Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2227

lusutrombopag 3mg film-coated tablets (Mulpleo®)

Shionogi

8 November 2019

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

ADVICE: following a full submission

lusutrombopag (Mulpleo) is accepted for use within NHSScotland.

Indication under review: for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

In two phase III studies, lusutrombopag was superior to placebo in reducing the need for platelet transfusions in thrombocytopenic patients with chronic liver disease undergoing invasive procedures.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.[1]

Dosing Information

The recommended dose is 3mg lusutrombopag once daily for 7 days. Tablets should be taken once daily with liquid, swallowed whole and should not be chewed, divided or crushed. Lusutrombopag can be taken with or without food.

The procedure should be performed from day 9 after the start of lusutrombopag treatment. Platelet count should be measured prior to the procedure.

Lusutrombopag should not be taken for more than 7 days.[1]

Lusutrombopag should be used when risk for bleeding is considered to be high according to clinical laboratory test values such as platelet counts and of the coagulation-fibrinolysis system, clinical symptoms and type of invasive procedure.

The efficacy and safety of lusutrombopag have not been established when administered before laparotomy, thoracotomy, open-heart surgery, craniotomy or excision of organs

Product availability date

November 2019

Summary of evidence on comparative efficacy

Lusutrombopag is a small molecule thrombopoietin (TPO) agonist that stimulates platelet production through its action on TPO surface cells of megakaryocytes. Lusutrombopag is the first medicine to be licensed for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.[1]

The evidence supporting the efficacy and safety of lusutrombopag primarily comes from L-PLUS 1 and L-PLUS 2, two multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase III studies. Patients aged ≥18 years (≥20 years in L-PLUS 1) were required to have severe thrombocytopenia (defined as a platelet count <50 x 10^9/L at screening) due to chronic liver disease, an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, and were due to undergo invasive procedure between 9 and 14 days after initiation of treatment.[2]

In L-PLUS 1 and L-PLUS 2, patients were randomised equally to receive lusutrombopag 3mg or matching placebo orally once daily for 7 days. Treatment was discontinued early on day 5, 6 or 7 if the platelet count was ≥50 x 10^9/L and had increased by ≥20 x 10^9/L from baseline, due to

concerns of increased thromboembolic risk. Invasive procedures were performed between day 9 and 14, but could be delayed further if required (up to day 35 in L-PLUS 2). Randomisation was stratified according to primary invasive procedure (liver ablation/coagulation or other procedure) and platelet count at screening (<35 x 10^9/L, ≥35 x 10^9/L to <45 x 10^9/L , or ≥45 x 10^9/L in L-PLUS1 and <35 x 10^9/L or ≥35 x 10^9/L in L-PLUS 2).[2] Rescue therapy for bleeding events using platelet preparations was permitted. L-PLUS 2 also allowed the use of other blood preparations, plasma and volume expanders.

The primary outcome for L-PLUS 1 was the proportion of patients that did not require platelet transfusion prior to the primary invasive procedure. Platelet transfusion was deemed necessary in patients with a platelet count <50 x 10^9/L after day 8 and immediately before the invasive procedure. Efficacy analyses were performed in the full analysis set (FAS) in L-PLUS 1, which included all randomised patients that had received at least one dose of study treatment, had a platelet count sample taken at baseline, and had at least one further platelet count sample taken after the initiation of study treatment.[2]

The primary outcome of L-PLUS 2 was the proportion of patients that did not require platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation to 7 days after the primary invasive procedure. Platelet transfusion was deemed necessary in patients with a platelet count <50 x 10^9/L on or after day 8, but no more than 2 days before the invasive procedure.[3] Efficacy analyses were performed in the intention to treat (ITT) population, defined as all patients who underwent randomisation in L-PLUS 2. A hierarchical statistical testing strategy was applied in the study with no formal testing of primary or secondary outcomes after the first non-significant outcome in the hierarchy.[2, 3]

