NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Fostamatinib for treating refractory chronic immune thrombocytopenia [ID5095

Appraisal Committee Meeting – 10 August 2022
1st Committee meeting

This is a rapid review of published guidance TA711 and is for the consideration of a new patient access scheme proposal only

The following documents are made available to the Committee:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Final Guidance TA759 Fostamatinib for treating refractory chronic immune thrombocytopenia**

2. **Company rapid review submission** from Grifols

NICE National Institute for Health and Care Excellence

NICE guidance

Fostamatinib for treating refractory chronic immune thrombocytopenia

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

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

Rituximab or mycophenolate are treatment options for refractory chronic immune thrombocytopenia after thrombopoietin receptor agonists, or if they are not suitable. Fostamatinib would be used at the same point in the treatment pathway.

Clinical evidence shows that fostamatinib is effective compared with placebo. There is no clinical trial evidence directly comparing fostamatinib with rituximab or mycophenolate. An indirect comparison shows that fostamatinib works better than rituximab at increasing platelet counts.

The cost-effectiveness estimates for fostamatinib compared with rituximab are 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) 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; BNF online, accessed October 2020)
- £4,635 per 60-tablet pack; each tablet contains 150 mg of fostamatinib (excluding VAT; BNF 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, 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 platelet destruction, leading to a low number of platelets circulating in the blood. Platelets are a type of cell involved in blood clotting. Thrombocytopenia is usually defined as having fewer than 100,000 platelets per microlitre of blood. Signs and symptoms include bruising easily, the appearance of red spots under the skin (petechiae), fatigue and bleeding. Frequency and severity of bleeding may differ in people with similar platelet counts. Some have no bleeding, some bleed from the skin, nose, or urinary tract and others have more serious intracranial and gastrointestinal bleeding. Because of the risk of bleeding, people may 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) are available, they do not work for everyone, and some people cannot take them. The patient and clinical experts explained that some of the treatment options suppress the immune system and increase 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 ITP involves high-dose oral corticosteroids or intravenous immunoglobulin (IVIg). Later treatments include:

- TPO-RAs (see NICE's technology appraisal guidance on romiplostim and eltrombopag)
- rituximab, which does not have a marketing authorisation for ITP
- surgical removal of the spleen (splenectomy)
- azathioprine, mycophenolate, cyclosporine, dapsone and danazol.

The clinical experts explained that the choice of treatment after corticosteroids or IVIg depends on time to relapse, but clinicians are most likely to offer TPO-RAs. They noted that clinicians avoid offering splenectomy in the first year after diagnosis and are unlikely to offer it 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 rarely used because of adverse effects, and dapsone is used as a last resort. The committee understood that danazol is no longer available in the UK. For people with platelet counts higher than 30,000 per microlitre of blood and at low risk of bleeding, clinicians may adopt a 'watch and rescue' approach. A patient expert explained that once his platelet count had stabilised after treatment with IVIg, 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 platelet count and other risk factors for bleeding, such as age and use of anti-platelet treatment. They explained that the objective of treatment is a platelet count higher than 30,000 per microlitre of blood to reduce the risk of bleeding. Platelet counts higher than 50,000 per microlitre may be used as a target for maintenance treatment, to avoid fluctuating platelet levels and minimise the chance of counts dropping below 30,000 per microlitre. The committee appreciated that treatment aims to achieve platelet counts lower than those used to define thrombocytopenia. It concluded that treatment decisions were 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 proposed 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. They noted that other treatments such as rituximab and mycophenolate may be used after TPO-RAs at the point when the company proposed using fostamatinib. The clinical experts noted that rituximab is considered more effective for young women and people with other autoimmune conditions. However, some people may be concerned about rituximab's immunosuppressive effects so would prefer an alternative treatment. The clinical experts also highlighted that for people at risk of blood clots, TPO-RAs would not be suitable so fostamatinib would be considered instead. They also noted that other treatments such as rituximab and mycophenolate may be used after TPO-RAs, but before fostamatinib. The committee acknowledged that treatment is individualised. It 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 As relevant comparators, NICE's final scope included the TPO-RAs romiplostim and eltrombopag, rituximab, splenectomy, cytotoxic agents, dapsone, danazol and 'watch and rescue'. However, the company excluded romiplostim and eltrombopag based on its positioning of fostamatinib after TPO-RAs, or when TPO-RAs are unsuitable. The company selected rituximab as the only comparator. For all other comparators, the company argued that there was little evidence to support comparisons with fostamatinib. The clinical experts agreed that many treatments used in practice do not have robust clinical trial data. They also noted that rituximab and mycophenolate are often used in clinical practice at the same point in the treatment pathway as the company proposed for fostamatinib (see section 3.4). The committee concluded that the relevant comparators for fostamatinib are rituximab and mycophenolate.

