The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using fostamatinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE’s guidance on using fostamatinib in the NHS in England.

For further details, see NICE’s guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 2nd December 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5
1 Recommendations

1.1 Fostamatinib is not recommended, within its marketing authorisation, for treating refractory chronic immune thrombocytopenia in adults.

1.2 This recommendation is not intended to affect treatment with fostamatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment for refractory chronic immune thrombocytopenia after thrombopoietin receptor agonists or when they are not suitable includes rituximab or mycophenolate. Fostamatinib would be used after thrombopoietin receptor agonists or when they are not suitable.

Clinical evidence shows that fostamatinib is moderately effective compared with placebo. There is no clinical trial evidence directly comparing fostamatinib with rituximab or mycophenolate. The company chose rituximab with ‘watch and rescue’ (monitoring until a bleed happens and treatment is needed) as its comparator. However, it did not provide any direct or indirect evidence comparing rituximab with fostamatinib.

This means that the cost-effectiveness estimates for fostamatinib are very uncertain. They are likely to be higher than what NICE normally considers cost effective. So, fostamatinib is not recommended.
2 Information about fostamatinib

Marketing authorisation indication

2.1 Fostamatinib (Tavlesse, Grifols Institute) is indicated ‘for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments’.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list prices of fostamatinib are:

- £3,090 per 60-tablet pack, each tablet contains 100 mg of fostamatinib (excluding VAT; British National Formulary online, accessed October 2020)
- £4,635 per 60-tablet pack, each tablet contains 150 mg of fostamatinib (excluding VAT; British National Formulary online, accessed October 2020).

The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Grifols Institute, a review of this submission by the evidence review group (ERG), NICE’s technical report, and responses from stakeholders. See the committee papers for full details of the evidence.
The condition

People and clinicians would welcome an additional treatment option

3.1 Chronic immune thrombocytopenia (ITP) is an autoimmune condition characterised by the destruction of platelets. This results in a low number of platelets circulating in the blood. Platelets are a type of cell involved in blood clotting. Thrombocytopenia is defined as having fewer than 100,000 platelets per microlitre of blood. Symptoms include bruising easily, the appearance of small red spots under the skin (petechiae), fatigue and bleeding. People with the disease may have a different frequency and severity of bleeding even if they have similar platelet counts. Some do not have any bleeding at all. Others have skin and nose bleeding, or more serious events such as intracranial, gastrointestinal, genital and urinary bleeding. Because of these differences and the unpredictable nature of bleeding, some people can become stressed or depressed. A particular concern is a sudden drop in platelets which can lead to life-threatening bleeds. Although new treatments called thrombopoietin receptor agonists (TPO-RAs) have become available in recent years, they do not work for everyone and some people cannot take them. The patient and clinical experts also explained that some of the treatment options suppress the immune system, increasing the risk of infection. The committee concluded that people and clinicians would welcome an additional treatment option.

Treatment pathway

The treatment pathway includes thrombopoietin receptor agonists followed mostly by rituximab and mycophenolate

3.2 Initial treatment for the first episode of ITP involves high dose corticosteroids or intravenous immunoglobulin. Subsequent treatments include TPO-RAs, see the NICE technology appraisal guidance on romiplostim and eltrombopag. Rituximab, which does not have a marketing authorisation for ITP, splenectomy (surgical removal of the
spleen) and other treatments such as azathioprine, mycophenolate, cyclosporine, dapsone and danazol are sometimes used. The clinical experts explained that treatment after corticosteroids or intravenous immunoglobulin depends on the time it takes for the disease to relapse, but TPO-RAs are the most likely to be used. They also noted that splenectomy is avoided in the first year after diagnosis and is unlikely to be considered as a second line of treatment. After TPO-RAs, rituximab and mycophenolate are the most common treatments, but azathioprine is offered to people who want to conceive. Cyclosporine is very rarely used because of adverse effects, while dapsone is reserved as a last resort. The committee understood that danazol is not available in the UK anymore. For people with platelet counts higher than 30,000 per microlitre and at low risk of bleeding, clinicians may adopt a ‘watch and rescue’ approach. A patient expert explained that once his platelet counts had stabilised after treatment with intravenous immunoglobulin, he went onto a watch and rescue approach for 15 years. The committee concluded that the treatment pathway after TPO-RAs includes many treatments, most commonly rituximab and mycophenolate.

