SMC2527

treosulfan powder for solution for infusion (Trecondi®)

Medac Pharma LLP

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, 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

treosulfan (Trecondi®) is accepted for restricted use within NHSScotland.

Indication under review: in combination with fludarabine as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases.

SMC restriction: in patients with malignant disease for whom a reduced intensity conditioning regimen is required.

Treosulfan plus fludarabine was non-inferior to another reduced intensity conditioning regimen for event-free survival (EFS) in adults undergoing alloHSCT for acute myeloid leukaemia (AML) or myelodysplatic syndrome (MDS) who were at increased risk with standard conditioning regimens.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Treosulfan is a prodrug of an alkylating agent with cytotoxic activity to haematopoietic precursor cells. Alkylating nucleophilic centres of deoxyribonucleic acid (DNA) induces cross-links which are considered responsible for its stem cell depleting and antineoplastic effects. Treosulfan is given intravenously over a number of days in the week prior to alloHSCT, with the weight-based dose and dose frequency varying based on patient characteristics and conditioning regimen.[1]

1.2. Disease background

AlloHSCT is potentially curative for leukaemias, MDS, lymphomas and multiple myelomas and it can be used for treatment of non-malignant diseases such as primary immunodeficiency, inborn errors of metabolism, haemoglobinopathies and bone marrow failure syndromes. In alloHSCT, to prepare the patient to receive the donor stem cells (which are derived from another person), a conditioning regimen is given to reduce tumour burden when the disease is malignant, to eliminate the self-renewing capacity of the patient's own haematopoiesis and to suppress their immune system to allow engraftment. Standard myeloablative conditioning regimens comprise chemotherapy alone or in combination with radiotherapy. Morbidity and mortality risks with these regimens preclude their use for older patients and those with co-morbidities. For these patients, reduced intensity conditioning regimens can facilitate alloHSCT.[2]

1.3. Company proposed position

The company has requested that SMC considers treosulfan when positioned for use in patients with malignant disease for whom a reduced intensity regimen is required.

1.4. Treatment pathway and relevant comparators

A variety of reduced intensity conditioning regimens have been used in alloHSCT. Fludarabine plus busulfan is a common regimen, with duration of busulfan (2 to 4 days) determining intensity: non-myeloablative, reduced intensity or myeloablative. Another frequently used reduced intensity conditioning regimen is fludarabine plus melphalan. An optimal regimen is not established and treatment decisions are influenced by patient and disease factors including age, comorbidities, disease status, and measurable residual disease.[2, 3]

1.5. Category for decision-making process (if appropriate)

Eligibility for a PACE meeting:
Treosulfan meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence in the submission is from MC-FludT.14/L Trial II which is detailed in Table 2.1 below.[2, 4, 5]

Table 2.1. Overview of relevant studies

Criteria	MC-FludT.14/L Trial II.[2, 4, 5]
Study Design	Open-label, international, phase III study.
Eligible Patients	Adults (18 to 70 years) with AML in complete haematological remission, with bone marrow blast count <5%, or MDS with bone marrow blast count <20% during disease history. Undergoing alloHSCT from a HLA-MRD or HLA-MUD. Karnofsky Index ≥60%. Unsuitable for standard myeloablative conditioning regimens due to age ≥50 years and/or HCT-CI score >2.
Treatments	Prior to alloHSCT (Day 0), patients received treosulfan (10g/m^2 IV on Day -4, -3 and -2; total dose 30g/m^2) or low dose busulfan (0.8mg/kg IV every six hours on Day -4 and -3; total dose 6.4mg/kg). Both were given in combination with fludarabine (30mg/m^2 IV daily on Day -6 to -2; total dose 150mg/m^2). Other therapies associated with alloHSCT were the same across the treatment groups.
Randomisation	Randomisation was stratified by study site, donor type (MRD versus MUD) and disease risk (AML beyond first complete remission; genetically adverse risk[a] AML at first complete remission; or MDS with high- or very high-risk[b] versus all other patients). Patients equally assigned to treatment groups.
Primary outcome	After two years' follow-up, EFS, defined as time from alloHSCT to disease recurrence or progression (based on investigator-assessed pre-specified morphological, cytogenetic or molecular criteria), graft failure (durable decline in blood neutrophil count <0.5x10^9 cells/L) or death from any cause.
Secondary outcomes	Secondary outcomes assessed for each patient over two-year follow-up from alloHSCT included overall survival, incidence of relapse or progression, primary and secondary graft failure; non-relapse mortality, transplant-related mortality.
Statistical analysis	Primary outcome was assessed in a hierarchy: non-inferiority in PPS then in FAS, then superiority in FAS. Secondary outcomes were not controlled for multiplicity.