Both L-PLUS 1 and L-PLUS 2 met their primary outcomes. A significantly higher proportion of patients in the lusutrombopag group of L-PLUS 1 did not require platelet transfusion before invasive procedure compared with placebo: 79% (38/48) versus 12% (6/48), relative risk 6.16 (95% confidence interval [CI]: 2.9 to 13.0), p<0.001.[2] Similarly, in L-PLUS 2, a significantly higher number of patients in the lusutrombopag group did not require platelet transfusion prior to invasive procedure and did not require rescue therapy from the time of randomisation to 7 days after procedure compared with placebo: 65% (70/108) versus 29% (31/107), difference: 37% (95% CI: 25 to 48), p<0.001 (ITT population). Sensitivity analysis of the primary outcome using a per-protocol population showed a greater treatment difference between lusutrombopag and placebo: 72% (66/91) versus 20% (18/89), difference: 53% (95% CI: 42 to 64). Subgroup analyses of both studies favoured lusutrombopag over placebo for the pre-specified subgroups (L-PLUS 1 pre-defined subgroups: performed invasive procedure, baseline platelet count, and Child-Pugh class; L-PLUS 2 pre-defined subgroups: age, sex, baseline platelet count, baseline weight, race, and Child-Pugh class).[2]

In both studies, a higher proportion of patients treated with lusutrombopag compared with placebo did not require platelet transfusion throughout the study, were classified as responders, and had a longer median duration of platelet count ≥50 x 10^9/L. Detailed results of the secondary outcome analyses are presented in Table 1 (L-PLUS 2) below. Further secondary outcomes

included frequency of platelet transfusion and dose transfused, and the time course of platelet count. In L-PLUS 2, all 34 patients who received platelet transfusion in the lusutrombopag group received one transfusion. In the placebo group, 61 patients required platelet transfusion; 6 patients received 2 platelet transfusions, 5 patients received 3 platelet transfusions, and 1 patient received 5 transfusions.[2]

Table 1. Secondary analysis of L-PLUS 2 (ITT population)[2]

	Lusutrombopag (n=108)		**Placebo (n=107)**	
Proportion of patients that did not require platelet transfusion during the total study period (pre- and post-procedure)	63%[B]		29%	
- Difference in proportion (95% CI)	35% (23 to 47)			
Proportion of responders[A]	65%[B]		13%	
- Difference in proportion (95% CI)	52% (42 to 63)			
	With PT (n=34)	**Without PT (n=74)**	**With PT (n=73)**	**Without PT (n=34)**
Median duration of increase in platelet count ≥50 x 10^9/L (days)	1.7	19.2	0.0	8.9
Proportion of patients who required rescue therapy for bleeding	0%		1.9%	

A= A responder was defined as a patient who achieved a platelet count of ≥50,000µL and increased ≥20,000µL platelet count from baseline at any point during the study; B = p<0.001 versus placebo; CI = confidence interval; PT = platelet transfusion; SD = standard deviation.

The submitting company performed a meta-analysis of three placebo-controlled lusutrombopag studies in patients with chronic liver disease and thrombocytopenia undergoing invasive procedure. The studies included the two key phase III studies described above (L-PLUS 1 and L-PLUS 2), and M0626, a phase 2b, double-blind, study (n=31; lusutrombopag n=16; placebo n=15). The submitting company concluded that lusutrombopag was superior to placebo in achieving most of the nine pre-planned outcomes. For the primary composite outcome of no platelet transfusion required and no rescue medication required for bleeding for up to 7 days after the procedure, lusutrombopag was superior to placebo.

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

Summary of evidence on comparative safety

Following their evaluation, the EMA concluded that lusutrombopag 3mg for up to 7 days was a safe and well tolerated treatment for patients with Child-Pugh class A or B chronic liver disease. However, there were concerns for patients with more severe disease (Child-Pugh class C) due to limited data.[2]

In analysis that combined data from L-PLUS 1 and L-PLUS 2, treatment-related adverse events (AE) were reported by 6.5% (10/155) of patients in the lusutrombopag group and 9.0% (14/155) in the placebo group. In the lusutrombopag and placebo groups respectively, patients reporting a serious AE were 5.2% versus 7.1%, and patients discontinuing therapy due to an AE were 0% versus 0.6%.[3]

The most frequently reported treatment-emergent AEs of any grade with an incidence >3% in the lusutrombopag group versus the placebo group of L-PLUS 2 were: headache (5.6% versus 1.9%), abdominal pain (4.7% versus 4.7%), fatigue (2.8% versus 6.5%), peripheral oedema (2.8% versus 3.7%), and nausea (1.9% versus 4.7%).[3] Pooled analysis of the placebo controlled studies identified other AEs reported in at least 2% more lusutrombopag-treated patients than placebo-treated patients including procedural pain (19% versus 17%), increased alanine transaminase (ALT) (8.8% versus 5.9%), and increased blood bilirubin (5.3% versus 2.4%).[2]

