Lusutrombopag (Mulpleta) for severe thrombocytopenia in patients with chronic liver disease undergoing an elective invasive procedure

NIHR HSRIC ID: 7743

Lay summary

Lusutrombopag is a new drug to treat one of the symptoms of long-term liver disease, where low numbers of blood cells called platelets lead to poor blood clotting. This can lead to uncontrolled bleeding during surgery or other procedures, which can lead to delay or cancellation of treatment. The drug increases the number of platelets to make important procedures safe to perform. Lusutrombopag is taken as a tablet once a day for up to seven days. Lusutrombopag may offer a new treatment for low platelet levels in patients with liver disease and may be an alternative to the use of donor platelet infusions.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Thrombocytopenia: severe; chronic liver disease in patients who are undergoing an elective procedure.

TECHNOLOGY

DESCRIPTION

Lusutrombopag (Mulpleta; S-888711) is a small molecule thrombopoietin receptor (c-Mpl) agonist that promotes proliferation and differentiation of bone marrow cells into megakaryocytes to stimulate platelet production. In phase III clinical trials lusutrombopag is administered orally at 3mg once daily for up to seven days\(^1\).

Lusutrombopag does not currently have Marketing Authorisation in the EU for any indication. Lusutrombopag is in phase II clinical trials for immune thrombocytic purpura.

INNOVATION and/or ADVANTAGES

If licensed, lusutrombopag will offer an additional oral treatment option for patients with severe thrombocytopenia associated with chronic liver disease who are undergoing an elective invasive procedure, as a pharmacological alternative to platelet transfusion.

DEVELOPER

Shionogi Inc.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Thrombocytopenia is characterised by a clinically significant lack of platelets circulating within the blood, and is most usually defined as a platelet count of less than 150\(\times\)10\(^9\) / l of blood\(^2\). It can arise through a number of mechanisms, including congenital abnormalities in platelet production (e.g. megakaryocytic hypoplasia and Bernard-Soulier syndrome), decreased production of platelets (e.g. viral infections, leukaemia, chemotherapy and alcohol), increased destruction of platelets (e.g. idiopathic thrombocytic purpura), platelet sequestration and dilution thrombocytic purpura\(^3,4,5\). External and internal bleeding are the most common signs of thrombocytic purpura. Symptoms of external bleeding include purpura and petechiae, prolonged bleeding from minor cuts, excessive bleeding from the mouth or nose, abnormal/heavy menstrual bleeding and excessive bleeding during/after surgery\(^2,6\). Internal bleeding into the intestines or the brain is considered the most serious symptom as it may be unrecognised and can be fatal. Signs of internal bleeding include blood in the urine or stools, and headaches\(^5\).
In up to 76% of cases, thrombocytopenia is associated with chronic liver disease\(^7,8,9\) and can either be a direct result of the liver pathology or a consequence of interferon-based anti-viral therapy. In either case, the numbers or function of platelets may be altered directly or indirectly through suppression of thrombopoiesis in the bone marrow\(^9\).

Mild to moderate thrombocytopenia rarely causes severe bleeding episodes during invasive procedures such as liver biopsy and liver transplants, but severe thrombocytopenia (<50x10\(^9\)/l) increases this risk and can have a significant impact on the clinical management of liver disease\(^8\). Thrombocytopenia may delay or prevent the initiation of interferon therapy, leading to increased morbidity and mortality and a reduced quality of patient care in some cases\(^8,10,11,12\).

**CLINICAL NEED and BURDEN OF DISEASE**

Estimating the size of the population with chronic liver disease and thrombocytopenia is complicated by studies with varying cut-off values and differences depending on the severity of disease\(^13\). Thrombocytopenia (platelet counts <150,000/μl) is a common complication in patients with chronic liver disease, reported in as many as 76% of cirrhotic patients\(^8\). In 2014-15, fibrosis and cirrhosis of the liver accounted for 5,623 hospital admissions, 8,466 consultant episodes, and 30,078 bed days\(^14\). Severe thrombocytopenia requiring platelet transfusions occurs in 1% of chronic liver disease patients\(^3\).

The population likely to be eligible to receive lusutrombopag could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

**NHS England Policies and Guidance**

**Other Guidance**
- None identified.

**CURRENT TREATMENT OPTIONS**

Treatment of thrombocytopenia associated with chronic liver disease aims to increase platelet levels, allowing other therapeutic interventions to continue. The primary existing option for treatment is platelet transfusion before procedures, but splenic artery embolisation, splenectomy and insertion of a transjugular intrahepatic portosystemic shunt may be helpful in those with portal hypertension\(^8,15\). Additionally, eltrombopag (a
thrombopoietin agonist) is licensed for the treatment of procedure limiting thrombocytopenia associated with chronic hepatitis C infection.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>L-PLUS 2, NCT02389621, 1423M0634, 2014-004942-91; lusutrombopag vs placebo: phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Shionogi.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants n=200 (planned); aged 18 years and older; platelet count &lt;50x10⁹/l at baseline; undergoing an elective invasive procedure.</td>
<td></td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to lusutrombopag 3mg oral once daily, or placebo oral once daily.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment for up to 7 days, follow-up 5 weeks.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Proportion of patients not requiring platelet transfusion and not requiring rescue therapy for bleeding.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Proportion of patients not requiring platelet transfusion, proportion of responders (≥20x10⁹/l platelet increase, resulting in ≥50x10⁹/l), duration of platelet count ≥50x10⁹/l, frequency of platelet transfusions, change from baseline platelet count over time, proportion of patients requiring rescue therapy for bleeding.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>November 2016.</td>
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</tbody>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of lusutrombopag is not yet known. The cost of eltrombopag for thrombocytopenia is outlined below¹⁶:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eltrombopag (Revolade)</td>
<td>Initially 25mg orally once daily, adjusted to achieve a platelet count sufficient to initiate antiviral therapy then a platelet count of 50-75x10⁹/l during antiviral therapy.</td>
<td>25mg, 28-tab pack £770.00</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:
- No impact identified
### Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other: None identified

- Decreased use of existing services: reduced need for platelet transfusion.
- Need for new services

### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
  - Other reduction in costs: reduced treatment delay/cancellation, lower number of platelet transfusions required.
- Other: uncertain unit cost compared to existing treatments

### Other Issues

- Clinical uncertainty or other research question identified: None identified

### REFERENCES

