

Lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing a planned invasive procedure

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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.

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This guidance should be read in conjunction with TA626.

1 Recommendations

- 1.1 Lusutrombopag is recommended, within its marketing authorisation, as an option for treating severe thrombocytopenia (that is, a platelet count of below 50,000 platelets per microlitre of blood) in adults with chronic liver disease having planned invasive procedures.

Why the committee made these recommendations

People with chronic liver disease often have low blood platelet levels. This means that they are more likely to bleed during invasive medical procedures, including surgery. Currently, they have a platelet transfusion before invasive procedures to help reduce their chances of bleeding.

Avatrombopag and lusutrombopag are oral therapies that raise platelet levels, the aim being to reduce (but not eliminate) the chances of a patient needing a platelet transfusion. Platelet transfusions rely on donors and are given intravenously, so the possibility of replacing them with an oral treatment is an improvement. The drugs have several other benefits, including:

- the convenience of fewer transfusions
- fewer hospital stays
- a decreased chance of having transfusion-related complications.

In addition, platelets are a limited resource and can only be stored for a short time. This means that there can be problems getting them to people in time for their procedure, which can delay surgery. On the other hand, avatrombopag and lusutrombopag need to be taken more than a week before a procedure, so can be used only for planned procedures.

Clinical trial evidence shows that fewer people need a platelet transfusion if they have avatrombopag or lusutrombopag rather than a placebo treatment. But whether the drugs improve survival compared with platelet transfusions has not been measured. There is also no clinical evidence that either drug is better than the other.

The economic modelling does not fully account for the benefits for patients and service delivery when using avatrombopag and lusutrombopag. If these are considered, using lusutrombopag would likely save the NHS money. So, lusutrombopag can be recommended for treating thrombocytopenia in people with chronic liver disease who need planned invasive procedures. It is not possible for NICE to make a recommendation for avatrombopag because the drug does not have a UK price.

2 Information about avatrombopag and lusutrombopag

Marketing authorisations

- 2.1 Avatrombopag (Doptelet, Sobi) is recommended 'for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure'.
- 2.2 Lusutrombopag (Mulpleo, Shionogi BV) is recommended 'for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures'.

Dosages in the marketing authorisations

- 2.3 The recommended dosage of avatrombopag is based on the patient's platelet count:
- below 40,000 platelets per microlitre of blood – 60 mg once daily
 - 40,000 to below 50,000 platelets per microlitre of blood – 40 mg once daily.
- Dosing should begin 10 to 13 days before the planned procedure. Patients should have their procedure 5 to 8 days after the last dose of avatrombopag. Avatrombopag is taken orally.
- 2.4 The recommended dosage of lusutrombopag is 3 mg once daily for 7 days. The procedure should be done from day 9 after the start of lusutrombopag treatment. Platelet count should be measured before the procedure. Lusutrombopag is taken orally.

Price

- 2.5 The company has stated that the price of avatrombopag is £640.00 or £960.00 per 5-day treatment course for the 40,000 to below 50,000 and

below 40,000 platelets per microlitre of blood groups respectively.

- 2.6 The company has stated that the cost of lusutrombopag is £800 per 7-day treatment course. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence from a number of sources. See the [committee papers](#) for full details of the evidence.

Treatment pathway

People with chronic liver disease and a count of below 50,000 platelets per microlitre of blood would be eligible for avatrombopag or lusutrombopag

- 3.1 The clinical experts explained that people with chronic liver disease and thrombocytopenia (traditionally defined as a platelet count below 150,000 platelets per microlitre of blood) have an increased risk of bleeding when having invasive procedures, including surgery. This is irrespective of whether the procedure is planned or an emergency. These procedures may include investigative or therapeutic procedures such as dental, multiple and repeated procedures. Because of this bleeding risk, people may have a platelet transfusion before the invasive procedure to aid blood clotting. The clinical experts acknowledged that they were unaware of trials testing whether platelets lowered the risk of bleeding. However, they agreed that transfusing platelets prophylactically was the standard of care. The clinical experts also stated that the risk of bleeding during a procedure depends on the platelet count, the specific procedure, other manifestations of liver disease, history of bleeding and age. [NICE's guideline on blood transfusion](#) recommends that prophylactic platelet transfusions should be considered for people having invasive procedures or surgery to raise the platelet count above 50,000 platelets per microlitre of blood. The committee heard that higher platelet counts might be needed for invasive procedures on some sites (such as the eyes). It noted that avatrombopag is licensed for treating thrombocytopenia when the platelet count is below 50,000 platelets per microlitre of blood. It also noted that, although the marketing authorisation for lusutrombopag does not define severe thrombocytopenia, the company and the assessment