a = risk defined by European Leukaemia Network recommendations; b = risk defined by Revised International Prognostic Scoring System for myelodysplatic syndrome. AlloHSCT = allogeneic haematopoietic stem cell transplant; AML = acute myeloid leukaemia; EFS = event-free survival; FAS = full analysis set, which comprised all randomised and treated patients who had at least one efficacy parameter assessed post-baseline; HCT-CI = haematopoietic cell transplant co-morbidity index (HCT-CI); HLA = human leucocyte antigen; IV =intravenous; MDS = myelodysplastic syndrome; MRD = matched related donor; MUD = matched unrelated donor; PPS = per protocol set, which comprised patients from the full analysis set (FAS) without protocol violations.

In November 2016, after the second interim analysis, recruitment to the study was stopped on the recommendation of the Data Monitoring Committee as non-inferiority (the primary objective) had been demonstrated. Data from 476 patients (460 patients in the full analysis set [FAS] and 449 patients in the per protocol set [PPS]) included in the second interim analysis inform the economic analyses in the submission. Subsequent analyses that included all 570 recruited patients (551 and 537 patients in FAS and PPS, respectively) are also detailed below. The second interim analyses indicated that the primary outcome, event-free survival (EFS) within 24 months of alloHSCT, was non-inferior with treosulfan compared with busulfan in the PPS and FAS. Superiority of treosulfan in the FAS was not demonstrated at the level pre-specified at this cut-off in the hierarchical testing strategy. Subsequently, in analyses of EFS in all recruited patients, treosulfan was non-inferior and superior to busulfan. Results are detailed in Table 2.2. [2, 4, 5]

Table 2.2 Results of MC-FludT.14/L Trial II study in Full Analysis Set.[2, 4-6]

Data cut-off	Second Interim Analysis		Analysis of All Patients	
	Treosulfan (N=220)	**Busulfan (N=240)**	**Treosulfan (N=268)**	**Busulfan (N=283)**
Event-Free Survival				
Events	68	100	97	137
HR (95% CI)	0.65 (0.47 to 0.90)*		0.64 (0.49 to 0.84)*,#	
EFS 24 months	64%	50%	66%	51%
EFS 36 months	-	-	60%	50%
Overall survival				
Deaths	52	82	81	112
HR (95% CI)	0.61 (0.42 to 0.88)		0.64 (0.48 to 0.87)	
OS 24 months	71%	56%	73%	60%
OS 36 months	-	-	67%	56%
Relapse / Progression Incidence				
Events	45	51	61	72
HR (95% CI)	0.87 (0.59 to 1.30)		0.82 (0.59 to 1.16)	
IR 24 months	25%	23%	22%	25%
Non-Relapse Mortality				
Deaths	23	41	35	56
HR (95% CI)	0.60 (0.36 to 1.01)		0.63 (0.41 to 0.97)	
NRM 24 months	11%	23%	12%	24%
Transplant-Related Mortality				
Deaths	23	45	33	58
HR (95% CI)	0.54 (0.32 to 0.91)		0.52 (0.34 to 0.82)	
TRM 24 months	12%	28%	13%	24%
GvHD and relapse/progression-free survival				
Events	93	128		
HR (95% CI)	0.72 (0.54 to 0.95)		0.73 (0.57 to 0.92)	
Event-free 24 months	51%	38%		

* significant for non-inferiority; # significant for superiority; analyses of all other outcomes are descriptive. At the second interim analysis, in per protocol set (treosulfan, n=215 and busulfan, n=234), the hazard ratio (95% confidence interval [CI]) was 0.67 (0.48 to 0.93) and p-value, 0.0000424, crossed the significance boundary, 0.000149.
CI = confidence interval; EFS = event-free survival; GvHD = graft versus host disease; HR = hazard ratio; IR = relapse / progression incidence; NRM = non-relapse mortality; OS = overall survival; TRM = transplant-related mortality.

