EU RISK MANAGEMENT PLAN (EU-RMP) for:
TEPADINA 15 mg powder for concentrate for solution for infusion;
TEPADINA 100 mg powder for concentrate for solution for infusion;
TEPADINA 200 mg powder and solvent for solution for infusion;
TEPADINA 400 mg powder and solvent for solution for infusion.

RMP version to be assessed as part of this application:

RMP Version number: 015

Data lock point for this RMP: 31/03/2023

Date of final sign off

Rationale for submitting an updated RMP: introduction of a new strength.

Summary of significant changes in this RMP: introduction of a new strength of TEPADINA.

Other RMP versions under evaluation: N.A.

Details of the currently approved RMP:

Version number: 014

Approved with procedure: EMEA/H/C/001046/X/0036

Date of approval (opinion date): 28/01/2021

PPD

Date: 08.01.2024

QPPV name: Marco Sardella

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´QPPV. The electronic signature is available on file.

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Part I: TEPADINA Overview

Table Part I.1 – Products Overview

Active substance(s) **(INN or common name)**	Thiotepa (N,N'N'-triethylenethiophosphoramide)
Pharmacotherapeutic group(s) (ATC Code)	L01AC01
Marketing Authorisation Holder>	*ADIENNE S.r.l. S.U.*
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	*TEPADINA*
Marketing authorisation procedure	Centralised (EMEA/H/C/1046)
Brief description of the product	Chemical class: • Thiotepa is a cytostatic agent. It is an ethylenimine-type compound. • The chemical name of thiotepa is N, N´, N´´-triethylenethiophosphoramide.
	Summary of mode of action: • Thiotepa is a cell cycle-phase independent, non-specific alkylating antineoplastic agent related to nitrogen mustard. • Thiotepa acts by disrupting DNA bonds via the release of ethylenimine radicals. Disruption of DNA causes cytotoxicity by interrupting cellular processes and biosyntheses especially the syntheses of nucleic acids and proteins.
	Important information about its composition *(e.g. origin of active substance for biologicals, relevant adjuvants or residues for vaccines):* *N.A.*
Hyperlink to the Product Information	See the Product Information –MOD.1 section 1.3.1 (SPC, Labelling and Package Leaflet).
Indication(s) in the EEA	<u>Current:</u> TEPADINA is indicated, in combination with other chemotherapy

	medicinal products: • 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; • when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.
	Proposed (if applicable): *N.A.*
Dosage in the EEA	Current: TEPADINA is administered via intravenous infusion at different dosages in combination with other chemotherapeutic medicinal products in patients prior to HPCT for haematological diseases or solid tumours. For detailed posology see SmPC.
	Proposed (if applicable): *N.A.*
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for infusion; 15 mg, 100 mg Powder and solvent for solution for infusion; 400 mg
	Proposed: Powder and solvent for solution for infusion; 200mg
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population

Epidemiology of the disease

The cytotoxic and immunosuppressive drug therapy includes different combinations of alkylators and well-know immunosuppressive drugs. Thiotepa holds a firm position in the field of the conditioning therapy before transplantation. Transplantations are highly complex procedures with a number of influencing factors ranging from the conditioning myelosuppressive therapy to the source of the stem cells, the degree of T-cell depletion, the matching or mismatching of the graft and finally the control of immunosuppression after bone marrow transplatation.

All of these factors influence the outcome in respect of toxicity as well as efficacy. Optimal doses, times or schedules tailored to thiotepa are therefore difficult to define.

Main primary diseases for conditioning therapy are:

- heaematological malignancies (acute and chronic myeloid leukaemia, acute lymphoid leukaemia, myelofibrosis, multiple myeloma, lymphoma, and chronic lymphocytic leukaemia);
- solid tumors (breast cancer, ovarian cancer, SNC and brain tumors, etc.)

In the last thirty years haematopoietic stem cell transplantation has become a standard therapy in patients with advanced haematological malignancies and malignant solid tumors resistant to standard chemotherapy.

The 2007 report of EBMT (European Group for Blood and Marrow Transplantation) highlighted the increasing role of allogeneic HSCT in treatment of AML. In 2007, there were 25563 first HSCTs, 10072 allogeneic (39%), 15491 autologous (61%) and 3606 additional transplants reported from 613 centers in 42 countries. The main indications were leukemias (8061 (32%; 89% allogeneic)); lymphomas (14627 (57%; 89% autologous)), solid tumors (1488 (6%; 96% autologous)) and non malignant disorders (1302 (5%; 91% allogeneic)). Peripheral blood was the main source of stem cells for autologous HSCT (98%) and the predominant source for allogeneic HSCT (71%). Among allogeneic HSCTs, the number of unrelated donor grafts equaled the number of HLA-identical sibling donor grafts for the first time (47% each). AML was the most frequent indication for allogeneic HSCT (32% of allallogeneic HSCTs), with an increase of 247 (8%) (Gratwohl et al. 2009).

