Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

thiotepa 15mg and 100mg powder for concentrate for solution for infusion (Tepadina®) SMC No. (790/12)

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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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

thiotepa (Tepadina) is not recommended for use within NHS Scotland.

Indication under review: In combination with other chemotherapy medicinal products:
1) with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;
2) when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

Two uncontrolled, non-randomised studies including patients with advanced non-Hodgkin's lymphoma or Hodgkin's disease have reported data for non-relapse mortality and overall survival.

The submitting company did not present sufficiently robust clinical and economic analyses to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

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Dosing Information

The dosage is variable and depends on age, disease setting, type of transplant used (autologous versus allogeneic) and type of chemotherapy regimen.

Thiotepa administration must be supervised by a physician experienced in conditioning treatment prior to HPCT.

Product availability date

21 May 2010
Thiotepa was granted orphan drug status in January 2007 in conditioning treatment prior to HPCT.

Summary of evidence on comparative efficacy

Thiotepa is a cell cycle-phase independent, non-specific alkylating antineoplastic agent, related to nitrogen mustard. Thiotepa acts by disrupting DNA bonds and is used in combination with other agents in conditioning regimens prior to haematopoietic stem cell transplantation (HSCT) in a number of haematological malignancies (HSCT and HPCT are alternative terms for the same procedure). Conditioning is the preparatory step before HSCT. Its aim is to eradicate the patient's disease prior to transplant, to create space for the donor cells and to suppress the host's immune system to prevent graft rejection. HSCT repopulates or replaces the haemopoetic system of the recipient either in total or in part. Stem cells can be derived from bone marrow or peripheral blood. Engraftment is the incorporation of the grafted tissue into the host.

The marketing authorisation for this formulation of thiotepa covers a wide range of indications and has been granted through the European Medicines Agency (EMA) based on 'well established use' for all indications, meaning that there is a very large body of evidence covering the full marketing authorisation. Therefore the submitting company has presented evidence and an economic case for use in high risk, aggressive and relapsed/refractory lymphoma and sibling donor transplants only. The studies are non-randomised and this patient population was selected by the company as it was able to identify datasets in the literature to compare with standard practice in Scotland. The submitting company has requested that SMC considers thiotepa when positioned for use in combination chemotherapy conditioning for aggressive or relapsed/ refractory non-Hodgkin's lymphoma patients prior to allogeneic HSCT.

The patient population under review was treated with reduced intensity conditioning (RIC). The RIC regimen in allogeneic transplants using thiotepa, cyclophosphamide and fludarabine is used for patients considered to be at risk of relapse but who are ineligible for myeloablative conditioning because of the high transplant-related toxicity and mortality with conventional allografts; this includes

patients with advanced age, co-morbidities, poor performance status and a previous regimen and autologous/allogeneic transplantation.

Two prospective non-randomised phase II studies[1,2] recruited a cohort of patients with mixed haematological malignancies for treatment with a RIC regimen of thiotepa 10mg/kg, cyclophosphamide 60mg/kg and fludarabine 60mg/m^2 followed by transplantation of marrow or granulocyte-colony stimulating factor mobilised peripheral blood haematopoietic stem cells. Graft versus Host Disease (GvHD) prophylaxis consisted of ciclosporin and a short course of methotrexate.

One of these studies recruited 170 patients in total, including 124 patients with relapsed/refractory non-Hodgkin's lymphoma (both indolent [n=63] and aggressive [n=61]) and 32 patients with relapsed/refractory Hodgkin's disease, all of whom received an allogeneic HSCT from an HLA-identical or one antigen mismatched sibling donor.[1] The median follow-up was 33 months. The primary outcome measure was non-relapse mortality (death from transplant-related causes), which was reported in 22 patients who died up to 23 months after transplantation. The most common cause of death was infection (n=12); nine patients had concurrent active GvHD, a further five had acute GvHD and two had chronic GvHD. The non-relapse mortality cumulative incidence was 11% (95% confidence interval [CI]: 7 to 18%) and 14% (95%CI: 9 to 21%) at 1 and 3 years, respectively.

Secondary outcomes included overall survival (OS), progression-free survival (PFS), incidence of relapse and engraftment. OS at 3 years was 69% in indolent and aggressive non-Hodgkin's lymphoma patients and 32% of Hodgkin's disease patients. The median time to disease progression was 6 months. Lymphoma type had a significant impact on relapse risk; the 3 year cumulative incidence of relapse was 29%, 31% and 81% for indolent non-Hodgkin's lymphoma, aggressive non-Hodgkin's lymphoma and Hodgkin's disease, respectively. Engraftment was 100% in the 133 patients tested at 1 to 3 months.

