

CADTH Reimbursement Recommendation

Fostamatinib (Tavalisse)

Indication: For the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to other treatments

Sponsor: Medison Pharma Canada Inc.

Final recommendation: Do not reimburse

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

What Is the CADTH Reimbursement Recommendation for Tavalisse?

CADTH recommends that Tavalisse not be reimbursed by public drug plans for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP).

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials showed that after 24 weeks of treatment, Tavalisse was only modestly effective in increasing the likelihood of achieving a sustained platelet count greater than 50,000/ μ L; in addition, treatment with Tavalisse did not significantly reduce bleeding occurrence or severity compared to placebo, and whether treatment with Tavalisse improves health-related quality of life (HRQoL) is not known.
- Patients identified a need for treatments that can reduce symptoms and bleeding events and improve other quality of life measures; there was not enough evidence to show that Tavalisse would meet this need.

Additional Information

What is Chronic Immune Thrombocytopenia?

Chronic ITP is a long-term condition where the immune system destroys platelets in the blood. Platelets are needed to help form blood clots and stop bleeding. Patients with ITP have low platelet counts and can suffer from fatigue and bruising, and can bleed easily. It is not known how many people in Canada suffer from chronic ITP. A 2010 narrative review of international studies suggested that the incidence of ITP among adults is approximately 3.3 per 100,000 per year, while the prevalence is 10 per 100,000 people.

Unmet Needs in Chronic Immune Thrombocytopenia

Not all patients respond to available therapies, and even if remission is achieved, long-term remission is not guaranteed. There is a need for treatments that are effective, easy to administer, and have a low risk of adverse effects.

How Much Does Tavalisse Cost?

Treatment with Tavalisse is expected to cost between \$59,035 and \$88,553 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that fostamatinib not be reimbursed for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to other treatments.

Rationale for the Recommendation

Two randomized controlled trials (RCTs) (FIT1 and FIT2; n = 76 and n = 74, respectively) suggest that fostamatinib may increase the likelihood of a stable platelet response after 24 weeks by 14% to 18% compared with placebo. However, only results from FIT1 were statistically significant. No significant differences in bleeding scores were observed. The need for rescue therapy was reduced by 11% to 19% in the fostamatinib group compared with placebo at various time points, but statistical significance was not assessed. Effect of fostamatinib on HRQoL was unclear in the trials. Neither of the studies compared fostamatinib to currently available therapeutic options for ITP. Published and sponsor-submitted indirect treatment comparisons with thrombopoietin receptor agonists (TPO-RAs) and rituximab were associated with numerous limitations, precluding definitive conclusions. Patients identified a need for treatments that would reduce symptoms and rates of bleeding events and improve other quality of life measures compared with currently available therapies, which was not demonstrated with fostamatinib.

Discussion Points

- CDEC recognizes that platelet count is a commonly used and clinically accepted surrogate marker for the clinical assessment of risk for bleed and patient response to treatment. There remains uncertainty in the relationship between platelet count threshold and bleeding in this patient population. CDEC also noted that other outcomes identified as important to patients and clinicians, such as bleeding symptoms and other HRQoL indicators, were associated with substantial uncertainty.
- Across the treatment groups in the FIT1 and FIT2 trials, at baseline, patients enrolled had a median platelet count that ranged from 13,500/ μ L to 21,000/ μ L, and an average platelet count that ranged from 15,860/ μ L to 17,333/ μ L. CDEC discussed that the platelet count at baseline for enrolled patients was either higher or not much lower than the target platelet level while receiving treatment (identified by the clinical expert and clinical practice guidelines), which is at least 20,000/ μ L in patients with chronic ITP.
- CDEC discussed the lack of comparative evidence, noting that FIT1 and FIT2 do not address the comparative clinical benefit of fostamatinib against the most appropriate comparators. CDEC was unable to make any conclusion on the efficacy and safety of fostamatinib compared with other drugs used for ITP, such as immunosuppressants and rituximab.
- CDEC noted that the sponsor is seeking reimbursement, in jurisdictions that reimburse TPO-RA, for those who had an inadequate response to a TPO-RA. In FIT1 and FIT2, there were a total of 150 recruited patients, of which just less than half received a prior TPO-RA.

The analysis performed in this population was exploratory and there were low numbers overall. Due to the limited evidence, support for the specific reimbursement request is lacking and the place in therapy of fostamatinib could not be established based on the information available.