An open-label, uncontrolled, phase II study (MC-FludT.17/M) recruited 70 children (age 28 days to <18 years) with AML or acute lymphoblastic leukaemia (ALL) in complete remission (with blast counts <5% in bone marrow) or juvenile myelomonocytic leukaemia (JMML) or MDS (with blast counts <20% in bone marrow at study entry). They required myeloablative conditioning prior to first alloHSCT or second alloHSCT due to disease relapse, graft failure or secondary malignancy after previous autologous HSCT or alloHSCT. Patients <16 years had Lanskey Index ≥70% and those >16 years had Karnofsky Index ≥70%. They all received treosulfan (IV on Days -6 to -4, dose 10g/m^2 if BSA ≤0.5m^2, 12g/m^2 if BSA >0.5 and ≤1m^2; 14g/m^2 if BSA >1m^2), fludarabine (IV 30mg/m^2/day on Day -7 to -3) and thiotepa (IV 2 x 5mg/kg on day -2, an option at the investigator's discretion). The primary outcome was freedom from transplant-related mortality, defined as death from any transplant-related cause from the first day of study drug to Day 100 after alloHSCT. At an interim analysis this was 91% as only one patient had died from a transplant-related cause, although in the

final analysis a further patient was reclassified as having transplant-related death before Day 100. After 12 months follow-up, seven patients had died due to transplant-related cause (n=3), relapse/progression (n=2), and other (n=2).[2]

2.2. Evidence to support the positioning proposed by the submitting company

Evidence from MC-FludT.14/L Trial II supports the proposed positioning as it relates to adults with malignant disease for whom a reduced intensity conditioning regimen would be required. Evidence from MC-FludT.17/M supports the use of treosulfan in children with malignant disease.

2.3. Supportive studies

Two open-label, uncontrolled studies recruited 75 and 45 adults (18 to 60 years) undergoing alloHSCT for AML (FludT.7/AML) and MDS (FludT.8/MDS), respectively, with HLA-identical sibling (matched related donor) or unrelated donor (matched unrelated donor). They had Karnofsky Index ≥80%. The majority of patients were suitable for a standard conditioning regimen: 75% (56/75) in FludT.7/AML and 91% (41/45) in FludT.8/MDS. Patients received treosulfan 14g/m² IV daily on Day -6 to -4 (which is higher than the licensed dose) in combination with fludarabine 30mg/m² IV daily on Days -6 to -2. Patients with a matched unrelated donor received anti-thymocyte globulin (ATG). Data were analysed descriptively. One patient in each study had secondary graft failure and one patient in the MDS study had primary graft failure. In the respective studies, at two years post alloHSCT, disease-free survival rates were 55% and 67% and cumulative incidences of relapse or progression were 34% and 16%. The overall survival rates were 61% and 71%, with cumulative incidences of non-relapse mortality of 11% and 17% at 24 months. Transplant-related mortality was only reported at 12 months and was 12% and 16% in the respective studies.[2, 7, 8]

3. Summary of Safety Evidence

In MC-FludT.14/L Trial II, at the second interim analysis, within the treosulfan-fludarabine and busulfan-fludarabine groups, adverse event were reported by 93% (206/221) and 95% (229/240) of patients, respectively, and these were considered treatment-related in 63% and 70%. They had severity grade ≥3 in 53% and 55% of patients, including treatment-related events, 27% and 31%, respectively. Serious adverse events were reported by 8.1% and 7.1% of patients and were treatment-related in 2.7% and 3.3%, respectively. No relevant differences were seen between these safety results and those in the final analysis.[2]