The other study aimed to investigate the effect of age and previous autologous transplantation, and recruited 150 patients in total, including 52 patients with aggressive non-Hodgkin's lymphoma.[2] Median follow up for the full population was 927 days. The key outcome measures were OS including death from any cause and non-relapse mortality defined as any death not caused by disease progression; both calculated using the Kaplan-Meier methodology. The 5 year OS and PFS rates in patients with non-Hodgkin's lymphoma and aggressive lymphoma were 72% and 59%, respectively. Results for the full population suggested that refractory disease was associated with worse OS (hazard ratio (HR) = 2.7). Eighteen patients (12%) died of non-relapse mortality. The most common causes of death were infection (n=10) and acute GvHD (n=4). The overall estimated 5-year non-relapse mortality rate was 15% and for aggressive non-Hodgkin's lymphoma this was 12%.

Summary of evidence on comparative safety

The safety information provided in the submission was for patients receiving autologous transplantation. No data for allogeneic transplantation were provided. Adverse events were not reported in the studies described previously. There are no comparative adverse event data. The Summary of Product Characteristics (SPC) notes the most common adverse events as infections, cytopenia, acute and chronic GvHD, gastrointestinal disorders, haemorrhagic cystitis and mucosal inflammation.

Summary of clinical effectiveness issues

Thiotepa has been granted orphan status for conditioning treatment prior to HSCT. Its marketing authorisation covers a wide range of indications and has been granted by the EMA via the 'well established use' route. This type of marketing authorisation application is based on extensive published literature rather than a prospective randomised clinical study.[3] The European Public Assessment Report (EPAR) states that 'well established use' is based on: time over which the medicine has been used, quantitative aspects, the degree of scientific interest and the coherence of scientific assessments. Thiotepa has been used in the European Union for the last 10 years.[3] Owing to the nature of the evidence base, the company have presented evidence for only a part of the licensed indication, in high risk, aggressive and relapsed/refractory lymphoma and allogeneic (sibling) donor transplants only.

Two uncontrolled, non-randomised studies including some patients with relapsed/refractory advanced non-Hodgkin's lymphoma or Hodgkin's disease, demonstrated an apparently acceptable level of non-relapse mortality and overall survival with thiotepa in combination with fludarabine and cyclophosphamide as a RIC regimen. The magnitude of benefit in comparison to other conditioning regimens is unknown.

Both thiotepa studies were phase II studies with no comparator, and patients with mixed haematological malignancies were included. One of the studies did not include relapsed/refractory disease as an inclusion criterion. The primary objective in both studies was not the efficacy and safety of the thiotepa regimen but either to investigate the practical role of RIC allogeneic HSCT in different histotypes of relapsed/refractory lymphomas or to establish the impact of age and previously failed autograft on non-relapse mortality and survival.

A number of different lymphoma subtypes were included in the studies. It is not known if the subgroup analyses in the patient population relevant to this submission were pre-specified or appropriately powered. Both studies were based in Italy and patients were recruited between 8 and 14 years ago. Previous lines of treatment are unknown and may not reflect current clinical practice. Co-morbidities and performance status of recruited patients are not known.

Data from one Scottish allograft transplantation unit would suggest that there are only small numbers of allograft transplantations carried out in patients with lymphoma in Scotland.

The company has provided limited information on the literature search, and the inclusion and exclusion criteria used in selecting the studies to include in the submission, although it was noted that the two studies described above were included in the EPAR for thiotepa in this patient population.

The company has provided a comparison between the thiotepa RIC regimen and the RIC regimen commonly used in Scotland comprising alemtuzumab, fludarabine and melphalan. The optimal outcome in HSCT is a balance between GvHD and non-relapse mortality. Pharmacologically, it would be anticipated that use of the thiotepa regimen would result in a higher incidence of GvHD, with a likelihood of more non-relapse mortality but less relapse-related mortality, while the alemtuzumab regimen would be likely to result in a lower incidence of GvHD but a higher relapse rate, and therefore more relapse-related mortality. However, the indirect comparison presented was a naïve indirect comparison providing little robust evidence to support the comparison between the thiotepa, fludarabine and cyclophosphamide regimen and the fludarabine, melphalan and alemtuzumab regimen. The indirect comparison had limitations in terms of internal validity, with insufficient detail

provided on the literature search, no synthesis of results and used unpublished audit data. Therefore, the robustness of the indirect comparison is questionable.