The 2010 annual survey of EBMT had for the first time reported more than 30’000 patients transplanted in a given year.

This trend continued with an additional increase by 6.3% in 2011. The EBMT transplant activity survey data office in Basel contacted 680 centers from 48 countries (39 European and 9 affiliated countries) for the 2011 annual survey; having a 95% return rate: 536 active EBMT member teams. 16 active teams failed to report in 2011 whilst 15 teams reported no activity due to transplant program development or closure.

In the EBMT review published in 2012, data and trends referred to the activity performed in 2010 are reported (Passweg JR et al, Bone Marrow Transplant. 2012 Jul;47(7):906-23). In all, 634 centers reported a total of 33.362 hematopoietic SCT (HSCT) with 30.012 patients receiving their first transplant (12.276 allogeneic (41%) and 17.736 autologous (59%)). Main indications were leukemias: 9355 (31%; 93% allogeneic), lymphoid neoplasias specifically Non Hodgkin's lymphoma, Hodgkin's lymphoma and plasma cell disorders: 17.362 (58%; 12% allogeneic), solid tumors: 1585 (5%; 6% allogeneic) and non-malignant disorders: 1609 (6%; 88% allogeneic). There were more unrelated donors than HLA-identical sibling donors (53% versus 41%); the proportion of peripheral blood as stem cell source was 99% for autologous and 71% for allogeneic HSCT. Cord blood was primarily used in allogeneic transplants (6% of total) with three autologous cord blood HSCT being reported. The number of transplants has increased by 19% since 2005 (allogeneic 37% and autologous 9%) and continued to increase by about 1100 HSCT per year since 2000. Patterns of increase were distinct and different. The data show the development of transplantation in Europe since 1990, with the number of patients receiving a HSCT increasing from 4.200 to over 30.000 annually. The most impressive trend seen is the steady increase of unrelated donor transplantation, in parallel to the availability of unrelated donors through donor registries.

In 2013, the EBMT Survey activity has been published (Passweg JR et al, Bone Marrow Transplant. 2013 Apr 15). 651 centers in 48 countries reported 35.660 hematopoietic SCT (HSCT) in 32.075 patients (13.470 allogeneic (42%), 18.605 autologous (58%)). The main indications were the same of the previous reports: leukemias; 10.113 (32%; 94% allogeneic); lymphoid neoplasias; non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasma cell disorders; 18.433 (57%; 12% allogeneic); solid tumours; 1573 (5%; 5% allogeneic); and non-malignant disorders; 1830 (6%; 92% allogeneic).The number of transplants has increased by 19% since 2005 (allogeneic 37% and autologous 9%) and continued to increase by about 1100 HSCT per year since 2000. In spite of the economic crisis in Europe there does not appear to be a decrease in transplant activity since 2009 but rather a continued annual increase in the use of HSCT technology.
In the last 10 years the overall number of transplants has increased by 53%. Allogeneic HSCT have doubled (7.272 to 14.476) whilst, autologous have increased by 32% and continued to increase by about 1,100 HSCT per year since 2001.
In 2023, the EBMT Survey activity has been published [Passweg JR et al, Bone Marrow Transplant 58, 647–658 (2023)]. In the year 2021 47,412 HSCT (19,806 (42%) allogeneic and 27,606 (58%) autologous) in 43,109 patients were reported by 694 European centers. 3494 patients received advanced cellular therapies, 2524 of which were CAR-T treatments, an additional 3245 received DLI. After the decrease in HSCT activity due to the SARS-CoV-2 pandemic reported in the 2020, the total number of transplants increased again by +4.5% (+5.4% allogeneic HSCT and +3.9% autologous HSCT).
Main indications for allogeneic HSCT were myeloid malignancies 10,745 (58%), lymphoid malignancies 5127 (28%) and non-malignant disorders 2501 (13%). Main indications for autologous HSCT were lymphoid malignancies 22,129 (90%) and solid tumors 1635 (7%). In allogeneic HSCT, use of haploidentical donors decreased by −0.9% while use of unrelated and sibling donors increased by

+4.3% and +9%. Cord blood HSCT decreased by −5.8%. Pediatric HSCT increased overall by +5.6% (+6.9% allogeneic and +1.6% autologous). Increase in the use of CAR-T was mainly restricted to high-income countries.