In MC-FludT.14/L Trial II, some gastrointestinal adverse events occurred at lower rates with treosulfan-fludarabine than busulfan-fludarabine: oral mucositis (35% versus 47%) and nausea (30% versus 41%). Other common gastrointestinal adverse events were reported at similar rates across the respective groups, including vomiting (20% and 21%), diarrhoea (15% and 20%), constipation (13% and 12%) and abdominal pain (9.5% and 10%). In the treosulfan arm, compared with the busulfan arm, eye disorders (3.6% versus 10%), vertigo (3.2% versus 7.9%), dyspnoea (3.6% versus 8.3%) and elevated gamma glutamyltransferase (7.2% versus 13%) were less frequently reported but cardiac disorders (15% versus 8.3%) were more common. Other common adverse events were reported at similar rates across the groups, including fever (32% and 34%), infections (26% and 24%), febrile neutropenia (15% and 12%), limb oedema (21% and 15%),

fatigue (10% and 13%), headache (15% and 19%), hypertension (15% and 19%), rash (13% and 9.6%), back pain (14% both groups) and bone pain (14% and 10%).[2]

In MC-FludT.14/L Trial II, transplant-related death rate was lower with treosulfan compared with busulfan (10% versus 19%) and cumulative incidence of transplant-related mortality in the FAS at 24 months was 11% and 28% in the respective groups. In the treosulfan group there was a lower incidence of transplant-related deaths involving GvHD (4.8% versus 7.4%) and infection (4.8% versus 7.4%).[2]

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below.

4.1. Key strengths

- In MC-FludT.14/L Trial II, treosulfan-fludarabine was non-inferior to busulfan-fludarabine for EFS, with a HR around 0.65. EFS were numerically (but non-significantly) higher with treosulfan at the second interim analysis and significantly higher in a subsequent analysis of all recruited patients, with increases of approximately 15% and 10% at two- and three-years post-alloHSCT, respectively. The higher rates appear mainly due to a reduction in deaths, as rates of relapse/progression and graft failure were similar across the groups.
- Treosulfan may be associated with improved overall survival rates, with rates increased by around 15% and 11% at two- and three-years post-alloHSCT, respectively. Reduction in deaths with treosulfan-fludarabine appears to be associated with decreases in non-relapse mortality and transplant-related mortality.[2]

4.2. Key uncertainties

- Economic analyses were based on data from the second interim analyses, which was the primary analysis of MC-FludT.14/L Trial II. Subsequent final analyses were generally consistent with this but included a larger number of patients with extended follow-up.
- There was no evidence for treosulfan-fludarabine versus other reduced intensity regimens, such as fludarabine plus melphalan.
- Although there is evidence (from MC-FludT.17/M) for the use of treosulfan in children with malignant disease, it is not controlled. In a regulatory review, it was noted that engraftment in this study was in the range found in six and five historical studies of treosulfan- and busulfan-based conditioning regimens, respectively. One-year overall survival of 91% in the MC-FludT.17/M study was above the ranges reported in the literature for treosulfan-based regimens (82% to 85%) and busulfan-based regimens (78% to 88%).[2]
- The population recruited to the actively controlled study, MC-FludT.14/L Trial II, comprised patients undergoing first alloHSCT for AML or MDS.[2, 4] There are no controlled data in patients undergoing second alloHSCT or undergoing alloHSCT for malignancies other than AML and MDS. All patients in the study had a human leucocyte antigen (HLA) matched donor, that is, a matched rated donor (MRD) or matched unrelated donor (MUD). There is no evidence for the use of treosulfan in a HLA mismatched unrelated donor (MMUD).

- MC-FludT.14/L Trial II was open-label.[2, 4] This design may limit assessment of subjective outcomes such as safety. Health-related quality of life was not assessed in the study.

4.3. Clinical expert input

Clinical experts consulted by SMC notes that treosulfan in this indication is a therapeutic advance as it had advantages compared with alternative reduced intensity regimens in efficacy, safety, administration and monitoring. They consider that it would be used in place of conditioning regimens containing fludarabine plus busulfan or melphalan.

5. Summary of Patient and Carer Involvement

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

- We received a joint patient group submission from Anthony Nolan and Leukaemia Care, both organisations are registered charities.

- Antony Nolan has received 6% pharmaceutical company funding in the past two years, with none from the submitting company. Leukaemia Care has received 27% pharmaceutical company funding in the past two years, with none from the submitting company.

- Allogeneic haematopoietic stem cell transplant (alloHSCT) is an intensive treatment with a profound impact on patients' quality of life. Patients undergoing alloHSCT must spend weeks to months in specialist hospital wards before and after their transplant, where they must adhere to strict isolation and infection control measures. Even after patients are discharged, the side effects of the conditioning therapy and the transplant can have a significant and long-term impact on their day-to-day lives.