**Treatment decisions are based on more than platelet count**

3.3 The clinical experts highlighted that they and people with ITP make treatment decisions based on a combination of platelet count and other bleeding risk factors such as age and use of anti-platelet therapy. They noted that different platelet count thresholds are used in practice to guide treatment. Typically, the objective of treatment is a platelet count higher than 30,000 per microlitre to reduce the risk of bleeding. However, platelet counts higher than 50,000 per microlitre may also be used as a target for maintenance therapy, to account for fluctuations in platelet levels over time and to minimise the chance of platelet count dropping below 30,000 per microlitre. The company explained that regulatory agencies use the value of 50,000 per microlitre. The committee concluded that treatment decisions are based on more than platelet count.
The company’s positioning of fostamatinib in the treatment pathway is broadly appropriate

3.4 Fostamatinib has a marketing authorisation for treating chronic ITP after previous treatments. The company proposes that fostamatinib is used after TPO-RAs (romiplostim and eltrombopag) or when TPO-RAs are not suitable. This is narrower than the marketing authorisation. The clinical experts considered the company’s proposed positioning to be reasonable. However, they noted that other treatments such as rituximab and mycophenolate may be used after TPO-RAs and before fostamatinib, depending on the circumstances of people with ITP. For example, rituximab is considered more effective for young women and people with other immune conditions. However, some people may be concerned about the immunosuppressive effects so would prefer an alternative therapy. The clinical experts also highlighted that for people who are concerned about prothrombotic risk, TPO-RAs would not be suitable, so fostamatinib would be considered instead. The committee acknowledged that therapies are not necessarily used in a sequence because treatment is individualised. The committee concluded that the company’s positioning of fostamatinib in the treatment pathway was broadly appropriate.

Rituximab and mycophenolate are relevant comparators for fostamatinib

3.5 NICE’s final scope included the TPO-RAs romiplostim and eltrombopag, immunosuppressive therapies including rituximab, splenectomy, cytotoxic agents, dapsone, danazol and ‘watch and rescue’ as relevant comparators. However, the company excluded romiplostim and eltrombopag based on their positioning of fostamatinib after TPO-RAs, or when they are unsuitable. The company selected rituximab plus watch and rescue as the only comparator. For all other comparators the company argued that there was a lack of robust evidence to support comparisons with fostamatinib. The clinical experts agreed that many of the treatments used in practice do not have robust clinical trial data and that fostamatinib would likely be used in a similar position in the treatment
pathway as rituximab (see section 3.2). However, 1 expert noted that mycophenolate is often used in clinical practice at this point in the treatment pathway. The committee concluded that the relevant comparators for fostamatinib are rituximab and mycophenolate.

Clinical effectiveness

Fostamatinib is moderately effective at increasing platelet count compared with placebo

3.6 FIT1 and FIT2 are 2 multinational, double-blind, randomised, phase 3 trials of identical design comparing fostamatinib with placebo. Rescue therapy was allowed in both trials. Therefore, the ERG considered these trials to represent fostamatinib plus rescue therapy compared with placebo plus rescue therapy. Both trials included adults with persistent or chronic ITP, an average platelet count of less than 30,000 per microlitre and who had at least 1 treatment before, but the disease had failed to respond. The primary endpoint in both trials was stable platelet response, defined as a platelet count of 50,000 per microlitre or more in at least 4 out of 6 assessments between weeks 14 and 24. Secondary outcomes included:

- the percentage of people with a platelet count higher than 50,000 per microlitre at weeks 12 and 24
- the percentage of people with a platelet count higher than 30,000 per microlitre and an increase of at least 20,000 per microlitre from baseline at weeks 12 and 24, after a platelet count of less than 15,000 per microlitre at baseline
- bleeding severity measured by the Immune Thrombocytopenic Purpura Bleeding Scale and World Health Organisation bleeding scores.

People enrolled in the FIT1 and FIT2 trials were also invited to participate in FIT3, a 5-year, open-label extension study. Pooled results from the FIT1 and FIT2 trials showed that rates of stable response
were higher in the fostamatinib arm (18%) than in the placebo arm (2%). Similarly, fostamatinib led to greater improvements compared to placebo in all secondary outcomes but these appear to decrease over time. For example, the pooled percentage of people with a platelet count higher than 50,000 per microlitre at week 12 in the fostamatinib arm was 23% compared to 16% at week 24. The committee concluded that fostamatinib increases platelet levels, but the proportion of people whose disease responds is moderate and decreases over time.