Clinical effectiveness

Fostamatinib is effective at increasing platelet count compared with placebo, based on the FIT trials

3.6 FIT1 and FIT2 are multinational, double-blind, randomised, phase 3 trials of the

same design comparing fostamatinib with placebo. Both trials included adults with persistent or chronic ITP that had not responded to at least 1 treatment. Their average platelet count was less than 30,000 per microlitre of blood. The primary endpoint in both trials was stable platelet response. This was defined as a platelet count of 50,000 per microlitre or more in at least 4 out of 6 assessments between week 14 and week 24. Secondary outcomes included:

- the percentage of people with a platelet count higher than 50,000 per microlitre at week 12 and week 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 week 12 and week 24, after a platelet count of less than 15,000 per microlitre at baseline
- bleeding frequency and severity, measured by the Immune Thrombocytopenic Purpura Bleeding Scale and World Health Organization bleeding scores.

People randomised to fostamatinib had 100 mg twice a day initially. This could be increased to 150 mg twice a day at week 4 if platelet count remained below 50,000 per microlitre and fostamatinib was well tolerated. Rescue treatments were allowed as needed in both treatment arms. People in FIT1 and FIT2 were invited to take part in FIT3, a 5-year open-label extension study, if they:

- completed the full 24 weeks of treatment or
- stopped the trials after at least 12 weeks of double-blind treatment because of lack of efficacy (including at least 4 weeks at the 150 mg dose of fostamatinib or placebo).

In FIT3, the initial fostamatinib dose was the dose that produced a platelet response in FIT1 and FIT2. If there was no platelet response in FIT1 and FIT2, the initial dose was 100 mg twice a day.

Pooled results from FIT1 and FIT2 showed that rates of stable response were higher in the fostamatinib arm (18%) than in the placebo arm (2%). Fostamatinib led to greater improvements than placebo for all secondary outcomes, but these benefits appeared 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 with 16% at week 24. The committee concluded that fostamatinib increased platelet levels, but only about 1 in 5 people had a platelet response, which may decrease over time.

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

3.7 Starting from week 12, the criteria used to define non-response in FIT1, FIT2 and the FIT3 extension study were:

- a platelet count of less than 50,000 per microlitre of blood or
- an increase of less than 20,000 per microlitre for people with baseline platelet counts of less than 15,000 per microlitre.

People with non-response could withdraw from the study. The clinical experts explained that less stringent definitions of response are typically used in practice. This is because platelet counts can vary as a result of infections or other clinical characteristics and may not affect the overall response to treatment. They noted that generally they would consider platelet counts of more than 30,000 per microlitre and doubling of platelet counts from the treatment starting point as an acceptable response (see section 3.3). They would recommend stopping treatment if:

- response was not acceptable
- adverse effects were intolerable
- platelet counts dropped to baseline levels or below 20,000 to 30,000 per microlitre.

The committee concluded that the criteria for non-response and stopping treatment in the FIT trials did 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 FIT1 and FIT2 was between 53 and 54 years. The ERG was concerned that people enrolled in these trials were about 10 years younger than in clinical practice and had a lower risk of bleeding, which 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, but the absolute benefit may differ from the trials.

Network meta-analyses 2 and 3 have limitations but are

considered for decision making

3.9 The committee recalled that there was no evidence directly comparing fostamatinib with rituximab or mycophenolate. The company's base case discussed at the first committee meeting included rituximab as the only relevant comparator. Clinical efficacy data for rituximab was based on clinical expert opinion, rather than published literature. After consultation, the company did a network meta-analysis comparing fostamatinib with rituximab, with an outcome of overall platelet response. The definition of overall platelet response varied across studies included within the meta-analysis, so the company did 3 separate analyses:

- Analysis 1 was based on the primary definition of response in each study and included FIT1, FIT2 and 4 rituximab studies.
- Analysis 2 used alternative definitions for response. Each focused on platelet counts greater than 30,000 per microlitre of blood and at least doubling from baseline, with and without rescue treatments at various time points. It included the same studies as analysis 1.
- Analysis 3 used the definition of response as an increase in platelet count greater than 30,000 per microlitre, at least doubling from baseline and without rescue treatment at 4 weeks. It included only FIT1, FIT2 and the Ghanima et al. (2015) study for rituximab.

The company preferred analysis 2 because the endpoints varied less than in analysis 1. The ERG noted that analysis 2 included both randomised and non-randomised evidence, which the Cochrane Handbook (11.3.4, version 6.2, 2021) does not recommend because of bias. The ERG preferred analysis 3, which included only randomised studies. The analyses showed that fostamatinib was more effective than rituximab, and rituximab was no better than placebo. The committee noted that the size of benefit differed between analyses. Analysis 2 showed a 4-fold increase in the odds of having a response with fostamatinib compared with rituximab, whereas analysis 3 showed a 3-fold increase. Analyses 1 and 2 included 4 different dosages of rituximab:

- 375 mg/m^2 body surface area per week for 4 weeks
- 100 mg fixed dose per week for 4 weeks

- 375 mg/m^2 per week for 2 weeks in people with early response and for 4 weeks in the others and
- 750 mg/m^2 per week for 2 weeks.