group only presented evidence (that is, clinical trial data, indirect clinical data and cost-effectiveness analyses) for people with a platelet count below 50,000 platelets per microlitre of blood. If people bleed during or after a procedure, they may need a 'rescue therapy', including further platelet transfusions, fresh frozen plasma or tranexamic acid. The committee concluded that people with chronic liver disease having a planned invasive procedure would be eligible for treatment with avatrombopag and lusutrombopag if they had a platelet count of below 50,000 platelets per microlitre of blood. It agreed to make recommendations for this group.

The appraisal applies to people needing planned procedures scheduled for 9 or 10 days in the future

3.2 The marketing authorisations stipulate that avatrombopag and lusutrombopag oral treatments need to be taken at least 10 days or 9 days respectively before a procedure. The clinical experts stated that it would be relatively straightforward to co-ordinate testing platelet levels and prescribing these treatments with a GP. Because of the time needed to increase the platelet count, the committee heard that avatrombopag and lusutrombopag would be appropriate only for planned elective procedures. However, these drugs would not have a role in planned procedures that need to be done within 9 or 10 days. The committee concluded that the appraisal applies to people with chronic liver disease and a platelet count below 50,000 platelets per microlitre of blood needing planned ('elective') invasive procedures rather than emergency procedures.

Avatrombopag and lusutrombopag raise platelet levels for longer than a transfusion, and are taken at home so reduce wastage and hospital stays

3.3 The clinical experts explained that a platelet transfusion increases platelet levels for only a short time. This means that patients need to have their procedures soon after having a transfusion. According to the clinical experts, about 50% of patients go into hospital to have a transfusion the evening before their planned procedure and, when

possible, the transfusion is given on the day of the procedure. If the 'treatment window' (that is, the time when platelet levels are raised) is missed, a patient would have another platelet transfusion before having the procedure. Avatrombopag and lusutrombopag have longer treatment windows in which to do planned invasive procedures than do platelet transfusions. Specifically, these windows are 10 to 13 days (stated in the marketing authorisation for avatrombopag) after starting avatrombopag and from day 9 (stated in the marketing authorisation for lusutrombopag) after starting lusutrombopag. The committee considered that this would ease procedure scheduling compared with platelet transfusion and may make it possible to carry out multiple procedures within a treatment window. It concluded that avatrombopag and lusutrombopag have some potential advantages over transfusing platelets. These include reducing wastage if an invasive procedure is delayed, increasing the time in which procedures can occur and reducing hospital stays.

People would welcome an oral treatment alternative to platelet transfusions

- 3.4 The patient expert stated that, typically, people with chronic liver disease and thrombocytopenia are sick and have many hospital appointments; this, and the associated travel, disrupts their lives. They would value any treatment that could reduce this burden. Avatrombopag and lusutrombopag are oral treatments, and would reduce the need for a trip to hospital for a transfusion. The clinical experts acknowledged that some people who develop chronic liver disease from intravenous drug use have poor venous access. For them, transfusing platelets is difficult without central venous access, for which a procedure is also needed. The patient expert stated that the risks of adverse effects associated with platelet transfusions are low. However, people perceive oral treatments to be safer, and even just the perceived risk of platelet transfusions can cause anxiety. The committee concluded that there are benefits related to an oral treatment compared with platelet transfusions, and that people would welcome an oral treatment option.

Reducing dependence on platelets would minimise problems associated with obtaining and transfusing platelets

3.5 Platelet transfusions, like all blood products, are a scarce resource limited by the number of donations received. The clinical experts explained that platelets also have a short shelf life (of 5 to 7 days) and need to be stored at room temperature. This means that larger hospitals store only limited amounts to avoid wastage, and that smaller hospitals do not store platelets on site. The clinical experts explained that patients can become refractory to repeated platelet transfusions. Repeated transfusions can also increase the risk of infection. Some people can react to the plasma contained in the platelets or develop antibodies against donor platelets after repeated transfusions. People who have an immune reaction to donated platelets may reduce their chance of having a successful liver transplant. The clinical experts also stated that, although donor platelets are not usually matched to the recipient, sometimes they have to be. This then makes it more difficult to find platelets, and means that no one else can use these matched platelets (for example, human leucocyte antigen matched). The committee agreed that obtaining, storing and administering platelets carries a number of practical implications for patients and for service delivery. It concluded that reducing dependence on platelets would minimise problems associated with obtaining and transfusing platelets.