Summary of comparative health economic evidence

The submitting company presented a simple cost-utility analysis. This compared treatment with thiotepa 10 mg/kg as part of a regimen with fludarabine and cyclophosphamide, against a regimen consisting of melphalan, fludarabine and alemtuzumab. The cost-utility analysis results were presented for two indications, aggressive NHL and relapsed and refractory lymphoma. The time horizons for the models differed because they used evidence for overall survival from different studies.

The clinical outcomes used in the economic analysis to estimate survival gains came from naive indirect comparisons. The utility score was estimated at 0.72 from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30). This is the score estimated 3 years after a stem cell transplant. The only resource use in the analysis related to the costs of the drugs in each treatment regimen.

There were a number of weaknesses with the base case analyses submitted for aggressive non-Hodgkin's lymphoma and relapsed and refractory lymphoma:

- For the analysis provided for aggressive non-Hodgkin's lymphoma, the clinical evidence provided was based on overall survival at 5 years for the thiotepa regimen and 4 years for the comparator regimen. It is standard practice that survival gains should be compared using the same period; that is, both should be assessed at either 4 years or 5 years.
- The analysis was very simple and did not include several key inputs including adverse events (GvHD and infection) and relapses, and drug administration costs.
- The submitting company failed to discount benefits appropriately in the analyses.

The submitting company was asked to provide revised analyses to address these issues. A revised base case was provided to include the cost of the drug regimen as well as the costs associated with acute and chronic GvHD, infection and relapse using a common time horizon for the aggressive NHL analysis.

The revised cost-effectiveness ratio for aggressive non-Hodgkin's lymphoma was a cost per quality adjusted life year (QALY) of £3,426 based on an incremental QALY gain of 0.90 and incremental costs of £3,083.

The revised cost-effectiveness ratio for relapsed and refractory lymphoma was a cost per quality adjusted life year (QALY) of £4,110 based on an incremental QALY gain of 0.75 and incremental costs of £3,083.

Sensitivity analyses were provided to show the potential variability in the results. For example, in the aggressive NHL group, the cost per QALY increased to £3,737 if a quality of life value of 0.66 was assumed or £17,128 if it was assumed that the survival benefit with the thiotepa regimen fell from 25% to 5%. An analysis combining both of these changes gave a cost per QALY of £18,685.

The key limitations with the analysis relate to the weaknesses of the naive indirect comparison used within the economic model. Given this, the submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

SMC considered the likely range of cost-effectiveness ratios for thiotepa in this setting and the remaining uncertainties in both the clinical and economic case. The committee considered thiotepa in

the context of the SMC decision modifiers for orphan medicines but concluded that it was unable to accept thiotepa due to the high level of uncertainty around its potential clinical benefits relative to the conditioning regimen that is currently in clinical use in Scotland.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: comparators

Other reduced intensity conditioning regimens used in NHS Scotland, e.g. fludarabine, melphalan and alemtuzumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Thiotepa **Cyclophosphamide** **Fludarabine**	**Thiotepa 10mg/kg** **Cyclophosphamide 60mg/kg** **Fludarabine 60mg/m^2**	**5,152** **441** **294**
Fludarabine Melphalan Alemtuzumab	Fludarabine 150mg/m^2 Melphalan 140mg/m^2 Alemtuzumab 100 mg	735 166 1056

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and MIMS on 3 April 2012. Body weight of 70kg and body surface area of 1.7m^2 used to calculate costs.

Additional information: budget impact

Based on the total number of transplants carried out in Scotland, the submitting company estimated the population eligible for treatment to be 260 in year 1 and 305 in year 5. Based on an estimated uptake of 3% in year 1 (8 patients) rising to 10% in year 5 (31 patients), the impact on the medicines budget was estimated at £45k in year 1 and £176k in year 5. The net medicines budget impact was estimated at £22k in year 1 rising to £87k in year 5 after accounting for the displacement of the current regimen. These budget impact estimates were not based on the aggressive and relapsed / refractory lymphoma population reflected in the company's proposed positioning.

References

The undernoted references were supplied with the submission.

1. Corradini P. et al., Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. *Leukemia (2007), 1–8*
2. Corradini P. et al., Effect of Age and Previous Autologous Transplantation on Nonrelapse Mortality and Survival in Patients Treated With Reduced-Intensity Conditioning and Allografting for Advanced Hematologic Malignancies. *J Clin Oncol 23:6690-6698. © 2005*
3. European Product Assessment Report (EPAR) for Tepadina. EMEA/H/C/001046 www.ema.europa.eu
4. ISD Scotland. Cancer statistics www.isdscotland.org. Last accessed 03 April 2012

This assessment is based on data submitted by the applicant company up to and including 11 May 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.