Analysis 3 included only the rituximab dosage of 375 mg/m^2 per week for 4 weeks. The ERG clinical adviser noted that 375 mg/m^2 per week for 4 weeks and the 100 mg fixed dose are used in clinical practice and are the most relevant (see section 3.16). The committee noted that the non-randomised study (Zaja et al. 2012) was the only study that included the rituximab 100 mg fixed dose. The ERG explained that when the company used analysis 2 in its model, it did not use the estimates from Zaja et al. (2012) to inform the efficacy of the rituximab 100 mg dose. Instead, the company assumed that the efficacy of rituximab 100 mg was the same as that of rituximab 375 mg/m^2. The ERG advised that this likely favoured rituximab, although it expected the size of bias to be small. When using analysis 3, the company and the ERG also assumed that both doses of rituximab had the same efficacy. The committee noted that analysis 2 also included Arnold et al. (2012), a randomised controlled trial comparing 375 mg/m^2 rituximab with placebo. It noted that the company could have done an additional analysis comparing the FIT trials with only the Ghanima et al. (2015) and Arnold et al. (2012) trials, because both assessed the efficacy of rituximab 375 mg/m^2. The committee agreed that analysis 1 was the least relevant because the endpoint definitions varied most across studies. It concluded that it would consider both analyses 2 and 3 in its decision making, because they both had limitations.

The clinical efficacy of mycophenolate is uncertain

3.10 The company excluded mycophenolate from its network meta-analysis because it did not identify any randomised trials. It noted that mycophenolate does not have a marketing authorisation for ITP. The company presented data from the UK ITP registry and a panel of clinical experts, who indicated that a substantial proportion of people do have mycophenolate after TPO-RAs. (The exact proportion is confidential and cannot be reported here). The committee noted that this further supports its use in NHS clinical practice. The ERG confirmed the lack of evidence for mycophenolate. The committee noted that relevant comparators are selected based on their routine use in NHS clinical practice, regardless of whether they have a marketing authorisation for that indication. It also noted that rituximab does not have a marketing authorisation for ITP, but the company included it as a relevant comparator. The committee maintained that both rituximab and mycophenolate are relevant comparators for

fostamatinib (see section 3.5). But it acknowledged that there is no published evidence showing how well mycophenolate works for people with ITP.

The company's economic model

The company's approach to merging partial and complete response health states has limitations but best reflects clinical practice

3.11 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 whether a person had intracranial bleeding. The company's original model included 3 health states in each group:

- response (a platelet count of more than 50,000 per microlitre of blood)
- 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 company explained that its thresholds were informed by the latest ITP consensus (2019) and the approach taken in previous NICE submissions for eltrombopag and romiplostim. The company estimated the probability of being in each state on pooled data from FIT1, FIT2 and the FIT3 extension study. The model included a lifetime time horizon. The clinical experts noted that intracranial bleeding is a 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). After consultation, the company merged partial and complete response into a single response health state. That is, the company's revised model included only 2 health states, non-response (platelet count less than 30,000 per microlitre) and response (platelet count more than 30,000 per microlitre). The company did a scenario analysis using the original health states, noting that it had a small impact on cost effectiveness. The ERG agreed that a model with 2 health states better reflected clinical practice than the 3-health state model. But it had concerns with the company's methodology because the revised model continued to follow a 3-state structure. The company simply set most inputs for partial response to be equal to the full response health state. The ERG noted that the company should have recalculated how likely people are to move between the 2 health states using data from the FIT trials. Instead, the company used the probabilities of moving between 3 health states from its original model. The ERG explained that these probabilities were based on a low number of events in the FIT trials so were uncertain. These uncertainties were further increased when extrapolating the probabilities over the model's lifetime time horizon and by the approach taken to apply the network meta-analysis results. The committee acknowledged the limitations of the company's approach to merging the health states. But it agreed that it preferred the merged 2-health state structure because it better reflected clinical practice than the 3-health state model.

The revised model criteria for non-response and stopping treatment are in line with NHS practice but should be applied at 12 weeks

3.12 The committee recalled that the criteria for non-response and stopping treatment in the FIT trials were not in line with clinical practice (see section 3.7). The company's original model followed the stopping rule from the FIT trials.