- For patients who cannot undergo high-intensity myeloablative conditioning treatments, low-dose busulfan with fludarabine is used as a reduced intensity conditioning treatment in Scotland prior to an alloHSCT. Other reduced intensity conditioning treatments, such as fludarabine plus melphalan and low dose total body irradiation, are also available. There is a clear need in Scotland for effective conditioning regimens for alloHSCT, such as treosulfan with fludarabine, that may have fewer side effects and could potentially improve patients' quality of life and experience of care.

- Patients welcome the introduction of any conditioning regimen that has a reduced toxicity and side effect profile and that could improve survival. When compared to the existing reduced intensity conditioning treatments currently used in Scotland, the patient group believe that the side effect profile of treosulfan could help reduce levels of stress and worry for the patients' family and carers, who undoubtedly will struggle emotionally when seeing their loved one suffering from the extreme side effects pre-transplant conditioning treatments can cause.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (40 years)
Population	The economic analysis aligns with the company's proposed positioning as outlined in Section 1.3.
Comparators	Treosulfan with fludarabine is compared with busulfan with fludarabine.
Model description	A partitioned survival model was presented, comprising of four model health states: induction/ HSCT, post-HSCT recovery (remission), relapsed/ progressed disease and death. All patients enter the economic model in the induction/ alloHSCT health state and, after the first cycle, transition to the post-alloHSCT recovery health state, the relapsed/ progressed disease state or death.
Clinical data	Clinical data from the MC-FludT.14/L study was used to inform survival modelling as well as the adverse event rates in the model.
Extrapolation	The extrapolation of EFS was based on a lognormal non-mixture cure model (NMCM) and overall survival was extrapolated using a Weibull NMCM. The submitting company considered that alloHSCT was a potentially curative treatment and included a 'cure point' at 5 years. Before the cure point, the selected extrapolation models for EFS and overall survival were used. After the cure point mortality in the model was based on life tables for the general population adjusted using a standardised mortality ratio for alloHSCT to reflect alloHSCT-specific mortality.
Quality of life	Health benefits were measured in quality adjusted life-years (QALYs) and included disutilities associated with adverse events. No health-related quality of life (HRQoL) data were collected in MC-FludT.14/L. Instead, published sources of health state utility values (HSUVs) used to inform the economic model were identified through a targeted and systematic literature review. Several identified sources collected quality of life information through the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), which was subsequently mapped to EuroQol 5 Dimension (3 level)(EQ-5D-3L) values for use in the model. Utility values ranged from 0.52 in the induction/ HSCT state to 0.81 for patients considered functionally cured.
Costs and resource use	Medicine costs included medicine acquisition, concomitant medicine costs, alloHSCT procedure costs, adverse event costs and relapse treatment costs. Medicines wastage was included in the base case. Time-dependent disease management costs for the post-HSCT recovery and relapse/ progression health states were included. For patients who relapse after one year, the submitting company included the cost of a second alloHSCT. Additionally, a one-off cost prior to death was included in the model.
PAS	The company has not proposed a Patient Access Scheme (PAS) for treosulfan.

6.2. Results

The base case results are presented in Table 6.2. The QALYs differences were primarily driven by treosulfan plus fludarabine patients staying in the relapse-free state longer than busulfan plus fludarabine patients. Cost savings for treosulfan plus fludarabine were primarily driven by a reduction in costs associated with relapse and progression of disease.

Table 6.2 Company base case results

Interventions	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Busulfan plus fludarabine	225,833	7.63	5.44	-	-	-	-
Treosulfan plus fludarabine	175,701	8.45	6.23	-50,132	0.82	0.78	Dominant

Abbreviations: Incr., incremental; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.
Dominant: Costs less with better health outcomes.

6.3. Sensitivity analyses

A number of sensitivity analyses were provided, and the key scenarios are summarised in Table 6.3. The ICER remained dominant for all key scenarios explored.