- CDEC discussed the results from the pooled analyses of the FIT1 and FIT2 trials; however, it concluded that the efficacy of fostamatinib was modest, and the pooled analysis did not alter the interpretation of the results, compared with when each study was considered individually.
- CDEC found that the lower rate of rescue therapy use among patients treated with fostamatinib compared to those treated with placebo in FIT1 and FIT2 could be meaningful and may warrant further study, but also noted that the relatively low event rates and lack of statistical certainty make it difficult to draw any conclusions.
- CDEC discussed the absence of relevant comparators in the pharmacoeconomic analysis, which resulted in the cost-effectiveness being unknown for the Health Canada indication and severely limited for the sponsor's reimbursement request.

Background

Fostamatinib has a Health Canada indication for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to other treatments. Fostamatinib is an antihemorrhagic spleen tyrosine kinase inhibitor. It is available as 100 mg or 150 mg oral tablets and the Health Canada–approved dose is 100 mg to 150 mg taken orally twice daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a systematic review that included 2 RCTs in patients with chronic ITP
- patients' perspectives gathered by Platelet Disorder Support Association (PDSA)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with ITP
- input from a group of 19 Canadian hematologists
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group submission was received for this review, authored by the PDSA. It was unclear how the data were collected to inform the submission, as this was not described; however, patient experiences with fostamatinib were gathered from the PDSA's Facebook group. The patient input submission suggested that patients with ITP are fearful of life-threatening bleeding, face physical and emotional consequences from their disease (e.g., fatigue, anxiety, depression), and restrict activities because of their disease. The submission also suggested that ITP and its treatment interfere with daily life and negatively impact HRQoL. Patients are often more concerned with managing symptoms and improving HRQoL than platelet counts. There are myriad treatment options available to manage ITP; it is difficult to predict who will respond to a particular treatment and who will develop resistance to a treatment over time. Further, patients may not be able to afford or access available options. Therefore, it is important that patients have options available in case they do not respond to a therapy, the therapy stops working, or they experience bleeding.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH suggested that standard first-line therapy for ITP includes corticosteroids, and IV immune globulin is often added when an immediate increase in platelets is required, although its effect is often transient. The experts noted that a significant proportion of patients will not respond to steroids and of those who do, many will relapse once steroids are tapered. At this point, traditional second-line therapy is splenectomy if patients are a suitable candidate. More recently, rituximab has emerged as an alternative second-line therapy. If both splenectomy and rituximab have failed (or are contraindicated), a large number of third-line therapies are available, including immunosuppressant medications such as azathioprine or cyclophosphamide, or TPO-RAs such as eltrombopag or romiplostim. There is very little evidence to guide the selection of second- or third-line therapy and decisions are dependent on both local reimbursement considerations and patient-specific factors.

The clinical experts consulted stated that treatment goals are to reduce bleeding and to prolong life. Increasing the platelet count is generally considered to be a reasonable surrogate for those 2 goals. Improving HRQoL is also an important goal.

The clinical experts highlighted that not all patients respond to available therapies, and even if remission is achieved, long-term remission is not guaranteed. They also noted how accessibility to appropriate second- and third-line therapies can be a challenge. This is because not all options are reimbursed in each province or because reimbursement criteria differ across provinces. Administration of existing therapies can also be a challenge as there are adverse effects with existing treatments. The availability of therapies with demonstrated efficacy, convenience of administration, and a low risk of adverse effects would therefore fill an unmet need for treatment of ITP.

The clinical experts consulted stated that contemporary ITP guidelines suggest that, in general, splenectomy or rituximab can be considered as second-line therapy. There are several third-line options available; however, the comparative efficacy of these drugs is unclear.

Therefore, it can be difficult to know what the best treatment option is for a particular patient, and there is often no single clearly defined treatment pathway. Decisions end up largely being driven by access. It is challenging to identify the optimal place in the therapeutic algorithm for fostamatinib. The clinical experts noted that rituximab or splenectomy are reasonable second-line choices (TPO-RAs may also be considered second-line choices in some patients). The safety profile of fostamatinib and the fact that it is administered orally suggest it might be considered a reasonable third-line therapy rather than reserved for patients who have failed or do not have access to TPO-RAs, as has been proposed by the sponsor. Regardless of where it sits in the therapeutic algorithm, however, the addition of fostamatinib as a treatment option would be advantageous for clinicians to have for specific patients. The clinical experts noted that the ITP population is very heterogenous, and it is generally not possible, with the available data and current understanding of ITP pathophysiology, to determine which specific patients will respond best to fostamatinib and which are most susceptible to adverse effects.