Concomitant medication(s) in the target population

The most common concomitant medications used with TEPADINA are alkylating agents (defined as "conditioning regimes"), immunosuppressive drugs and drugs for the infection's prophylaxis.

The conditioning regimens consist in the combination of more alkylating agents with or without TBI. The use of more mieloablative agents cause a profound mielotoxicity that permits to perform the HSCT but at the same time it is correlated with haematological toxicity and adverse events due to the overlap toxicity profiles of these medicinal products.

The immunosuppressive drugs used for GvHD prophylaxis are mainly ciclosporine, tacrolimus, mofetil micophenolate and steroids.

Finally, medications for antibacterial, antiviral and antifungal profilaxys are invariably used in patients undergoing HSCT.

In the table below a list of medications frequently used with TEPADINA are reported with the reference papers where the association is described.

Conditioning regimen	Ref.	GvHD	Ref.	Infection	Ref.	Other	Ref.	Induction therapy	Ref.
Busulfan	6-7-13-19-24-28-29-32-33	ATG	1-5-7-8-10-17-20-25-29-35-36	Trimethoprim	5-7-36	G-CSF	14-16-22-23-24-28-30-35-36	Cortisco steroids	26
Fludarabine	1-2-3-4-5-7-8-10-12-16-17-21-23-24-28-29-35-36	Cyclosporine	1-2-3-8-23-24-29-32	Fluconazole	7- 10-24-29	Mesna	22-24	Carmustine	26
Cyclophos phamide	6-8-16-20-21-23-25-28-32-33	Tacrolimus	5-30-36	Acyclovir	7-9-24-36	Diphenyl-hydantoin,	29	Metotrexate	26
Treosulfan	1-2	MMF	5-23-24-29	Ciprofloxacin	7-29	clonazepam or lorazepam	13-29	Etoposide	26
Total Body Irradiation (TBI)	9-16-17-20-21-23-34-35-36	Corticosteroids	29-36	Levofloxacin	24	levetiracetam	6-13	Adryamicine	11
Melphalan	5-13-19-34	Methotrexate	2-7-8	Rituximab	9	Phenytoin	6	Vincristine	11
Carmustine	3-15-26	OKT3	12	iv IG	10-28	Ursodiol	6	Amsacrine	30
Etoposide	11-27	Alemtuzumab	3-4	Itraconazole	29-36				
Carboplatin	11-14-15-22-27-31	Basiliximab	7	Voriconazole	5-29-36				
Topotecan	14	Cyclophos pamide	5-24	Cotrimoxazole	10-28-29				
Cytarabine	30			Pentamidine	5-29-36				
Cladribine	18			Ganciclovir	3-36				
				Foscarnet	3-36				
				Atovaquone	16				
				Liposomal Amphotericine B	32				
				Valacyclovir	3-5				
				Vancomycine	16				

References in the table:

1. Bernardo Blood.2012;120(2):473-476
2. Choudhary Biol Blood Marrow Transplant 19 (2013) 492-503;
3. Christopoulos Biol Blood Marrow Transplant 18: 1430-1437 (2012);
4. Christopoulos1 Bone Marrow Transplantation (2013), 1–7;
5. Ciurea Biol Blood Marrow Transplant 18: 1835-1844 (2012);
6. Cote Biol Blood Marrow Transplant 18: 76-83 (2012);
7. Di Bartolomeo Blood. 2013;121(5):849-857;
8. Dodero Leukemia (2011), 1–7;
9. Dominietto Bone Marrow Transplantation (2011), 1–6
10. Dvorak Bone Marrow Transplantation (2012), 1–6;
11. Falzetti Clin Exp Med. 2012 Sep;12(3):165-71;
12. Federmann Haematologica | 2012; 97(10);
13. Ganguly Bone Marrow Transplantation (2011), 1–2;
14. Gilheeney Pediatr Blood Cancer 2010;54:591–595
15. Gilman Pediatr Blood Cancer 2011;57:506–513;
16. Jakubowski Biol Blood Marrow Transplant 17: 1335-1342 (2011);
17. Jakubowsky Biol Blood Marrow Transplant 19 (2013) 208e213;
18. Larsen JT, et.al -Leuk Lymphoma. 2012 Dec 31
19. Lee Bone Marrow Transplantation (2010) 45, 801–802
20. Pasquini J Clin Oncol 30:3194-3201;
21. Perales Bone Marrow Transplantation (2010), 1–9;
22. Pizer EUROPEAN JOURNAL OF CANCER 47 (2011)1389 –1397;
23. Ponce Biol Blood Marrow Transplant 19 (2013) 799-803;
24. Raiola et Biol Blood Marrow Transplant 19 (2013) 117-122;
25. Rambaldi Leukemia (2012) 1 – 7;
26. Reddy Bone Marrow Transplantation (2012) 47, 1265 – 1268;
27. Saarinen-Pihkala Pediatr Blood Cancer 2012;59:1190–1197;
28. Sanz Biol Blood Marrow Transplant 16:86-94, 2010;
29. Sanz Bone Marrow Transplantation (2012) 47, 1287 – 1293;
30. Saure et al. Biol Blood Marrow Transplant 18:466-472, 2012
31. Schechter et al. Biol Blood Marrow Transplant 19 (2013) 235-239;
32. Sodani Blood, 11 February 2010 _ Volume 115, Number 6
33. Soussain Haematologica 2012;97(11):1751-1756;
34. Sung Bone Marrow Transplantation (2012), 1–6;
35. Weisdorf Biol Blood Marrow Transplant-: 1-8 (2012);
36. Yoshihara Bone Marrow Transplantation (2011), 1–5;