Summary of clinical effectiveness issues

Thrombocytopenia is the most common haematological complication associated with chronic liver disease, and is associated with poorer prognosis. Severe thrombocytopenia, defined as a platelet count of $<50 \times 10^9$/L, is rare but considered to increase the risk of potentially serious bleeding during and after invasive procedures or surgery. This increased risk of bleeding can complicate routine care of patients with chronic liver disease, as it may lead to the delay or cancellation of procedures. At present, the main medical intervention available to correct severe thrombocytopenia in patients with chronic liver disease prior to procedure is platelet transfusion, which has several limitations such as risk of adverse events and in some cases reduced effectiveness. Clinical experts consulted by SMC considered that lusutrombopag fills an unmet need in this therapeutic area, as there are very limited treatment options available.[2, 3]

The key evidence in support of lusutrombopag comes from L-PLUS 1 and L-PLUS 2. Both studies met their primary outcome.[3] These results were also considered clinically relevant by the EMA. The primary outcome of L-PLUS 2 was considered more clinically relevant as it demonstrated a prolonged benefit in the prevention of bleeding events during the healing period. These results were further supported by positive, clinically relevant secondary outcomes.[2] Both studies demonstrated the treatment effect of lustrombopag but the size of the treatment effect compared with placebo differed between the two studies. This may be due to difference between

the study populations: L-PLUS 1 was performed in Asian patients and L-PLUS 2 in patients from 22 different countries.

In L-PLUS 2 there was a substantial number of protocol deviations; there were 18 instances where the rules related to platelet transfusions were ignored. This had an impact on the results using the ITT population, as 3 patients in the lusutrombopag group and 10 patients in the placebo group did not receive platelet transfusion that should have. However, the effects of the protocol deviations were limited in the per-protocol population, the results of which were positive for lusutrombopag.[2]

There were several generalisability issues identified with the two key studies. Firstly, the exclusion of patients with history of thrombosis, concomitant interferon use, and severe hepatic impairment (Child-Pugh Class C) limits the generalisability of the study results to a significant proportion of patients with thrombocytopenia due to chronic liver disease. Additionally, only patients that had a low risk of bleeding who were undergoing procedures associated with a low to moderate risk of bleeding were eligible for L-PLUS 1 and L-PLUS 2. The generalisability of the findings for patients requiring major surgery, such as laparotomy, thoracotomy, open-heart surgery, craniotomy or excision of organs, is uncertain.

A further issue is the disparity between the licensed treatment regimen and the regimen that patients received in the key studies. In both key studies, patients had their platelets monitored from day 5 to day 7 of treatment, and treatment was discontinued if platelet count was ≥50 x 10^9/L and had increased by ≥20 x 10^9/L from baseline. The rationale for this was due to safety concerns, as a substantial increase of platelets may be associated with increased thrombotic risk. During the two key studies, 73% of patients received 7 days of lusutrombopag. The SPC does not advise the monitoring of platelets on Days 5 to 7, and instead all patients should receive 7 days of treatment. Therefore, the results seen in clinical practice may differ slightly from what has been reported in clinical studies. The evidence to support the 7-day course of lusutrombopag without platelet monitoring comes from a phase IIIb post-marketing study conducted in Japan.

Lastly, L-PLUS 1 was a Japanese study. When baseline characteristics were compared with the multinational population of L-PLUS 2, notable differences in mean bodyweight and causes of chronic liver disease were observed.[2]

The most relevant comparator for this indication is platelet transfusion. While this was available to patients in both arms of L-PLUS 1 and L-PLUS 2, these studies were placebo-controlled. Lusutrombopag has therefore not been directly compared with platelet transfusion, although this may be challenging to do in practice.

The meta-analysis that has informed some of the economic analyses had several important limitations that should be considered. Firstly, the systematic literature review (SLR) was not reported, and therefore it is not clear if all the available evidence has been identified. Secondly, there were considerable differences in placebo rates between the included studies, which may indicate heterogeneity in the study populations. L-PLUS 1 and M0626 were Japanese studies, in

contrast to the multinational study, L-PLUS 2. Baseline characteristics, particularly race, bodyweight, and cause of chronic liver disease were notably different, and do not appear to have been adjusted for in the statistical analysis. The responder rates were higher in the Japanese studies than the multinational study, which may make extrapolating results of the meta-analysis to the Scottish population more problematic. The wide confidence intervals reported with the primary outcome highlight the uncertainty in the results.[2] A meta-regression analysis may have been more informative.