**The criteria for non-response and stopping treatment in the FIT clinical trials does not reflect NHS clinical practice**

3.7 The criteria used to define non-response in the FIT1 and FIT2 clinical trials and the FIT3 extension study were a platelet count of less than 50,000 per microlitre or an increase of less than 20,000 per microlitre for people with baseline platelet counts of less than 15,000 per microlitre. The company stated that the 50,000 per microlitre threshold was a regulatory requirement. However, the clinical experts explained that less stringent definitions of response are typically used in practice. This is because platelet counts can drop between visits as a result of infections or other clinical characteristics without substantially affecting the overall response to treatment. They noted they would consider platelet counts of more than 30,000 per microlitre or doubling of platelet counts from the treatment starting point as an acceptable response (see section 3.3). They would stop treatment if there were side effects or if platelet counts dropped to baseline levels or below 20,000 to 30,000 per microlitre in more refractory disease. In the FIT trials, treatment with fostamatinib was stopped if a platelet count higher than 50,000 per microlitre after 12 weeks was not achieved. The committee concluded that the criteria for non-response and stopping treatment do not reflect clinical practice.
The results of the FIT clinical trials are likely to be generalisable to NHS clinical practice

3.8 The average age at baseline in the FIT1 and FIT2 clinical trials was between 53 and 54. The ERG was concerned that people enrolled in the FIT clinical trials were about 10 years younger than clinical practice (65 or over) and had a lower risk of bleeding. Bleeding risk increases with age. The clinical experts highlighted that fostamatinib is likely to work equally well in clinical practice regardless of age. The committee concluded that the results of the FIT clinical trials are likely to be generalisable to NHS practice.

Evidence from published literature should inform the comparison between fostamatinib and comparators

3.9 The committee recalled that there were no data directly comparing fostamatinib with rituximab or mycophenolate. Although the company selected rituximab as the comparator, it did not present any clinical evidence based on published literature. Instead the company used opinions from clinical experts. Evidence for rituximab for treating ITP is available from observational studies, small clinical trials and meta-analyses and is presented in a 2014 NICE evidence summary. The ERG highlighted that there are public network meta-analyses about treatments for ITP, which include randomised clinical trials of rituximab compared with placebo. The ERG also noted a recent network meta-analysis in which fostamatinib is compared with rituximab but cautioned that it may have methodological limitations. The company explained that it had not done a network meta-analysis because the study design, duration and definitions of outcomes were too different between fostamatinib and rituximab. The committee acknowledged the differences between studies and the uncertainty of the estimates. However, it stated that estimates based on published literature would better inform the appraisal and are preferable to opinion from clinical experts. The committee concluded that
evidence from published literature should inform the comparison between fostamatinib, rituximab and mycophenolate.

The company’s economic model

A scenario analysis combining partial and complete response would be useful

3.10 The company used a Markov cohort state transition model to estimate the cost effectiveness of fostamatinib compared with rituximab. The model cohort was split into 2 groups based on an intracranial bleed occurring. The model included 3 health states in each group: response (a platelet count of more than 50,000 per microlitre), partial response (a platelet count of 30,000 to 50,000 per microlitre) and non-response (a platelet count of less than 30,000 per microlitre). The probability of being in each state was based on pooled data from the FIT1 and FIT2 clinical trials, and the FIT3 extension study. The model included a lifetime time horizon. The clinical experts noted that intracranial bleeding is a very rare event, but it is associated with substantial disability and morbidity, which may also affect carers’ quality of life. The clinical experts explained that health states split into non-response (platelet count less than 30,000 per microlitre) and response (platelet count more than 30,000 per microlitre) would better reflect clinical practice (see section 3.3). The ERG noted that combining the partial response and response health states would mean that the transition probabilities are based on more data. The company highlighted that the platelet counts used to inform the model health states are based on previous technology appraisals and regulatory requirements. The committee noted that it was unclear if a different model structure would affect the results, and by how much. It concluded that it would be useful to see a scenario analysis combining the partial response and response health states.
The company’s modelling assumptions for rituximab do not reflect published evidence