Clinical evidence

Avatrombopag and lusutrombopag reduce the number of platelet transfusions

3.6 The avatrombopag randomised placebo-controlled trials (ADAPT 1 and ADAPT 2) assessed 2 doses of avatrombopag: 40 mg for people with a platelet count of between 40,000 and below 50,000 platelets per microlitre of blood and 60 mg for people with a platelet count below 40,000 platelets per microlitre of blood. The lusutrombopag trials (L-PLUS 1, L-PLUS 2 and JapicCTI 121944) assessed 3 mg lusutrombopag in people with a platelet count below 50,000 platelets per microlitre of blood. To compare the lusutrombopag results with the

avatrombopag results, the assessment group chose to separate lusutrombopag results into the same subgroups as avatrombopag. That is, it considered the lusutrombopag trial results for 2 subgroups: people with a platelet count of between 40,000 and below 50,000 platelets per microlitre of blood; and people with a platelet count below 40,000 platelets per microlitre of blood separately. However, the assessment group also presented analyses for lusutrombopag for the full population. The avatrombopag and lusutrombopag trials measured the proportion of people needing a platelet transfusion before an invasive procedure. Across all subgroups, at least 40% fewer people needed a platelet transfusion if they were randomised to avatrombopag or lusutrombopag compared with placebo. The committee concluded that the trial evidence presented was appropriate for decision making. It further concluded that the evidence showed that avatrombopag and lusutrombopag reduce the number of platelet transfusions before invasive procedures in people with chronic liver disease and thrombocytopenia when compared with placebo.

Although both drugs' trials include people fitter than those having platelet transfusions in UK clinical practice, the results are generalisable

3.7 One way to categorise the severity of chronic liver disease is by Child-Pugh score. People in the Child-Pugh A category have less severe disease and the best prognosis; people in the Child-Pugh C category have the most severe disease and the poorest prognosis. The regulatory trials of avatrombopag included between 8.6% (40,000 to below 50,000 platelets per microlitre of blood subgroup in the avatrombopag arm of ADAPT-1) and 15.2% (in the same subgroup of the avatrombopag arm of ADAPT-2) of people in the Child-Pugh C category. The trials of lusutrombopag excluded people with disease scored as Child-Pugh C (although 3.6% of the pooled-trials population were in the Child-Pugh C category). The summary of product characteristics for both drugs state that they should only be used in people with Child-Pugh C liver disease if the expected benefits outweigh the expected risks. The clinical experts explained that patients with thrombocytopenia tend to have Child-Pugh B or C liver disease, and that people with Child-Pugh A liver disease rarely have thrombocytopenia. The committee agreed that this

meant that the avatrombopag and lusutrombopag trials were carried out in people who were fitter than people who would have the drugs in UK clinical practice. The clinical experts explained that outcomes might be better in clinical practice than in the trials. This was because using a thrombopoietin receptor agonist such as avatrombopag or lusutrombopag in people with more severe disease and less ability to make thrombopoietin has a larger effect than in people with less severe disease. The committee agreed that this seemed a reasonable expectation, but that there was no evidence to support it. Overall, however, the committee concluded that the trial results were generalisable to NHS practice.

There is no trial evidence to determine whether avatrombopag or lusutrombopag increase life expectancy compared with platelet transfusions

3.8 The trials of avatrombopag and lusutrombopag had a follow up of 5 weeks and did not measure survival as a clinical outcome. The committee considered that survival on avatrombopag or lusutrombopag compared with standard care may depend on:

- **Death rate associated with platelet transfusion:** People having avatrombopag or lusutrombopag would, on average, have fewer platelet transfusions (see [section 3.6](#)). The clinical experts explained that the risk of death with a platelet transfusion was very small (see [section 3.11](#)).
- **Fatal bleeds:** The company for lusutrombopag (Shionogi) showed data suggesting that lusutrombopag was associated with fewer severe bleeds than placebo. The committee considered it plausible that there would be fewer bleeds with a thrombopoietin receptor agonist because these drugs raise platelet levels for a longer time than a platelet transfusion. It also considered that it was difficult to use the rates of rescue therapy for bleeding (which had been measured in the avatrombopag and lusutrombopag trials) as a proxy measure for bleeding rates. This was because the definition of rescue therapy differed between the trials.
- **Adverse events associated with avatrombopag or lusutrombopag:** The committee acknowledged that thrombopoietin receptor agonists increase the

risk of thromboembolic events, but that the short-term trial results did not show a difference in thromboembolic events between placebo and avatrombopag or lusutrombopag.