However, after consultation, the company changed the stopping rule in its economic model to a platelet count of less than 30,000 per microlitre of blood, in line with clinical practice. The ERG explained that the model applied this stopping rule at 12 weeks, with a half-cycle correction. Applying a half-cycle correction effectively means that treatment would be stopped 2 weeks earlier, at 10 weeks, if a platelet count of 30,000 per microlitre or more was not reached. The company noted this was a conservative assumption because a clinical expert panel advised that treatment could be stopped earlier, by 8 weeks, if platelet response was not reached. The committee noted that fostamatinib's marketing authorisation includes a 12-week stopping rule if platelet count is 'not sufficient'. The ERG explained that removing the half-cycle correction applied to the stopping rule increased the cost-effectiveness estimates. This was because treatment costs for people whose disease does not respond to treatment are incurred for longer. The committee concluded that the revised criteria for non-response and stopping were in line with clinical practice but should be applied at 12 weeks, without a half-cycle correction.

The company's revised approach to modelling subsequent treatments is acceptable

3.13 In the company's original submission, people who had fostamatinib moved to watch and rescue treatment if their platelet count fell below 30,000 per microlitre of blood (non-response). However, people who had rituximab did not move to watch and rescue treatment. Instead, they remained in the less than 30,000 per microlitre health state and could never have a platelet count higher than 30,000 per microlitre after cycle 4 in the model. This led to a worse modelled outcome than was seen with placebo in the fostamatinib clinical trials. The company explained that its clinical experts had advised that in clinical practice, people do not have other treatments at the same time as rituximab. The clinical experts at the committee meeting agreed but noted that rituximab is used only for a short time. After that, treatment is offered to raise platelet counts to a level higher than 30,000 per microlitre. The committee also noted that some people who do not have a response to fostamatinib may get rituximab, rather than watch and rescue treatment. At its first meeting, the committee concluded that subsequent treatments should be modelled consistently between arms and include all relevant sequences. After consultation, the company updated its base case to allow watch and rescue treatment after rituximab, when platelet count is less than 30,000 per

microlitre. The ERG confirmed that the company applied the change correctly. The committee noted that the company's revised approach did not include all relevant treatment sequences. For example, it did not include an option of having rituximab after fostamatinib. The ERG explained that modelling a full treatment sequence across the pathway was difficult because of evidence limitations. This was a key model limitation and contributed to the overall uncertainty. The committee concluded that the company's revised approach to modelling subsequent treatments had limitations but was acceptable for decision making.

It is not appropriate to assume that people can taper or stop treatment without any loss of clinical benefit

3.14 The company explained that its base case did not include tapering dosages or stopping treatment in people with a sustained platelet response. It assumed that those people remain on the full treatment dose until loss of response or death. However, the company stated that tapering was common with other ITP treatments and was likely with fostamatinib. The company did a scenario analysis in which it assumed that 40% of people with a sustained platelet response to fostamatinib (platelet counts above 30,000 per microlitre of blood after 1 year) stop active treatment but maintain the full clinical benefit. This scenario improved fostamatinib's cost-effectiveness estimates, as did an ERG scenario in which only people with a sustained platelet count of more than 50,000 per microlitre taper treatment. But, the company recognised that it did not have data to support tapering or stopping fostamatinib without losing benefit. The committee recognised that maintaining treatment benefit after tapering or stopping treatment was speculative. It also noted that fostamatinib's marketing authorisation does not include treatment tapering or stopping in people with a sustained platelet response. The committee concluded that it is not appropriate to assume that people with sustained platelet response can taper or stop treatment without losing clinical benefit.

Basing the use of rescue treatment on UK ITP registry data is likely to reflect clinical practice

3.15 In its original base case, the company used FIT trials data to inform the frequency and type of rescue treatments. After consultation, it used the UK ITP registry data instead. The use of rescue treatments in the UK ITP registry

depended on platelet count and included IVIg, intravenous methylprednisolone, platelet transfusion, oral prednisolone and oral dexamethasone. The company justified using the UK ITP registry because:

- the FIT trials included locations outside the UK
- in the trials, people had their platelet counts measured more often than expected in clinical practice and
- the trial populations had a relatively lower risk of bleeding.

In its base case, the company applied frequency and type of rescue treatments separately for each health state defined by platelet count. The non-response health state had greater costs, driven by the increased frequency of events needing rescue treatments and increased use of IVIgG compared with oral prednisolone. The ERG accepted that the UK ITP registry data is likely generalisable to NHS clinical practice and used this source in its base case. However, the ERG was concerned that the company did not provide data comparing the populations in the UK ITP registry and FIT trials. The company explained that it could not get demographic information from the UK ITP registry. But it noted that everyone included in the analysis had previously had treatment with TPO-RAs, consistent with the company's positioning of fostamatinib in the treatment pathway (see section 3.4). The ERG was concerned about using different data sources to inform different parts of the model. For example, using the UK ITP registry for frequency and type of rescue treatment, and the company's network meta-analysis for the probability of reaching platelet response with watch and rescue. To address this, the ERG did a scenario analysis using the FIT trial data to inform all inputs for rescue treatments and for prophylaxis before surgery (see section 3.17). The committee acknowledged the limitations of the company's approach. But it concluded that the UK ITP registry was likely to reflect use of rescue treatment in NHS clinical practice.