Table 6.3 Key sensitivity analyses

	Scenario	Base case approach	Scenario approach	ICER
	Base case	-	-	Dominant
1	**Utility mapping algorithm**	Use of EORTC-QLQ-C30 mapping algorithm by Proskorovsky *et al*.[9]	Use of alternative EORTC-QLQ-C30 mapping algorithm by McKenzie *et al*.[10]	Dominant
2	**Source of utilities**	Utility values based on Grulke *et al,* Proskorovksy *et al* and Kurosawa *et al*.[9, 11, 12]	Utility values based on Castejon *et al* and Stein *et al*.[13, 14]	Dominant
3	**MDS relapse/progression utility value**	MDS relapse/progression utility based on Proskorovsky *et al*.[9]	Alternative MDS relapse/progression utility based on Szende *et al*.[15]	Dominant
5	**Busulfan dosing**	Busulfan dosing of 4 x 0.8 mg/kg/day	Alternative busulfan dosing (3.2 mg/ kg)	Dominant
6	**EFS and OS extrapolation**	Overall EFS and OS extrapolation	Weighted AML and MDS EFS and OS extrapolation	Dominant
7	**Time horizon**	Lifetime horizon (40 years)	5-year time horizon	Dominant
8			10-year time horizon	Dominant
9	**Cure point**	5 years	2 years	Dominant
10			7 years	Dominant
11			10 years	Dominant
12	**Health state unit costs**	Scottish costs book/ NHS reference costs	NHS references	Dominant

6.4. Key strengths

- The model structure was considered appropriate.
- The economic analysis used head-to-head clinical evidence for treosulfan plus fludarabine versus busulfan plus fludarabine in the population of interest.
- The analysis used a comprehensive approach to valuing health state utilities and estimating costs and resources.

6.5. Key uncertainties

- The clinical data used in the economics were from patients suffering from AML or MDS. There was uncertainty whether the cost-effectiveness results were generalisable to malignancies other than AML and MDS.
- Melphalan plus fludarabine was considered a relevant comparator, but the submitting company assumed efficacy was similar to busulfan plus fludarabine, and thus they did not present a cost-effectiveness case for that regimen.
- Clinical data used in the model were based on the interim data analysis from MC-FludT.14/L study. Final analysis from the study was available but not used. Use of the latest data would have reduce uncertainty in the economic model, although given the consistency in clinical results between the two time points the implications were likely small.
- No cost-effectiveness analyses for children with malignant disease was conducted due to limited data availability and the generalisability of the central economic results to this group was uncertain. However, as treosulfan is indicated for patients who would be eligible for a reduced intensity conditioning regimen, it was considered that the number of children eligible for treosulfan would be small.

7. Conclusion

After considering all the available evidence, the Committee accepted treosulfan for restricted use in NHSScotland.

8. Guidelines and Protocols

The European Society for Blood and Marrow Transplantation (EBMT) Handbook: Haematopoietic Stem Cell Transplantation and Cellular Therapies was published in 2019. See here.

9. Additional Information

9.1. Product availability date

1 April 2020.

9.2. Summary of product characteristics

See SPC for further information including dosing and safety. Treosulfan powder for solution for infusion (Trecondi®) SPC.

Table 9.1 List price of medicine under review

Medicine	Dose regimen (in adults with malignant disease)	Cost per course (£)
Treosulfan Fludarabine	**Adults with malignant disease** 10g/m² intravenous (IV) infusion on Day -4, -3, and -2 30mg/m² intravenous (IV) infusion on Day -6, -5, -4, -3, -2	5,710
Treosulfan Fludarabine	**Children with malignant disease (FT_{10-14} regimen)** 10 to 14g/m² intravenous (IV) infusion on Day -6, -5, and -4 30mg/m² intravenous (IV) infusion on Day -7, -6, -5, -4, -3	3,656 to 5,710

Costs, based on body surface area of 1.7m² for adults and 0.5m² to 1.2m² for children, from BNF online on 19 January 2023. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 30 patients eligible for treatment with treosulfan in year 1 increasing to 151 in year 5. The estimated uptake rate was 25% in year 1 and 50% in year 5. This resulted in eight patients estimated to receive treatment in year 1 rising to 75 patients in year 5. The gross impact on the medicines budget was estimated to be £375k in year 1 rising to £752k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £21k in year 1 and £42k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 20 April 2023.

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.