The committee concluded that there were no data to determine whether avatrombopag or lusutrombopag increase or decrease life expectancy compared with platelet transfusions, but that they were unlikely to. It further concluded that it was appropriate to assume no difference in death rates between people treated with or without thrombopoietin receptor agonists.

Avatrombopag and lusutrombopag are expected to be of similar clinical effectiveness to each other

- 3.9 There were no head-to-head trials comparing avatrombopag with lusutrombopag, and the assessment group carried out a network meta-analysis. The committee agreed with the assessment group's concerns about comparing the clinical trials for avatrombopag and lusutrombopag. It noted that the trials defined rescue therapy differently, and had different criteria defining when platelet transfusions were indicated. The clinical experts and the company explained that they did not expect the effectiveness to differ between avatrombopag and lusutrombopag, which share the same mechanism of action. The committee agreed that this seemed plausible, and also noted that the indirect analyses mostly showed that there were no differences between drugs. The committee concluded that there was no evidence that either avatrombopag or lusutrombopag was more effective than the other.

Cost-effectiveness evidence

It is not possible to consider the cost effectiveness of avatrombopag because it does not have a UK price

- 3.10 Shionogi (who manufactures lusutrombopag) and the assessment group provided estimates of cost effectiveness. The assessment group presented the results comparing lusutrombopag with established care (without a thrombopoietin receptor agonist), which it split by baseline platelet level (see [section 3.6](#)). It also provided a pairwise comparison not

split by baseline platelet level. The company for avatrombopag stated that it did not have a UK list price for its drug, at this time. The committee noted its earlier conclusion that there was no evidence that avatrombopag or lusutrombopag differed in clinical effectiveness. However, without a known price, the committee could not judge whether avatrombopag represented a cost-effective use of NHS resources. The committee agreed that it could make recommendations only for lusutrombopag.

The assessment group's and Shionogi's models are structured similarly but model bleeds differently

- 3.11 The models from Shionogi and the assessment group shared a similar structure because the assessment group adapted Shionogi's model. The company's model included a short-term decision tree to model the clinical trial period (35 days). It also included a Markov model to model the life expectancy of a person with chronic liver disease over the long term (50 years). However, the models differed in how they modelled quality of life and survival related to bleeding and death associated with platelet transfusion. Shionogi modelled a risk of death associated with platelet transfusion of 0.3315%, and assumed that death happens before surgery. The assessment group's model estimated a lower (0.0005%) risk of death associated with platelet transfusion, which could occur before, during or after the procedure. The clinical experts explained that the assessment group's model was more plausible. Shionogi modelled risk of bleeding separately to risk of having rescue therapy, and assumed a lower rate of bleeds with lusutrombopag compared with established care. The assessment group did not model bleeding separately from rescue therapy. The clinical experts explained that people who bleed have rescue therapy, even after being discharged from hospital. Both Shionogi and the assessment group assumed that bleeding lowered quality of life and increased the risk of dying. The assessment group's approach resulted in about a 90-minute difference in quality-adjusted life years (QALYs; 0.00018 in its base case) between lusutrombopag and established care without a thrombopoietin receptor antagonist. The Shionogi approach resulted in a larger (but still small) difference in QALYs (0.015 in its base case). The committee concluded that it was plausible that lusutrombopag plus a platelet transfusion and rescue therapy would

be associated with similar long-term quality of life and risk of death as a platelet transfusion and rescue therapy.

Baseline utility values are low but appropriate for decision making

3.12 The baseline utility value, applied by both Shionogi and the assessment group to people who did or did not have a thrombopoietin receptor agonist, was 0.544. The committee considered that this seemed low. The patient expert explained that the estimate seemed reasonable because this population is very unwell. The committee was aware that the assessment group conducted a scenario analysis using a higher baseline utility of 0.801, which minimally affected the cost-effectiveness results. The committee agreed that the baseline utility values used in the assessment group's and company's base cases were appropriate for decision making.