Bleeding is a very important outcome in treatment of ITP, and ultimately any treatment should reduce the occurrence of clinically important bleeding while improving HRQoL. In practice, clinicians rely on platelet response which is assumed to reduce risk of clinically relevant bleeding and, as a secondary benefit, reduce the need for rescue therapy. In general, an increase in platelet count can be seen as early as 2 weeks into treatment with fostamatinib, although some patients may not respond until week 12. If a response is observed, clinicians would likely continue to use the treatment long-term with monthly monitoring. A sustained response would generally be considered a platelet count of 30,000/ μ L to 50,000/ μ L for the duration of a treatment cycle (e.g., 24 weeks). If a response has not been seen by approximately 24 weeks, clinicians would generally consider that the treatment has not been effective and would discontinue it. If there are issues related to safety or tolerability, treatment would generally be discontinued earlier, particularly if it is impacting a patient's health-related quality of life.

Clinician Group Input

A group of 19 Canadian hematologists submitted input on fostamatinib. The clinician group submission echoed the opinions of the expert panel. The clinician group submission suggested that fostamatinib would be likely used after first-line therapy, as second-line or subsequent-line therapy. The clinician group submission reported that fostamatinib would be used as a single drug after first-line therapy has failed. Fostamatinib was felt to be an alternative to other second- and subsequent-line therapies and should be considered before splenectomy, immunosuppressive drugs, rituximab, and its biosimilars, and be used at a similar line of therapy to maintenance treatments such as the TPO-RAs. The clinician group submission stated that patients earlier in their ITP disease course may respond better to fostamatinib. Thus, using it in the second line may have advantages such as limiting exposure to complications or toxicities from other drugs. However, the greatest need is still in patients who have relapsed multiple times despite treatment.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for fostamatinib:

- issues with concomitant drug use and onset of action
- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- care provision issues.

Clinical Evidence

Description of Studies

FIT1 (N = 76) and FIT2 (N = 74) were identically designed 24-week double-blind RCTs that evaluated the efficacy and safety of fostamatinib versus placebo in patients with primary ITP for more than 3 months who had received at least 1 previous ITP treatment, and had a baseline platelet count of less than 30,000/ μ L from at least 3 counts in the preceding 3 months. FIT1 was conducted in Australia, Canada, 4 countries in Europe (Denmark, Hungary, Italy, the Netherlands), the UK, and the US, while FIT2 was conducted in countries in Europe (Austria, Bulgaria, Czech Republic, Germany, Norway, Poland, Romania, and Spain). In the FIT1 trial, 51 patients were randomized to fostamatinib and 25 to placebo, while in the FIT2 trial, 50 patients were randomized to fostamatinib and 24 to placebo. The primary efficacy end point in both trials was achievement of stable platelet response defined as a platelet count of 50,000/ μ L or greater at 4 of the last 6 study visits between weeks 14 and 24. These trials also measured the use of rescue therapy, bleeding-related serious adverse events (SAEs), and HRQoL (via the 36-Item Short-Form Survey [SF-36]) along with harms.

In the FIT1 trial, the mean age in the fostamatinib group was 57 years (standard deviation [SD] = 18) and was 53 years (SD = 16) in the placebo group. In the fostamatinib group, 59% of patients were female compared to 68% in the placebo group. The mean duration of ITP was 13 years (SD = 14) in the fostamatinib group versus 9 years (SD = 10) in the placebo group. Patients in the fostamatinib group has used a median of 5 prior ITP treatments (range = 1 to 10) while patients in the placebo group had used a median of 3 (range = 1 to 9). More patients in the placebo group had used steroids (100%) and TPO-RAs (60%) than in the fostamatinib group (90% for steroids and 51% for TPO-RAs). In FIT1 and FIT2, the rate of concomitant steroid use was higher in the placebo group (56% in FIT1 and 63% in FIT2) compared to the fostamatinib group (37% in FIT1 and 44% in FIT2). In FIT1, the rates of prior splenectomy were similar (40%) in both groups. In FIT2, the mean age in the fostamatinib group was 49 years (SD = 15) and was 50 years (SD = 17) in the placebo group. In the fostamatinib group, 62% of the patients were female compared to 54% in the placebo group. The mean duration of ITP was 12 years (SD = 13) in the fostamatinib group versus 11 years (SD = 8) in the placebo group. Patients in both groups had used a median of 3 previous ITP treatments (range = 1 to 10). The rate of previous individual ITP medication use was similar between groups. The rates of prior splenectomy were higher in the placebo group (38% versus 28% in the fostamatinib group).