3.11 The committee recalled that the company used clinical expert opinion to support its assumptions about rituximab’s effectiveness. The company assumed that for people having treatment with rituximab, 30% will have a platelet count response over 30,000 per microlitre and 30% will have a platelet count response of 50,000 per microlitre. Also, it assumed the length of response with rituximab is 16 weeks. The ERG noted that there is published evidence for rituximab and proposed alternative assumptions based on it (see section 3.9). The response rate for platelet count over 50,000 per microlitre was 57%, based on a systematic review and meta-analysis of uncontrolled prospective and retrospective observational studies (Auger et al. 2012). The ERG assumed that the remaining 43% represented the non-response rate (platelet count below 30,000 per microlitre). The ERG sourced the length of response with rituximab of 49 weeks from the same systematic review (Auger et al. 2012). The ERG stated that the published evidence aligned with the expectation of its clinical expert, but that it comes from a naive comparison and should be interpreted with caution. The committee acknowledged the limitations of the published evidence. However, it concluded that the company’s modelling assumptions for rituximab do not reflect the available evidence.

Subsequent treatments should be modelled consistently between arms and include all relevant sequences

3.12 In the company’s model, people who take fostamatinib move to ‘watch and rescue’ treatment if their platelet count falls below 30,000 per microlitre (non-response). However, in the model people who have rituximab do not move to watch and rescue treatment, so they remain in the less than 30,000 per microlitre health state and can never achieve a higher platelet count than 30,000 per microlitre after cycle 4 in the model. This leads to a worse outcome than was seen with placebo in the fostamatinib clinical trials. The company explained that their clinical

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Issue date: November 2020
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experts had advised them that in clinical practice, people do not have other therapies at the same time as rituximab. The clinical experts agreed but noted that rituximab is only used for a short amount of time. After that, people would be offered some form of treatment in practice to raise their platelet counts higher than 30,000 per microtitre. The ERG presented alternative analyses in which people in the rituximab arm were able to have rescue therapies after loss of response. This substantially increased the cost-effectiveness estimate compared with the company’s base case. The committee noted that some people who take fostamatinib and do not have a response may go on to have rituximab, rather than ‘watch and rescue’ treatment. It concluded that subsequent treatments should be modelled consistently between arms and include all relevant sequences.

Two doses of rituximab are used in clinical practice and both should be used in decision making

3.13 The committee recalled from the NICE evidence summary of rituximab that 2 doses have been studied in trials. A higher dose of 375 mg per m² of body surface area per week has been used in most studies of rituximab. However, more recent studies have used 100 mg per week. Also, international guidelines for ITP recommend 100 mg per week as an alternative dosing schedule. Commissioning statements from several clinical commissioning groups in the NHS exclusively recommend the lower dose. One clinical expert explained she uses a dosing schedule of 100 mg per week. She noted that data from an ITP registry suggests this dose achieves effects equivalent to the 375 mg per m² of body surface area per week regimen. The other clinical expert noted he uses the higher dose in practice. The committee concluded that although the dose of rituximab used in clinical practice varies, the lower dose is more likely to be used. However, it would consider both in decision making.
The ERG’s assumptions about intravenous immunoglobulin and oral prednisolone for surgical prophylaxis reflect clinical practice

3.14 The company assumed that the treatments used to increase the platelet count of people with ITP needing surgery are the same as the ones used for an active rescue event. These included intravenous immunoglobulin, intravenous methylprednisolone and platelet transfusions, but not oral prednisolone. However, the ERG noted that only 1 course of treatment is used, and this is based on the type of surgery (minor or major). It suggested that intravenous immunoglobulin was used for major surgery, which the ERG’s clinical expert estimated accounts for 44% of people having surgery. Oral prednisolone was used for minor surgery in the remaining 56% of people. This affected the cost-effectiveness estimates because prednisolone costs much less than immunoglobulin. The clinical experts explained that oral prednisolone is used in clinical practice, contrary to the company’s assumption. Also, they emphasised that the use of surgical prophylaxis therapy depends on surgery timing. For example, intravenous immunoglobulin has a quicker response time than oral prednisolone. The clinical experts noted that the 44% figure for intravenous immunoglobulin may be an overestimate based on its use in the UK. Oral prednisolone is more likely to be used, especially if people have had a response to it before, and because it can raise platelet counts to acceptable levels even for major surgery (higher than 80,000 per microlitre). The committee concluded that the ERG’s assumptions more closely reflect clinical practice.

