

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Appraisal**

**Treosulfan with fludarabine for non-malignant disease before allogeneic stem cell transplant**

**Draft scope**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of treosulfan with fludarabine within its marketing authorisation as a conditioning treatment for non-malignant diseases prior to allogeneic haematopoietic stem cell transplantation.

**Background**

An allogeneic haematopoietic stem cell transplantation (HSCT) involves replacing the bone marrow stem cells of a patient (after high-dose conditioning treatment), with stem cells from a tissue-type matched or mismatched donor. Before a patient receives HSCT they need to have a type of treatment called a 'conditioning treatment' which prepares the body by eradicating the abnormal bone marrow to minimise the chance of the body rejecting the healthy donor cells. HSCT is a potentially curative treatment for various non-malignant diseases such as inborn errors of metabolism (metabolic disorders), primary immunodeficiencies, haemoglobinopathies and bone marrow failure syndromes.

Primary immune deficiency disorders are a rare group of genetic diseases that are classified according to the nature of the deficiency (for example severe combined immunodeficiency, combined immune deficiency with or without associated disorders, antibody deficiency, phagocytic disorders, immune regulatory disorders and innate immune defects). Although the treatments vary according to the disorder and its complications, common treatments include immunoglobulin infusions, anti-microbial drugs and biological (monoclonal antibody) therapies.<sup>1,2</sup>

Registry data from the [British Society of Blood and Marrow Transplantation](#) (BSBMT) shows that over 100 allogeneic stem cell transplants were carried out in the UK in 2016 for non-malignant conditions including thalassaemia, immune deficiencies, inborn errors and autoimmune disorders.

The type of conditioning treatment depends on the type and severity of disease but usually involves chemotherapy with or without total body irradiation. Standard high-dose intensity conditioning regimens are associated with high morbidity and mortality and are generally used in people who are younger and more able to tolerate treatment. Reduced intensity conditioning is also used if treatment is less likely to be tolerated or if there are comorbidities.

Draft scope for the appraisal of treosulfan with fludarabine for non-malignant disease before allogeneic stem cell transplant

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### The technology

Treosulfan (Trecondi, Medac GmbH) is the prodrug of a bifunctional sulfonate alkylating agent with myeloablative, immunosuppressive, and antineoplastic activities. It is administered intravenously.

Treosulfan in combination with fludarabine is a reduced-toxicity conditioning treatment. Treosulfan with fludarabine does not have a marketing authorisation as a conditioning treatment before HSCT for non-malignant diseases. It has been studied in a clinical trial compared with busulfan with fludarabine as a conditioning treatment before allogeneic haematopoietic stem cell transplant in adults with non-malignant disease such as inborn errors of metabolism, primary immunodeficiencies, haemoglobinopathies and bone marrow failure syndromes. It has also been studied in children and young people up to 17 years with non-malignant disease.

<b>Intervention(s)</b>	Treosulfan with fludarabine
<b>Population(s)</b>	Adults with non-malignant disease before allogeneic haematopoietic stem cell transplantation
<b>Comparators</b>	<p>Standard high-dose intensity (myeloablative) conditioning regimens:</p> <ul style="list-style-type: none"> <li>• cyclophosphamide and total body irradiation</li> <li>• cyclophosphamide and busulfan</li> <li>• cyclophosphamide and thiotepa</li> <li>• high-dose busulfan with fludarabine with or without thiotepa</li> </ul> <p>Reduced intensity conditioning regimens:</p> <ul style="list-style-type: none"> <li>• low-dose busulfan with fludarabine</li> <li>• melphalan and fludarabine</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• event-free survival</li> <li>• rates of relapse</li> <li>• success of stem cell transplantation (engraftment)</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p><b>Appraisals in development (including suspended appraisals)</b></p> <p><a href="#">‘Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant’</a> [ID1508]. Publication to be confirmed.</p>
<b>Related National Policy</b>	<p>Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4 and 5. <a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a></p> <p>NHS England (2018/2019) <a href="#">NHS manual for prescribed specialist services (2018/2019)</a></p>

### Questions for consultation

When is allogenic haematopoietic stem cell transplant used in clinical practice for non-malignant diseases?

- Does the use of allogenic haematopoietic stem cell transplant differ by the type of disease and risk profile?
- What is the aim of treatment?

Have all relevant comparators for treosulfan with fludarabine been included in the scope?

- Where in the treatment pathway is conditioning treatment used?
- In clinical practice, what conditioning therapies are used before haematopoietic stem cell transplant for non-malignant disease?

- Are different conditioning therapies used for different types of non-malignant disease, if so, please specify?
- Should high dose intensity conditioning treatments be included as comparators, if so, please specify?
- Are any conditioning therapies used only for children and young people, if so, please specify?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom treosulfan with fludarabine is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which treosulfan with fludarabine will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider treosulfan with fludarabine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of treosulfan with fludarabine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

NICE has published an addendum to its guide to the methods of technology appraisal (available at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf>), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

### References

1 NHS England Haematopoietic Stem Cell Transplantation (HSCT, All Ages) 2015. Available from <https://www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/f01/> Accessed November 2018

2 NHS England Allogeneic stem cell transplantation for adults with Primary Immune Deficiency disorders 2018. Available from: <https://www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/f01/> Accessed November 2018