Efficacy Results

In the FIT1 trial, 18% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (risk difference [RD] = 18%; 95% confidence interval [CI], 7.2 to 28; P = 0.026). In the FIT2 trial, 18% of patients in the fostamatinib group experienced stable platelet response compared to 4% in the placebo group (RD = 14%; 95% CI, 0.5 to 27; P = 0.15), a difference which was not statistically significant.

In FIT1, 31% of patients in the fostamatinib group required rescue therapy before week 10 compared to 44% of patients in the placebo group. After week 10, 14% of patients in the fostamatinib group required rescue therapy compared to 28% in the placebo group. In FIT2, 18% of patients in the fostamatinib group required rescue therapy before week 10 compared to 29% of patients in the placebo group. After week 10, 2% of patients in the fostamatinib group required rescue therapy compared to 21% in the placebo group. In FIT1, █ of patients in the fostamatinib group experienced a bleeding-related SAE compared to █ in the placebo group. In FIT2, █ of patients in the fostamatinib group experienced a bleeding-related SAE compared to █ in the placebo group. There was no statistical testing done for these outcomes.

For the quality-of-life outcome, there were no differences in SF-36 scores between the fostamatinib and placebo groups at any time point in FIT1. At week 24, there █ providing SF-36 data in the placebo group and █ patients in the fostamatinib group. In FIT2, there were no differences in SF-36 scores between the fostamatinib and placebo groups at week 12 or week 24. At week 24 in FIT2, there were █ patients providing SF-36 data in the placebo group and █ patients in the fostamatinib group. The effect of fostamatinib on HRQoL is unclear from the FIT1 and the FIT2 trials.

Both FIT1 and FIT2 trials conducted subgroup analyses for the primary efficacy end point. In FIT1, among patients with prior TPO-RA treatment, 15% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (RD = 15%; 95% CI, 1.5 to 29). Among patients without prior TPO-RA treatment, 20% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (RD = 20%; 95% CI, 4.3 to 36). In FIT2, among patients with prior TPO-RA treatment, 15% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (RD = 15%; 95% CI, -0.6 to 31). Among patients without prior TPO-RA treatment, 20% of patients in the fostamatinib group experienced stable platelet response compared to 7% in the placebo group (RD = 13%; 95% CI, -6.8 to 33). In FIT1, among patients with prior splenectomy, 15% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (RD = 15%; 95% CI, -0.6 to 31). Among patients without prior splenectomy, 19% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (RD = 19%; 95% CI, 5.4 to 33). In FIT2, among patients with prior splenectomy, 21% of patients in the fostamatinib group experienced stable platelet response compared to 0% in the placebo group (RD = 21%; 95% CI, -0.1 to 43). Among patients without prior splenectomy, 17% of patients in the fostamatinib group experienced stable platelet response compared to 7% in the placebo group (RD = 10%; 95% CI, -7.5 to 28).

The following outcomes identified in the protocol were not reported in FIT1 or FIT2: duration of response, symptoms, hospitalizations, or emergency department visits.

Harms Results

In the FIT1 trial, among patients in the fostamatinib group, the most common adverse events (AEs) (i.e., appearing in ≥ 5%) were diarrhea (41%), nausea (29%), alanine transaminase increase (18%), aspartate aminotransferase increase (16%), headache (14%), dizziness (18%), epistaxis (18%), fatigue (12%), and hypertension (26%). The most common AEs in the placebo group were diarrhea (16%), headache (24%), dizziness (16%), epistaxis (16%), and dyspnea (12%). In the FIT2 trial, the most common AEs in the fostamatinib group were diarrhea (18%), epistaxis (12%), and hypertension (14%). The most common AEs in the

placebo group were diarrhea (13%), nausea (13%), headache (13%), hypertension (13%), and thrombocytopenia (13%).