The model should capture differences in adverse events between fostamatinib and rituximab

3.15 The company assumed that the rates of adverse events with rituximab are the same as fostamatinib. The ERG noted that there is evidence from literature for rituximab adverse events and that they were different from fostamatinib. The committee recalled that rituximab is commonly associated with infusion-related reactions and more rarely with death
because of serious infections or progressive multifocal leukoencephalopathy (PML). One clinical expert highlighted that rituximab is well tolerated at the 100 mg per week dose and PML happens rarely. The committee concluded that adverse events for rituximab should be modelled separately instead of assuming they are the same as fostamatinib.

**The utility values in the model are appropriate, as is including carer quality of life**

3.16 The company sourced utility values for the model health states from published literature because of the low number of responses to the quality of life questionnaire used in the FIT clinical trials (36-Item Short Form Survey). The committee noted that the utility values used for the health states of the cohort without intracranial bleeding were sourced from NICE’s technology appraisal guidance on romiplostim. For the cohort with intracranial bleeding, the company sourced utility values from published literature and included the effect on quality of life of caring for someone after an intracranial bleed. The company also confirmed that the model only included the most severe types of intracranial bleeding, which are most likely to require caregiving. The ERG noted that including carer quality of life after an intracranial bleed only affected the cost-effectiveness estimates slightly, because it is a rare event. The committee concluded that the utility values and including carer quality of life are appropriate.

**Cost-effectiveness estimates**

**The company and the ERG’s cost-effectiveness estimates are very different**

3.17 In the company’s base-case analysis, fostamatinib was both more effective and less expensive than rituximab. The company’s analysis was based on the list price of biosimilar rituximab. The ERG’s analysis was based on the following assumptions:
- rituximab response rate and duration of response from the literature (see section 3.11)
- consistent modelling of rescue therapies between arms (see section 3.12)
- 100 mg dose of rituximab (see section 3.13).

The ERG’s analysis also included the confidential NHS commercial medicines unit price for rituximab biosimilar. The ERG’s analyses suggested that fostamatinib was more effective than rituximab, but the incremental quality-adjusted life year (QALY) gain was smaller than in the company’s analyses. Instead of costing less than rituximab, the incremental cost of fostamatinib was higher in the ERG’s analyses. Overall, this meant that the ERG’s estimate of cost effectiveness was more than £1,000,000 per QALY gained. The exact result cannot be reported because of the confidential price for rituximab.

The company and the ERG’s analyses do not reflect the committee’s preferred assumptions

3.18 The committee noted that the clinical and cost-effectiveness modelling assumptions made by the company and the ERG were very uncertain. In particular, the committee considered mycophenolate a relevant comparator (see section 3.4), but there were no analyses comparing fostamatinib with mycophenolate. The committee concluded it would prefer to see analyses based on:

- clinical effectiveness estimates for the comparators from a network meta-analysis (see section 3.9)
- modelling subsequent treatments consistently between arms (see section 3.12)
- therapies used for surgical prophylaxis in clinical practice including intravenous immunoglobulin and oral prednisolone (see section 3.13)
• treatment specific adverse event rates (see section 3.14).

The committee would also like to see scenarios in which the:

• partial response and response health states are merged (see section 3.10)
• rituximab dose is 100 mg (see section 3.13).

Innovation

Fostamatinib has a novel mechanism of action, but all benefits are captured in the modelling

3.19 The patient and clinical experts explained that fostamatinib is considered an additional treatment option, which is valuable for individualised treatment. Also, the committee noted the novel mechanism of action and the lack of immunosuppression associated with fostamatinib. The clinical experts highlighted that the rates of death because of infection are similar to rates of death because of bleeding in people with ITP. Therefore, a treatment that does not suppress immune response would be beneficial in preventing infections and subsequent deaths. The committee considered that infections should be captured under adverse events (see section 3.15). It concluded that once the adverse events are appropriately modelled all benefits would be captured.

Equalities

There are no equalities issues identified for fostamatinib

3.20 No equalities issues were identified during scoping, submission or technical engagement.
Conclusion

**Fostamatinib is not recommended**

3.21 The committee had not seen cost-effectiveness estimates with its preferred modelling assumptions, so it concluded that it could not recommend fostamatinib for treating refractory chronic immune thrombocytopenia.

4 **Proposed date for review of guidance**

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
October 2020

5 **Appraisal committee members and NICE project team**

**Appraisal committee members**

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.
The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

**NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**George Braleanu**  
Technical lead

**Ross Dent**  
Technical adviser

**Joanne Ekeledo**  
Project manager

ISBN: [to be added at publication]