medical therapies not already used such as mycophenolate mofetil , rituximab, azathioprine, dapsone, and danazol.[5] Fostamatinib meets SMC orphan equivalent criteria for this indication. Clinical experts consulted by SMC considered that there was an unmet need for patients who are refractory to currently available therapies.

The submitting company has requested that SMC consider fostamatinib when positioned for use for the treatment of patients with severe symptomatic ITP or with a high risk of bleeding who have not had a suitable response to other therapies, including a TPO-RA, or where use of a TPO-RA is not appropriate. The eligibility criteria of FIT1 and FIT2 studies did not stipulate if patients for whom use of a TPO-RA was not appropriate, were eligible for inclusion. Pooled data from both studies indicate that 48% (72/150) had received a TPO-RA.

The primary outcome of stable platelet response was met in FIT1 but not in FIT2. The pooled analysis of FIT1 and FIT2 demonstrated that treatment with fostamatinib significantly increased stable platelet response rate versus placebo (17% versus 2%, respectively). The increase in stable platelet response rate although modest, was considered clinically relevant by the EMA. However, due to small sample size, the confidence intervals of the between groups absolute difference are very wide and approach zero, thus it cannot be excluded that, in clinical practice, fewer response rates than in the clinical studies may be observed. All secondary endpoints were only descriptive. Results of the key platelet-related secondary endpoints were consistent with the primary outcome. Results of the further secondary endpoints of bleeding-score were very similar between the two treatment groups. The studies did not allow clear conclusions on the effects of fostamatinib on bleeding risks to be drawn.[3]

A number of exploratory subgroup analyses was conducted and these were generally consistent with the primary analysis, including in the subgroup of patients who previously received a TPO-RA therapy, which accounted for approximately half of all patients (of relevance in the proposed positioning). However, the EMA noted that due to the small size of the studies and low numbers of responding patients, no conclusions could be drawn for various subgroups.[3]

Patients could receive some allowed concomitant ITP therapies at stable doses; however, the study was not designed to assess the role of any combination therapy (for example fostamatinib in combination with glucocorticoids) and the effect of any combination is uncertain.

The studies did not permit comparison of the efficacy of the two different regimens of fostamatinib 100mg or 150mg twice daily. There were also some methodological limitations and protocol deviations, which may have affected the results.[3]

Patients were included in the key studies if they had a KPS >70 and no severe bleeding score of 2 at any site on the ITP Bleeding Scale, therefore it is not known if the study results would apply to patients in the Scottish population with poorer performance status or severe bleeding scores.

In FIT1 and FIT2, fostamatinib was compared with placebo. In the proposed positioning, treatment options include mycophenolate mofetil, rituximab, splenectomy, azathioprine, cyclophosphamide, ciclosporin, dapsone, vinca alkaloids and danazol, thus uncertainty remains around the relative efficacy and safety versus all comparators. However, there is a lack of robust evidence for these therapies in this patient group and these may be less relevant comparators. Clinical experts consulted by SMC generally considered that fostamatinib would not displace any medicine but would be used if the standard second line therapies either fail or are not suitable for a patient.

Clinical experts consulted by SMC considered that fostamatinib is a therapeutic advancement as it is a new licensed treatment option with a new mechanism of action for patients who are refractory to or not candidates for currently available therapies. They considered that its place in therapy was in chronic and refractory ITP after TPO-RA therapy and that there may be limited service implications associated with the introduction of fostamatinib due to side effects monitoring requirements (blood pressure and liver function monitoring).

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of fostamatinib, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Patients with refractory ITP are at increased risk of bleeding, including life threatening and fatal bleeding. The risk of bleeding can trigger anxiety for patients and their families/carers, and impact their quality of life. Patients also often experience severe fatigue.
- There remains an unmet need for patients who are refractory to or ineligible for the currently available treatments.
- It is expected that, in patients who do respond to fostamatinib, a meaningful and stable platelet count improvement would result in reduced bleeding risk and symptoms (including fatigue and bruises) and thus be associated with an improved quality of life and reduced anxiety for the patients and their families/carers.
- Fostamatinib has some distinct advantages over other available ITP treatments in that it does not cause immunosuppression and it is orally administered.
- The service implications and side-effects burden associated with fostamatinib use are also expected to be low.

Additional Patient and Carer Involvement

We received a patient group submission from the ITP Support Association, which is a registered charity. The ITP Support Association has received 70% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from the ITP Support Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The economic model presented by the submitting company was a multi-state Markov model to assess the cost-effectiveness of fostamatinib versus watch and rescue for the treatment of ITP. Watch and rescue is defined as periods of no ITP treatment (watching) punctuated by administration of platelet transfusion, intravenous steroids, and intravenous immunoglobulin (rescue) following profound mucocutaneous or other internal bleeding requiring hospitalisation, or in those at a high risk of bleeding due to severe thrombocytopenia.

The model used a 35-year, lifetime horizon, and tracked disease progression through seven unique health states. The model structure was used to capture the chronic nature of treatment resistant ITP, and to link to the frequency of rescue events and severity of bleeds. Patients could transition between health states after each 4-week cycle. The model incorporates a dose escalation stopping rule whereby patients are assessed for response to 100mg twice daily fostamatinib at week 4, and after a further 8 weeks patients receiving 150mg twice daily will be assessed for response. Patients who respond to fostamatinib treatment move to either the response or partial response health states, with transition probabilities informed by the FIT clinical studies and extension study.