In the FIT1 trial, 16% of patients in the fostamatinib group had at least 1 SAE (i.e., febrile neutropenia, immune thrombocytopenic purpura, thrombocytopenia, retinal tear, diarrhea, pneumonia, syncope, vaginal hemorrhage, epistaxis) compared to 20% in the placebo group (i.e., anemia, congestive cardiac failure, gastrointestinal hemorrhage, menorrhagia, chronic obstructive pulmonary disease, epistaxis) while in the FIT2 trial, 10% of patients in the fostamatinib group had at least 1 SAE (i.e., epistaxis, bronchitis, contusion, platelet count decrease, plasma cell myeloma, transient ischemic attack, hypertensive crisis) compared to 26% in the placebo group (i.e., thrombocytopenia, menorrhagia, muscle rupture, infection, petechiae). In FIT1, 16% of patients in the fostamatinib group withdrew due to any AE (i.e., abdominal pain, diarrhea, neutropenia, thrombocytopenia, alanine transaminase increase, chest pain, pneumonia, syncope) compared to 8% in the placebo group (i.e., abdominal discomfort, epistaxis). In FIT2, 4% of patients in the fostamatinib group withdrew due to any AE compared to 9% in the placebo group. In the fostamatinib group, 1 patient (2%) withdrew due to plasma cell myeloma and 1 due to headache. In the placebo group, 1 patient (4%) withdrew due to diarrhea and 1 due to hypertension. One patient in FIT1 died in the placebo group due to sepsis. In FIT2, 1 patient died in the fostamatinib group due to plasma cell myeloma.

In the FIT1 trial, █ of patients in the fostamatinib group experienced an infection compared to █ in the placebo group. In the FIT2 trial, █ of patients in the fostamatinib group and █ of patients in the placebo group experienced an infection. In both FIT1 and FIT2, █ of patients in the fostamatinib group experienced neutropenia compared to █ in the placebo group. In FIT1, █ of patients in the fostamatinib group experienced a liver transaminase elevation compared to █ in the placebo group. In FIT2, █ of patients in the fostamatinib group experienced a liver transaminase elevation compared to █ in the placebo group.

Critical Appraisal

FIT1 and FIT2 were at an overall low risk of bias, though there were some concerns regarding selective outcome reporting (sensitivity analyses and subgroup analyses that were not prespecified) and potential for unblinding due to high dropout rate due to lack of response. In both FIT1 and FIT2, the fostamatinib and placebo groups were generally balanced in baseline characteristics, though in each trial there were some baseline imbalances that may have introduced bias. For example, there were differences in the rates of specific previous ITP treatments used in FIT1 and differences in the rate of prior splenectomy in FIT2, as well as higher concomitant steroid use in the placebo group in both FIT1 and FIT2. The rate of study discontinuation was high in both FIT1 and FIT2 and was imbalanced between study groups in both trials, primarily due to discontinuation from the trials because of lack of treatment response. Patients discontinuing due to lack of response were treated as nonresponders and an intention-to-treat analysis approach was used; thus, the high discontinuation rate did not appear to introduce bias for the primary outcome. However, for the SF-36 outcome, the high study discontinuation rate meant there were limited data available at week 24 (e.g., 1 patient in the placebo group at week 24 in FIT1, and 2 patients in the placebo group at week 24 in FIT2). Thus, it was not possible to draw any meaningful conclusions from the SF-36 data at week 24 due to the limited amount of data from study discontinuations. Given the small number of patients in each subgroup and low event rates, there was likely insufficient power to detect any differences between treatment groups in these subgroups. This is reflected by wide CIs in the RD.

The small number of patients and low event rates for certain outcomes (i.e., ITP Bleeding Score and WHO bleeding scores, bleeding-related SAEs, use of rescue therapy) make it challenging to draw conclusions surrounding any difference between treatment groups for these secondary end points. These outcomes may also have been biased by imbalances in concomitant steroid use. Neither FIT1 nor FIT2 were powered for secondary end points and there was no adjustment for multiplicity for secondary end points; thus, these outcomes should be interpreted with caution.