In clinical practice, 2 doses of rituximab are used, and both should be included in the model

3.16 The committee recalled that the trials included 2 doses of rituximab (see section 3.9). In the 2014 NICE evidence summary for rituximab in ITP, most studies included the higher dose of 375 mg/m^2 per week. Some used a fixed dose of 100 mg per week. International guidelines for ITP recognised that 100 mg per week is an alternative dosing schedule. Statements from several NHS clinical

commissioning groups recommended only the lower dose. One clinical expert explained that she offers a dose of 100 mg per week. She noted that ITP registry data suggested that the effects of this dose are equivalent to the 375 mg/m^2 per week dose. The other clinical expert noted that he uses the higher dose in practice. After consultation, the company analysed the use of rituximab in the UK ITP registry in people who had prior treatment with TPO-RAs. It found that both doses were used (exact usage is confidential and cannot be reported here). The company updated its base case to include a mean dose of rituximab calculated from the UK ITP registry. It also did a scenario analysis using the 100 mg rituximab dose. The ERG was concerned that the company may have underestimated the mean rituximab dose in the UK ITP registry. The ERG corrected this, which led to a small increase in the mean dose. However, it explained that it preferred to use the lower, fixed 100 mg dose which was increasingly recommended for use in NHS clinical practice. The committee considered the clinical advice and UK ITP registry data and agreed that both rituximab doses are used in NHS clinical practice. Therefore, it concluded that both doses are relevant and should be included in the model.

The company's revised approach to modelling prophylaxis before surgery reflects clinical practice

3.17 People who have a platelet count below 30,000 per microlitre of blood may need prophylactic treatment to increase platelet count before surgery. In its original submission, the company assumed that prophylactic treatments were the same as rescue treatments. These include IVIgG, intravenous methylprednisolone and platelet transfusions, but not oral prednisolone. At the first committee meeting, the ERG explained that only 1 course of treatment is used, and this is based on the type of surgery (minor or major). It suggested that IVIgG 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 IVIgG. 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 prophylaxis before surgery depends on the timing of the surgery. For example, IVIgG works more quickly than oral prednisolone. After consultation, the company asked a panel of 8 clinical experts about which treatments are used as prophylaxis before surgery in NHS clinical practice. Oral prednisolone was the

most frequently used treatment for both minor (average use 54% [range 0% to 100%]) and major surgery (62% [0% to 100%]). This was followed by IVIgG for both minor (45% [10% to 75%]) and major (49% [10% to 85%]) surgery. The company assumed the same proportions of minor (56%) and major (44%) surgery as the ERG. The ERG agreed with the company's approach to estimating the use of prophylaxis before surgery and noted it was consistent with its expert opinion. The committee was satisfied that the revised company base case was in line with NHS clinical practice.

The company's revised approach to modelling adverse events is acceptable

3.18 The company's base case discussed at the first committee meeting used pooled data from FIT1 and FIT2 for people 65 years and over to estimate the rate of adverse events for fostamatinib. This age group was considered more relevant because it is in line with the starting age in the model. This group had a higher rate of adverse events than the younger people in the trial. The company assumed that the rate of adverse events with rituximab was the same as with fostamatinib. At its first meeting, the committee concluded that adverse events with fostamatinib and rituximab were different and should be modelled separately. After consultation, the company agreed that rituximab was associated with fewer adverse events than fostamatinib and watch and rescue treatments. In its revised base case, adverse events with rituximab were based on a randomised controlled trial comparing 375 mg/m^2 rituximab with placebo (Ghanima et al. 2015). The ERG was satisfied with the company's revised approach but noted some limitations. Rituximab can cause very rare fatal progressive multifocal leukoencephalopathy, which the company excluded from its analysis. The median age in the Ghanima et al. (2015) trial was 46 years, compared with the starting age in the model of 65 years. Adverse events in older people are likely to be more frequent, as seen with fostamatinib in the FIT trials. The committee noted that these assumptions likely favoured rituximab. The ERG explained that the rate of adverse events with the 100 mg weekly dose was likely to be lower than with the higher dose. The committee recalled that at its first meeting, a clinical expert explained that the 100 mg per week dose is well tolerated. The committee noted that assuming equal rates of adverse events with both doses favours fostamatinib. The ERG also explained that the company applied adverse events for rituximab for as long as response was maintained, even though it is only taken for 4 weeks (see section 3.9). However,

the ERG advised that this likely has a small impact on the cost-effectiveness estimates, because cycle-specific costs and disutilities of adverse events with watch and rescue are similar to rituximab. In terms of modelling adverse events with fostamatinib, the company applied the same rate of adverse events for the full duration of treatment when in the response health state. The ERG noted that the company could instead have used the longest available data from the FIT3 extension study to model long-term adverse events with fostamatinib. However, the company explained that this data was not yet available. But it noted that new long-term safety issues were unlikely to emerge because fostamatinib's long-term safety profile in rheumatoid arthritis was consistent with the earlier data in that disease. The committee acknowledged the limitations of the company's approach to modelling adverse events with fostamatinib and rituximab. It noted that overall, it was not clear if this approach favoured rituximab or fostamatinib. However, it concluded that the company's approach was acceptable for decision making.