Clinical evidence informing the base case analysis was obtained from the FIT1 and FIT2 studies. Transition probabilities from baseline to week 24 were based on data from FIT1 and FIT2. Beyond week 24 of the model, the weighted average of all transition matrices between baseline and week 24 is applied to fostamatinib and 'watch and rescue'. Loss of response to fostamatinib is informed by data from the FIT3 extension study.

The company consider that quality of life data from the FIT1 and FIT2 clinical studies lacked comparability to normal clinical practice due to patients being selected for low bleed risk as an inclusion criterion. Additionally, the company was unable to generate robust SF-6D values from the clinical studies as by week 24, fewer than 25% of the patients who provided baseline assessments responded to the SF-36. As a result, the utilities used were the result of a pooled analysis using the romiplostim study data and previously published literature. Where possible, EQ-5D data valued using the UK tariff were used as the preferred metric to value QoL. The values referenced in the romiplostim submission do not match those used in the model. The company has been asked to clarify this discrepancy.

The analysis included acquisition costs for fostamatinib, rescue treatment costs, severe bleed event costs, surgical prophylaxis costs, routine management costs and adverse event costs.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount is offered on the list price of the medicine. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price results can be presented. Using the list price, the company estimated a base case incremental cost-effectiveness ratio (ICER) of £102,691 per quality-adjusted life-year (QALY).

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. A single scenario analysis was performed to investigate treatment cost waning with continued treatment benefit. Table 3 presents some key results from the sensitivity and scenario analyses. A comparison with rituximab was also provided as a sensitivity analysis but was not considered robust.

Table 3: Selected scenario analysis results (list price)

Scenario	ICER (Incremental cost-effectiveness ratio)
Cycle 6+ fostamatinib Response >50,000/ microlitre treatment cost	£75,636 - £135,539
Fostamatinib loss of response per cycle (upper bound)	£108,241
After year 1, all patients would come off treatment with 40% of patients continuing to experience treatment benefit	£88,227
Model time horizon 20 years	£103,024
Model time horizon 10 years	£119,606

The key uncertainties of the economic evidence are summarised below:

- The transition probabilities for week 5-12 of watch and rescue are affected by zero patient numbers in the 'response >50,000 microlitre' health state at the start of the period. The company assumed that transitions followed an identical distribution to the 'partial-response 30-50,000 microlitre' health state. The company provided scenario analyses using more conservative approaches which had minimal impact on the ICER, thus confirming this is not a key driver of results.
- Clinical data were not able to capture the high-risk patients on active treatment and as such the population in the model may not accurately reflect the disease population in clinical practice.
- The model assumes that only patients experiencing post-intracranial haemorrhage disability of 4-5 on the modified Rankin scale would incur healthcare costs in future cycles. This is likely to underestimate the costs of intracranial haemorrhage and therefore be considered a conservative assumption. A carer disutility has also been applied in these health states but sensitivity analysis showed removal of this had minimal impact on the ICER.

Despite the limitations outlined above, the economic case has been demonstrated.

Additional information: guidelines and protocols

An International consensus report on the investigation and management of primary immune thrombocytopenia was published in 2010 and was subsequently updated in 2019.[5] This consensus guidance states that fostamatinib is a medical therapy for ITP, which is supported by robust evidence. The initial recommended treatment for ITP is steroids, and intravenous immunoglobulin (IVIg) or intravenous anti-D immunoglobulin (IV anti-D Ig) can be used, followed by medical therapies and then surgical interventions (splenectomy, only after failure of medical therapies and depending on patient age and comorbidities). Subsequent medical therapies with robust evidence

include TPO-RAs (eltrombopag, avatrombopag, and romiplostim), rituximab and fostamatinib. The guidance make specific recommendations for patients who have failed multiple prior therapies, and recommends that consideration is given to the use of other medical therapies if not already used. The list of treatments included in the guideline is mycophenolate mofetil, fostamatinib, rituximab, azathioprine, dapsone, and danazol. Switching from one TPO-RA to another is also an option and has been shown to have a positive effect on response and AEs. [5]

Additional information: comparators

Off-label therapies including mycophenolate mofetil, rituximab, azathioprine, cyclophosphamide, ciclosporin, dapsone, vinca alkaloids and danazol. Splenectomy.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Fostamatinib	**100mg daily to 150mg twice daily**	**18,746 to 56,238**

Costs from BNF online on the 21st August 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Grifols UK Ltd. Fostamatinib film-coated tablets (Tavlesse®). Summary of product characteristics. Electronic Medicines Compendium http://www.medicines.org.uk/emc Last updated 04.06.2020.
2. Bussel J, Arnold DM, Grossbard E, Mayer J, Treliński J, Homenda W*, et al.* Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. American Journal of Hematology. 2018;93(7):921-30.
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4. Food and Drug Administration (FDA). NDA Multi-disciplinary review and evaluation NDA 209299 Tavalisse (fostamatinib). 2018. Avaialble at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209299Orig1s000MultidisciplineR.pdf.
5. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T*, et al.* Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Advances. 2019;3(22):3780-817.

This assessment is based on data submitted by the applicant company up to and including 16 October 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.