Clinical experts consulted by SMC considered that lusutrombopag is a therapeutic advancement as it is the first medicine to be licensed for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures. Lusutrombopag would reduce the number of platelet transfusions used in this context, which is seen as beneficial as platelet transfusions can cause adverse events and in some cases patients may become refractory to treatment. Lusutrombopag is expected to be used as an alternative to platelet transfusion in circumstances where patients can wait at least nine days to undergo invasive procedure.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis of lusutrombopag within its licensed indication, for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures. As no medicines are currently available within NHS Scotland, platelet transfusions were assumed to represent standard of care and were used as the comparator in the economic analysis.

The submitting company provided a model comprising a short-term decision-tree structure (thirty-five days), after which point patients remaining alive entered a Markov model comprised of two states (alive and dead). Nodes included within the decision tree comprised outcomes associated with receipt of platelet transfusions; receipt or delay to planned invasive procedures; the occurrence of bleeding events and death at various points in the pathway. The Markov model had a lifetime horizon and used a one-year cycle length. An NHS Scotland and social care perspective was taken.

Clinical data were derived from the meta-analysis of three lusutrombopag clinical trials described above; however, due to heterogeneity in the baseline characteristics between the trials, a scenario was provided for the only multinational study (L-PLUS2). Effectiveness data were derived in the form of odds ratios to estimate the relative proportion of lusutrombopag patients requiring a platelet transfusion versus placebo. However, an assumption was applied that all comparator patients will receive a transfusion. Other key probabilities were derived from the clinical trials, whilst mortality rates made use of a separate observational study. Utility data were obtained from the literature and generally aligned with appropriate methods of measuring and valuing health.

In terms of treatment costs used in the model, medicines acquisition costs were included for lusutrombopag and for the comparator, the average number of units of platelets per transfusion

was estimated by clinical experts consulted by the company. Costs of medicines wastage and adverse event management, as well as downstream costs of managing bleeding were also included. The resource implications of platelet transfusions were based upon a previous NICE technology appraisal (TA293)[4], however a scenario utilising NHS Reference Costs was also provided. Costs of delayed or cancelled procedures were applied by the submitting company to represent the opportunity cost ("sunk cost") associated clinician/ theatre time that was assumed not to be able to be used. This was tested in sensitivity analysis and had negligible influence on the base case.

The submitting company provided the following estimates of cost-effectiveness (Table 2):

Table 2: Base case results

Technologies	**ICER (£/QALY)**
Lusutrombopag versus platelet infusion	Dominant

QALYs: Quality-adjusted life years; ICER: Incremental cost-effectiveness ratio

A number of scenario analyses were provided during the submission process to test the implications of key assumptions and methods. Key scenario analyses are summarised in Table . This highlights that the key drivers are largely related to the costs of platelet transfusions within standard practice. A conservative combined scenario highlights the extent of impact a reduced cost of current practice may have. However, discussion at the NDC suggested the use of an alternative (higher) NHS reference cost estimate may be more appropriate in this scenario, which could plausibly improve the cost-effectiveness of lusutrombopag. Sensitivity analysis 5 in table 3 represented the preferred set of assumptions and in this analysis, the incremental cost-effectiveness ratio was £7,737.

Table 3: Key scenario analyses

		ICER (£/QALY)
	Base case	Dominant
1.	L-PLUS2 as efficacy source (ITT population) [base case: pooled analysis]	Dominant
2.	Platelet transfusion cost: NHS reference costs (mixed inpatient + day case) [base case: NICE TA293]	£8,999.60
3.	Platelet transfusion cost: NHS reference costs (all inpatient visits) [base case: NICE TA293]	Dominant
4.	Trial-derived proportions of placebo patients requiring transfusion [base case: 100%]	£5,667
5.	Combined scenario: Average units of platelets from L-PLUS2 placebo arm (3.5 units, base case 3 units) + scenarios 1+ 3+4	£7,737

6.	Combined scenario: 2 units of platelets + scenario 5	£19,113

QALY- Quality adjusted life year ICER- incremental cost effectiveness ratio

The key limitations in the company base case presented in table 2 are as follows:

- An assumption is applied regarding the proportion of patients requiring a platelet transfusion which is inconsistent with the submitted clinical evidence and the responses received from SMC clinical experts. Use of relative effect estimates from the clinical trial is likely more appropriate and results in a higher ICER.
- Several inputs used for the estimation of costs of delivering each infusion are potentially inappropriate (namely the number of units of platelets and source of cost estimates per transfusion). The use of NHS reference costs results in a significant upwards effect on the ICER, which is heightened when a combination of these changes is applied. However, if the higher estimate of NHS reference costs is assumed (scenario 3), the impact on the ICER may not be as significant.
- The pooled analysis of lusutrombopag studies is highly heterogeneous and as noted in the clinical effectiveness section above, may not be generalisable to a Scottish population. The use of the L-PLUS2 scenario alone is preferred and results in reduced estimates of incremental QALYs gained. Although this does not impact the results in isolation (lusutrombopag remains dominant), this reduction increases the sensitivity of the results to changes in the estimated costs.

Accounting for these limitations, sensitivity analysis 5 in table 3 represented the preferred set of assumptions and in this analysis, the incremental cost-effectiveness ratio was £7,737. Given this, the economic case was considered demonstrated.

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

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the British Liver Trust and the Primary Biliary Cholangitis (PBC) Foundation, which are both registered charities.

- The British Liver Trust has received 11.4% pharmaceutical company funding in the past two years, with none from the submitting company. The PBC Foundation has received 24.5% pharmaceutical company funding in the past two years, with none from the submitting company.

- Patients who have chronic liver disease and thrombocytopenia tend to have end stage liver disease and many will be on the list for transplant. These people are extremely unwell,

suffer from severe tiredness, feel vulnerable, anxious and often express sadness. Having to go into hospital for multiple appointments and procedures can put an incredible additional strain on individuals and their family members. Severe thrombocytopenia associated with chronic liver disease is a condition that affects relatively small numbers of PBC patients with advanced liver disease, however the risks are considerable to this small group of patients.

- Patients with chronic liver disease who have significant thrombocytopenia often require multiple platelet infusions every time they have invasive procedures as they are at increased risk of bleeding. These transfusions can take up considerable time and sometimes involve an overnight stay.

- The convenience of taking a tablet that might avoid multiple transfusions is seen as an improved option for patients who are already very sick. It will likely be of particular benefit to those with medical beliefs that prevent them from using blood products (e.g. Jehovah's Witnesses); those who have to have long distances to travel to hospital and those who have recurrent needs for procedures. Patients also highlighted a preference to take therapy orally than to be subject to more discomfort, procedures, and needles.

Additional information: guidelines and protocols

"NICE guideline 24: Blood transfusion" was published in November 2015 and offers guidance on the administration of platelet transfusions prior to invasive procedure or surgery. For patients undergoing invasive procedure or surgery, the guideline advises:

- Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.

The American Gastroenterological Association (AGA) published a clinical practice update: expert review in July 2019, titled "AGA Clinical Practice Update: Coagulation in Cirrhosis".[5] In relation to TPO agonists such as lusutrombopag, the advice is as follows:

- TPO agonists are a good alternative to platelet transfusion, but require approximately 10 days to increase platelet counts.[5]

Additional information: comparators

Platelet transfusion

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Lusutrombopag	**3mg orally once daily for 7 days**	£800

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 247 patients**.** Based on an estimated uptake of 25 patients in year 1 and 99 patients in year 5, the impact on the medicines budget was estimated at £20k in year 1 and £80k in year 5. As lusutrombopag was assumed to results in a reduction in the use of platelet transfusions, the net medicines budget impact was estimated at savings of £3k and £13k in years 1 and 5 respectively.

References

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2. European Medicines Agency (EMA). European Public Asessement Report. Lusutrombopag (Lusutrombopag Shionogi). EMEA/H/C/004720/0000. 13 December 2018. www.ema.europa.eu.
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4. National Institute for Health and Care Excellence (NICE). TA293: Eltrombopag for adult patients with chronic immune thrombocytopenic purpura (cITP). 2012.
5. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology. 2019;157(1):34-43. e1.

This assessment is based on data submitted by the applicant company up to and including 11 October 2019.

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

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

Advice context:

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

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