The company's revised base case overestimates the risk of dying from ITP

3.19 In the company's original base case, it estimated the risk of dying in the non-response health state from the General Practice Research Database (Schoonen et al. 2009). The risk of dying was 1.6 times higher than that of the age- and sex-matched general population, with 13% of deaths from bleeding and 19% from infection. The risk of death was reported for everyone diagnosed with ITP, that is, it was not reported separately by platelet count. The company assumed all excess deaths happened in the lowest platelet count health state (non-response). All other health states had a risk of death that matched the general population. The ERG noted that assuming all deaths in Schoonen et al. (2009) happened in the non-response health state was an important limitation of the company's approach. After consultation, the company identified 2 new studies reporting the risk of dying from ITP and used them in its revised base case. In the 3-health state model, the hazard ratio for mortality was 4.2 in the non-response state (Portielje et al. 2001), 2.5 in the partial response state (Adelborg et al. 2019) and 1.0 in the complete response health state. The 2-health state model used a hazard ratio for mortality of 4.2 in the non-response health state and 1.0 in the merged response health state. The ERG had concerns with the new sources:

- Portielje et al. (2001) reported hazard ratios for mortality specifically in people with platelet counts below 30,000 per microlitre of blood but the study had a small sample size and was not based in the UK.
- Adelborg et al. (2019) was a larger study but reported hazard ratios for everyone with a platelet count less than 50,000 per microlitre.

  The clinical experts agreed with the ERG that using Adelborg et al. (2019) for the partial response (platelet count of 30,000 to 50,000 per microlitre) health state was not appropriate. This was because most deaths in people with platelet counts below 50,000 per microlitre could be a result of deaths in people with a platelet count below 30,000 per microlitre. This meant that the model may overestimate mortality in the partial response state. The committee discussed the 3 potential sources of mortality data, noting that all have limitations. It recalled clinical expert advice that many factors influence the risk of dying from ITP, including platelet count, bleeding, age, and treatment. It also recalled advice that treatment had changed over time, and the risk of dying from ITP is now lower than in the past. In the past, deaths related to infection were as high as for bleeding, and likely reflected higher use of splenectomy and heavy immunosuppression. But since the introduction of TPO-RAs, it is rare for people to have chronic platelet counts below 20,000 to 30,000 per microlitre, and rare to have deaths from ITP treatments. The committee agreed that Portielje et al. (2001) may overestimate the current risk of dying from ITP because of the progress in treatment for this disease. It also noted that the risk of dying from intracranial bleeding is already accounted for in the model. So, using hazard ratios for mortality from Portielje et al. (2001) would overestimate mortality in people without intracranial bleeding. Also, the committee discussed that the company did not provide any evidence that fostamatinib reduces the risk of dying from ITP. The model predicts such a reduction, based on less time spent in the non-response health state compared with rituximab. But the committee noted that without any evidence to support this, the effect of fostamatinib on the risk of dying was uncertain. It also noted that mortality assumptions have the biggest effect on the cost-effectiveness estimates. The committee concluded that the company's revised approach overestimates the risk of dying from ITP. It preferred the company's original approach, using estimates from the General Practice Research Database (Schoonen et al. 2009).

The utility values in the model are appropriate, including those for carers

3.20 The company used 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 (SF-36). The committee noted that the company used utility values for the health states of the group without intracranial bleeding from NICE's technology appraisal guidance on romiplostim. The company's original base case applied a lower utility value for people in the partial and no response health states than in the response health state. This was because the romiplostim appraisal used different utility values for people with platelet counts of 50,000 per microlitre of blood or more (response) and those with platelet counts below 50,000 per microlitre (non-response). In its revised base case after consultation, the company applied different utility values to the response (platelet count of 30,000 per microlitre or more) and the non-response health states (platelet count below 30,000 per microlitre). The committee acknowledged that people with platelet counts below 30,000 per microlitre would be unlikely to feel worse than people with platelet counts of 30,000 per microlitre or above. But if a person knows that they are at higher risk of bleeding, this could cause anxiety and affect their daily life if they avoid their usual activities. For the group who had severe intracranial bleeding and for their carers, the company used published utility values. The ERG noted that because intracranial bleeding is rare, including carer quality of life affected the cost-effectiveness estimates minimally. The company also applied a transient disutility for people with other bleeds, adverse events or when needing rescue treatment. The committee concluded that the utility values in the model, including those for carers of people who had severe intracranial bleeding, were appropriate.