Costs of platelet transfusions and delayed surgery could offset lusutrombopag drug costs, but the models do not include all relevant costs

3.13 Shionogi modelled a higher cost for platelet transfusions than did the assessment group. It assumed a person would have an average of 3 units of platelets. The assessment group assumed an average of around 1 unit. The assessment group based its calculations on the volume of platelets transfused in the lusutrombopag trials divided by the number of platelets estimated to be in a unit of platelets obtained by apheresis. The clinical experts stated that the costs of a platelet transfusion likely fell between Shionogi's and the assessment group's estimates. The committee considered that the incremental costs for lusutrombopag compared with established care modelled in the assessment group's base case (£603) may have overestimated the true costs. This was because the assessment group did not include all relevant costs. In particular, neither models included the costs of admitting patients to hospital the night before a procedure for transfusion or took into account that transfusion costs increase for patients who develop immunity. In addition, using NHS reference costs, Shionogi modelled wasted surgery time for delayed or

cancelled procedures, but the assessment group did not. The committee did not see evidence that avatrombopag or lusutrombopag resulted in fewer cancelled or delayed procedures. However, it accepted that there would likely be fewer delays and cancellations with the drugs because of the longer treatment window in which platelet counts are expected to remain high (see [section 3.3](#)). The clinical experts explained that, when procedures are cancelled, some resources are redirected elsewhere, but the NHS likely accrues unrecoverable costs. The committee agreed that the models did not take into account all the costs that might be averted.

Avatrombopag and lusutrombopag are innovative treatments

3.14 The patient and clinical experts explained that they considered avatrombopag and lusutrombopag to be a step change in terms of preparing people with chronic liver disease and thrombocytopenia for planned invasive procedures. This is because they are oral treatments that, on average, reduce the need for intravenous platelet transfusion. The committee agreed that benefits not captured in the QALY calculation included:

- the lower risk of developing antiplatelet antibodies
- increasing the availability of platelets for emergency procedures
- that it is an oral treatment rather than a transfusion.

The committee agreed that lusutrombopag and avatrombopag are innovative, and took this into account in its decision making for lusutrombopag.

Because of costs and benefits not captured in the economic modelling, lusutrombopag is highly likely to be value for money

3.15 The base case from the assessment group showed that, compared with established care without a thrombopoietin receptor agonist, lusutrombopag cost £603 more and was associated with 0.00018 more QALYs. This resulted in an incremental cost-effectiveness ratio (ICER) of £3.4 million per QALY gained. The committee noted that the ICER was very large, and that the QALY difference was extremely small. The

Shionogi base case (updated after consultation on the assessment group report) was £9,599 per QALY gained (incremental costs £38, incremental QALYs 0.0040). The committee agreed that neither Shionogi nor the assessment group modelled the following benefits:

- avoiding the costs of admitting patients to hospital the night before a procedure to have a platelet transfusion
- lowering the risk of developing antiplatelet antibodies and the need for matched platelets
- making donated platelets more readily available for emergency procedures
- increasing the 'treatment window' and available scheduling when using lusutrombopag
- offering an oral treatment for people with poor venous access.

The committee agreed that although it could not quantify the effect on the ICER of these benefits, the factors would lower the incremental costs and increase the incremental QALYs. It was aware that, because these drugs generated very small incremental QALYs, small changes to the incremental costs or QALYs would have large effects on the estimate of cost effectiveness. The committee noted its conclusion that avatrombopag and lusutrombopag represent an innovative treatment (see [section 3.14](#)). It concluded that the benefits not captured in the model made it highly likely that lusutrombopag would reflect a good use of scarce NHS resources.

Using blood products or platelets from someone of a different ethnic origin is not an equalities issue

- 3.16 For some people, using blood products including platelets is against their religious beliefs. The clinical experts explained that the chance of developing antiplatelet antibodies is higher if a person having platelets is of a different ethnic origin to the person donating the platelets. The committee considered that it was possible that the donating population would represent a different ethnic mix than the population with chronic liver disease and thrombocytopenia. It agreed that these were not equalities issues because they did not make it any harder for these

groups to access thrombopoietin receptor agonists.

Conclusion

Lusutrombopag would be a good use of scarce NHS resources

3.17 The committee concluded that:

- lusutrombopag did not improve survival compared with established care
- the economic modelling had not included all the potential benefits of lusutrombopag in terms of quality of life and costs
- lusutrombopag is innovative
- including the benefits not captured in the model would make it highly likely that lusutrombopag would reflect a good use of scarce NHS resources.

Therefore, the committee concluded that lusutrombopag could be recommended for treating thrombocytopenia in people with chronic liver disease needing planned invasive procedures.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make it available within the period set out in the paragraphs above. This means that, if a patient has chronic liver disease with severe thrombocytopenia and the doctor responsible for their care thinks that lusutrombopag is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

Mary Hughes

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Update information

June 2020: Section 2 of the guidance updated to include the price for avatrombopag.

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