Clinical experts indicated that the population of FIT1 and FIT2 are broadly comparable to the population of patients with ITP in Canada; thus, the results of these trials are likely generalizable in Canada. The long duration of ITP and multiple previous treatments among patients in FIT2 mirrors what is common for patients with ITP seen in clinical practice in Canada. However, the clinical experts did note generalizability concerns with FIT1 and FIT2 in some Canadian contexts, as patients in FIT1 and FIT2 were predominantly White. The experts also noted that patients with secondary ITP were excluded from FIT1 and FIT2; thus, trial findings may not be generalizable to those with secondary ITP. Further, the specific types of previous treatments used in FIT1 and FIT2 differ from those commonly seen at a similar point in ITP treatment in Canada. The clinical experts pointed out that based on the duration of ITP for patients in FIT1 and FIT2, a higher portion of patients with chronic ITP in Canada would have had a prior splenectomy. Moreover, the extent of previous rituximab use in FIT1 is higher than what would be seen in Canada at a similar stage of treatment. In terms of outcome assessment in FIT1 and FIT2, the clinical experts noted that bleeding outcomes are likely the most important in practice, but that measurement of platelet counts is commonly how treatment response is assessed.

FIT1 and FIT2 provided limited data on clinically important outcomes such as HRQoL, rescue therapy, and bleeding events. The clinical experts do not use the ITP Bleeding Score and WHO bleeding scales in practice; thus, the relevance of the bleeding outcome scales used in FIT1 and FIT2 is unclear. Further, the event rates for the post hoc bleeding-related SAE outcome made it challenging for the clinical experts to comment on the relevance or meaningfulness of these findings. The clinical experts found that the lower rate of rescue therapy use among patients treated with fostamatinib compared to placebo in FIT1 and FIT2 could be meaningful, but also noted the relatively low event rates. Similarly, given the small numbers and low event rates in the subgroup analyses, the clinical experts could not draw meaningful conclusions on whether any subgroup differences were likely to exist (e.g., based on prior splenectomy or TPO-RA treatment). Another challenge with both FIT1 and FIT2 is that the comparator is placebo. In chronic ITP, if platelet count is below 20,000/ μ L, as it was at baseline for patients in FIT1 and FIT2, clinical experts (and clinical practice guidelines) indicate that treatment would be warranted. Thus, placebo may not be an appropriate comparator for fostamatinib. Indeed, FIT1 and FIT2 do not address the comparative efficacy of fostamatinib against other second- or third-line ITP treatments.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Health Canada indicated population: Adult patients with chronic ITP (> 12 months), who are either resistant or refractory to previous lines of treatment. Reimbursement requested population: Adult patients with chronic ITP (> 12 months), who have had an insufficient response to a TPO-RA in jurisdictions where TPO-RA reimbursement is available, or after failure of corticosteroids and other earlier line treatments in jurisdictions where TPO-RA reimbursement is not available.
Treatment	Fostamatinib
Submitted price	Fostamatinib: \$80.87 per 100 mg tablet \$121.31 per 150 mg tablet
Treatment cost	At the submitted price, the average 28-days of fostamatinib is estimated to be \$5,600 per patient for those receiving 200 mg daily and \$8,400 per patient for those receiving 300 mg daily.
Comparators	Rituximab Watch and rescue
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (59 years)
Key data source	FIT1 trial, FIT2 trial, FIT3 trial, and an NMA
Key limitations	<ul style="list-style-type: none"> The sponsor did not consider comparators that clinicians consulted by CADTH deemed relevant, such as TPO-RAs, long-term steroids, and immunosuppressant drugs. Additionally, experts consulted by CADTH did not agree that watch and rescue was a suitable comparator at this stage of therapy. The cost-effectiveness of fostamatinib compared to the missing comparators is unknown. The modelled target population is only aligned with the reimbursement request, which places fostamatinib's line of therapy conditional on jurisdictional reimbursement of TPO-RAs, and does not reflect the Health Canada indication. Therefore, the cost-effectiveness of fostamatinib for the Health Canada indication is unknown, given the absence of cost-effectiveness data on fostamatinib compared to TPO-RAs and other relevant comparators. Loss of response while on fostamatinib, a key driver in the model, was estimated using an exponential distribution (alternative distribution fits were not considered), and what the sponsor refers to as the median time to loss of response from the FIT3 trial. However, since the median time to loss of response has not been observed in the FIT3 trial, the sponsor used the maximum time to loss of response in the FIT3 trial as a median proxy.