The ERG's exploratory analysis for mycophenolate assumes equal efficacy and safety to rituximab, which is uncertain

3.21 The ERG did an analysis for mycophenolate as a comparator, assuming equal efficacy and safety to rituximab. It assumed that mycophenolate is taken twice a day as a 500 mg tablet and stopped at 12 weeks if platelet response is not reached, or later if this response is lost. The analysis predicted that median treatment duration is 12 to 16 weeks, which is longer than the median duration of mycophenolate treatment in the UK ITP registry (exact figures are confidential and cannot be reported here). The model predicted that mycophenolate had higher total treatment costs than 100 mg rituximab at its list price, but lower than 375 mg/m^2 rituximab at its list price. The ERG highlighted that this analysis is exploratory, because assuming equal efficacy of

rituximab and mycophenolate is uncertain. It noted that there were lower complete and partial responses to mycophenolate in Taylor et al. (2015) compared with responses to rituximab in Ghanima et al. (2015). The ERG emphasised that this comparison was highly uncertain because it reflects a naive comparison between 2 different studies, and Taylor et al. (2015) was a small, non-randomised, retrospective study. Clinical experts confirmed that assuming equal efficacy of mycophenolate and rituximab is uncertain. They explained that there are no head-to-head comparisons between these 2 treatments, but they expect their efficacy and safety to differ. The 2 drugs are used for different groups of people. Mycophenolate is generally well tolerated and taken as a tablet, so it does not cause infusion-related reactions. The committee agreed that mycophenolate was unlikely to have the same efficacy and safety as rituximab and this was a limitation of the exploratory analysis. It concluded that it would focus on the comparison of fostamatinib with rituximab in its decision making.

Cost-effectiveness estimates

The most likely cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources

3.22 The committee discussed the company's base case, revised after consultation. It noted how the company attempted to address its preferences from its first meeting, namely:

- using clinical effectiveness estimates for the comparators from a network meta-analysis (see section 3.9)
- modelling subsequent treatments consistently between arms (see section 3.13)
- using prophylactic treatments before surgery in line with clinical practice, that is, including both IVIgG and oral prednisolone (see section 3.17)
- including treatment-specific adverse event rates (see section 3.18)
- considering a scenario analysis in which partial response and response health states are merged (see section 3.11)

- considering a scenario analysis with 100 mg rituximab (see section 3.16).

The ERG had concerns about the company's revised base case. So, the ERG presented its preferred base case, applying the following changes to the company's base case:

- using network meta-analysis 3 rather than analysis 2, to inform clinical effectiveness estimates for the comparators (see section 3.9)
- following the 3-health state model structure, rather than the 2-health state model with merged response health state (see section 3.11)
- using the 100 mg rituximab dose, rather than the average rituximab dose from the UK ITP registry (see section 3.16).

The ERG's analysis also included the confidential NHS Commercial Medicines Unit price for biosimilar rituximab.

The committee did not agree with the updated preferences for the stopping rule (see section 3.12), dosing of rituximab (see section 3.16), and hazard ratios for mortality (see section 3.19) in the company's revised base case. The committee agreed that its preferred analysis included the following assumptions:

- using both network meta-analysis 2 and 3 results (see section 3.9)
- following the 2-health state model structure (see section 3.11)
- stopping fostamatinib at 12 weeks if platelet response had not been reached (see section 3.12)
- using both doses of rituximab used in clinical practice (see section 3.16)
- using lower hazard ratios reflecting the association between the non-response health state and mortality (see section 3.19).

Applying confidential discounts for fostamatinib and rituximab, and considering its preferences, the committee noted that all the cost-effectiveness estimates were higher than what NICE normally considers an acceptable use of NHS resources regardless of which network meta-analysis results or rituximab dose was used. Because of these confidential discounts, the cost-effectiveness results cannot be reported here. Therefore, the committee could not recommend fostamatinib for use in the NHS.

Innovation

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

3.23 The patient and clinical experts value individualised treatment. The committee noted fostamatinib's novel mechanism of action and the lack of immunosuppression associated with it. This is important because the clinical experts highlighted that the rates of death from infection and from bleeding are similar in people with ITP. The committee considered that infections and other benefits are captured in the model (see section 3.18).

4 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 Braileanu and Summaya Mohammad
Technical leads

Ross Dent and Ewa Rupniewska
Technical advisers

Joanne Ekeledo
Project manager

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Accreditation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

1 Introduction

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective.

Patient access schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If companies want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (https://www.nice.org.uk/process/pmg9/chapter/introduction)
- 'Guide to the processes of technology appraisal' (https://www.nice.org.uk/process/pmg19/chapter/introduction)

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary

- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Tavlesse ® (fostamatinib disodium hexahydrate) for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments

3.2 Please outline the rationale for developing the patient access scheme.

Tavlesse® is not cost-effective at list price. Grifols believes that Tavlesse® represents a much-needed treatment option for ITP patients, and therefore proposes to enter into a simple PAS to guarantee access for underserved patients.

3.3 Please describe the type of patient access scheme.

Simple PAS. A discount is offered to the list price of Tavlesse®

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The proposed discount applies to the whole indicated population

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain

criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen?

There are no criteria for application of PAS

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All the population (100%)

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Simple PAS, in the form of confidential discount to list price.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

Simple PAS, in the form of confidential discount to list price. No additional information required.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

N/A

3.10 Please provide details of the duration of the scheme.

N/A

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any

concerns identified during the course of the appraisal? If so, how have these been addressed?

N/A

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

None of the above are available.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence'. You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

N/A. Population remains the same.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Model updated

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been implemented as a simple discount from list price of fostamatinib.

The only changes to the economic analysis are an update to the PAS price for fostamatinib, and the correction of a calculational error in cell I70 in the "Cost inputs" sheet (changed from a division to a multiplication).

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data can be found in sections B1 and B2 of the original NICE submission (uploaded to NICE docs).

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs.

No costs. Simple PAS in the form of confidential discount to list price

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

No costs. Simple PAS in the form of confidential discount to list price

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3 Base-case cost-effectiveness results (with PAS)

	Fostamatinib	Rituximab
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	[redacted]
ICER (£)	N/A	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows.[2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 4 Base-case incremental results (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 5 Base-case incremental results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1: Base case tornado diagram (with PAS) evaluating net monetary benefit (NMB)

[redacted]

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Table 6 Probabilistic mean incremental results (1000 iterations)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Figure 2: Incremental cost effectiveness plane

Figure 3: Cost-effectiveness acceptability curve

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

The company submission follows NICE requirements and focuses on scenarios which consider 1) which NMA analysis results are used to inform comparative

efficacy, 2) what percentage of patients receive each dose of rituximab, and 3) what discount from list price is applied to rituximab. Please take into account:

- NICE preferred analysis 2 and 3 of the company´s presented NMA (Network Meta-analysis) vs rituximab
- NICE considered the off-label rituximab dose of 100mg vs the company´s proposal based on the rituximab mean dose according to the UK ITP Registry
- As the rituximab discount to the NHS England is confidential, the company provides different potential discounts

The scenario results associated varying these parameters simultaneously are presented in the tables below:

Table 7. **ICER (£) incremental (QALYs) with PAS** - *List price of rituximab*

	100mg dose of rituximab	Registry mean of both relevant doses of rituximab (375mg/m^2 and 100mg)
NMA analysis 2	[redacted]	[redacted]
NMA analysis 3	[redacted]	[redacted]

Table 8. **ICER (£) incremental (QALYs) with PAS** - *Assumed 85% discount of list price of rituximab*

	100mg dose of rituximab	Registry mean of both relevant doses of rituximab (375mg/m^2 and 100mg)
NMA analysis 2	[redacted]	[redacted]
NMA analysis 3	[redacted]	[redacted]

Table 9. **ICER (£) incremental (QALYs) with PAS** - *Assumed 90% discount of list price of rituximab*

	100mg dose of rituximab	Registry mean of both relevant doses of rituximab (375mg/m^2 and 100mg)
NMA analysis 2	[redacted]	[redacted]
NMA analysis 3	[redacted]	[redacted]

Table 10. **ICER (£) incremental (QALYs) with PAS** - *Assumed 95% discount of list price of rituximab*

	100mg dose of rituximab	Registry mean of both relevant doses of rituximab (375mg/m^2 and 100mg)
NMA analysis 2	[redacted]	[redacted]
NMA analysis 3	[redacted]	[redacted]

Table 11. **ICER (£) incremental (QALYs) with PAS** - *Assumed 100% discount of list price of rituximab (zero cost)*

	100mg dose of rituximab	Registry mean of both relevant doses of rituximab (375mg/m^2 and 100mg)
NMA analysis 2	[redacted]	[redacted]

NMA analysis 3	[redacted]	[redacted]

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable. Whole indicated population eligible.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 12* Results showing the impact of patient access scheme on ICERs

	ICER for intervention versus:	
	Rituximab	
	Without PAS	**With PAS**
Scenario 1 (base-case)	£226,338	[redacted]
Scenario 2 (Using NMA analysis 3 results)	£237,247	[redacted]
Scenario 3 (100% of rituximab patients use 100mg dose)	£231,357	[redacted]
Scenario 4 (100% discount to Rituximab price)	£237,900	[redacted]
Scenario 5 (Scenarios 2 + 3 + 4)	£249,236	[redacted]

PAS: patient access scheme. (*): Note that this table is listed as table 5 in the NICE template.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

See attached PAS application form accepted by NHSE / PASLU (uploaded to NICE docs).