Component	Description
	<ul style="list-style-type: none"> • Extrapolation of transition probabilities past the clinical trial follow-up period is associated with significant uncertainty given the small sample size supporting the model parameters and ad hoc assumptions due to limited follow-up. This extrapolated data was used to inform transition probabilities beyond the time horizon of the FIT1 and FIT2 trials. • The utility estimates used in the economic evaluation were taken from a number of sources, using different elicitation methods. Key utility estimates did not rely on indirect elicitation methods, such as EQ-5D, as recommended by CADTH. • The relative benefit of fostamatinib compared to rituximab and watch and rescue was assumed to be constant over time. Clinical experts consulted by CADTH indicated this was unlikely to be the case, as the observed benefit of fostamatinib during the FIT1 and FIT2 trial period (24 weeks) is likely to be different than after 10 or 20 years. • The rate of rescue events among responders (blood platelet counts > 50,000/μL) receiving watch and rescue is higher than deemed likely by the clinicians consulted by CADTH, which biases the results in favour of fostamatinib. • There were several limitations with the NMA, which was used by the sponsor to estimate the relative benefit of fostamatinib compared to watch and rescue and rituximab. Primarily, there was no consistent definition of platelet response across the NMA's included studies, and platelet level specific efficacy estimates were not generated. Therefore, the relative benefit of fostamatinib in the model is the same for both those who have low and high blood platelet counts. • Parameter uncertainty was not incorporated as per CADTH guidelines, as the sponsor did not source uncertainty estimates for most of the parameters. Instead, 98% of model parameters used an arbitrary standard error set at 20% of the mean. As such, uncertainty has not been effectively captured within the cost-effectiveness estimates, which likely biases results, though the direction of bias is unknown. • The economic model relies on blood platelet counts, a surrogate outcome that in the model, predicts survival and health-related quality of life. While clinical experts consulted by CADTH indicated that blood platelet counts were appropriate proxies for effective disease control, this introduces additional uncertainty to the sponsor's model.
CADTH reanalysis results	<ul style="list-style-type: none"> • The following changes were made to derive the CADTH base case: corrected modelling errors; extrapolated transition probabilities by weighting those probabilities observed during the follow-up period of FIT1 and FIT2 by the number of individuals at risk; altered the rate of rescue medication usage; and revised blood platelet health state utilities. • Due to missing comparators, the cost-effectiveness of fostamatinib in the Health Canada indication, for adult patients with chronic ITP who have had an insufficient response to other treatments, is unknown. • According to the sequential analysis for the reimbursement request, fostamatinib was associated with an ICER of \$212,783 per QALY when compared to watch and rescue (incremental costs = \$164,368; incremental QALYs = 0.77). The probability of fostamatinib being cost-effective at a \$50,000 per QALY threshold was < 0.01%. A price reduction of 60% would be required for fostamatinib to achieve an ICER of \$50,000 per QALY. • The interpretation of the CADTH base case is limited by the omission of relevant comparators; the inability to model the full Health Canada indication; the lack of appropriate assessment of parameter uncertainty; the uncertainty of fostamatinib's duration of clinical benefit; and extrapolations of loss of response.

ICER = incremental cost-effectiveness ratio; ITP = immune thrombocytopenia; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; TPO-RA = thrombopoietin receptor agonists.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the full indicated population was not considered; jurisdictions are assumed to use reimbursement criteria from other jurisdictions for different medication; the population size is uncertain due to a lack of

data on the proportion of patients with ITP using TPO-RAs; appropriate comparators were left out; the proportion of patients who will be publicly reimbursed is uncertain; fostamatinib discontinuation was not accounted for; the frequency of rescue therapy is uncertain; plans may be paying substantially less for comparators than estimated; and uncertainty in the predicted market capture of fostamatinib.

Due to limitations in the sponsor's analysis that could not be adjusted, CADTH was unable to report a base case. In a combined exploratory reanalysis, CADTH incorporated a higher proportion of patients eligible for TPO-RAs, a higher percentage of eligible patients who would be publicly reimbursed, the discontinuation of fostamatinib in patients who do not respond, a lower cost of IV immune globulin, and a higher market uptake of fostamatinib.

Although the sponsor suggested that fostamatinib would be associated with a budget impact of \$19,796,525 over the 3-year time horizon, based on the CADTH combined exploratory reanalysis, the reimbursement of fostamatinib would be associated with a budgetary increase of \$11,895,184 in year 1; \$14,520,317 in year 2; and \$20,605,888 in year 3, for a 3-year total incremental cost of \$47,021,389.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Initial meeting date: December 15, 2021

Regrets: Three expert committee members did not attend

Conflicts of interest: None

Reconsideration meeting date: March 23, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None