As can be seen from the table, the use of other concomitant medications with TEPADINA has been widely described in different articles in worldwide literature.

Important co-morbidities found in the target population

The most important co-morbidities found in the target population that could have an impact on HSCT procedure can be: arrhythmia, inflammatory bowel disease, rheumatologic disease, peptic ulcer, moderate and severe pulmonary comorbidity, prior solid tumor, heart valve disease. cardiac disease, diabetes mellitus, cerebrovascular disease, mild hepatic comorbidity, moderatere renal comorbidity, and moderate/severe hepatic comorbidity, obesity, peritransplant infections, psychiatric disturbances, bleeding, headache, osteoarthritis, osteoporosis, asthma, hypertension, gastrintestinal disease, peripheral vascular disease. Many of the previous co-morbidities could be directly correlated with the neoplastic disease and/or with the therapies use to treat the patient (Sorror et al. "Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool for risk assessment before allogeneic HCT" Blood. 2005;106: 2912-2919).

Part II: Module SII - Non-clinical part of the safety specification

As detailed in GVP Module V.C.3.1 (d) for products authorised under Article 10 (a) of Directive 2001/83 as "well-established use" the present Module of the RMP is not required.

Part II: Module SIII - Clinical trial exposure

As detailed in GVP Module V.C.3.1 (d) for products authorised under Article 10 (a) of Directive 2001/83 as "well-established use" the present Module of the RMP is not required.

Part II: Module SIV - Populations not studied in clinical trials

As detailed in GVP Module V.C.3.1 (d) for products authorised under Article 10 (a) of Directive 2001/83 as "well-established use" the present Module of the RMP is not required.

Part II: Module SV - Post-authorisation experience

Since TEPADINA was first authorized by European Medicines Agency (EMA) there have been no actions taken for safety reasons related to either investigational use or marketing experience that had either a significant influence on the risk-benefit balance.

In particular:

- no marketing authorisation withdrawal,
- no revocation or suspension,
- no failure to obtain a marketing authorisation renewal,
- no restrictions on distribution,
- no clinical trial suspension,
- no dosage modification,
- no formulation changes of the products,
- no changes in target population or indications.

SV.1 Non-study post-authorisation exposure

The number of patients exposed to the medicinal product TEPADINA was calculated on the available sales data as no clinical trials have been sponsored by the MAH.
Sales data were collected from the ADIENNE's logistic and marketing department and from the Local Representatives in relevant territories.

SV.1.1 Method used to calculate exposure

The cumulative patient exposure from marketing experience since IBD to 31 March 2023 is described here below. Overall, in the period between 15 March 2010 (IBD) and 31 March 2023 364.640 vials of 15 mg and 537.934 vials of 100 mg TEPADINA® and 513 Multi-Chamber Flexible Bag (MCFB) of TEPADINA® 400 mg have been sold in Europe and in Extra-EU Countries.

Table SV.2.2.1 – Overall estimation of quantity of product sold in the period covered by this report - 10 March 2010 (IBD) to 31 March 2023

Country	No. of 15 mg vials	No. of 100 mg vials	No. of 400 mg MCFB	Tot. TEPADINA mg sold
EUROPE				
CCI [redacted]				
TOTAL EUROPE	**197268**	**344512**	**465**	**37596220**
CCI [redacted]				

CCI

[redacted]

Country	No. of 15 mg vials	No. of 100 mg vials	No. of 400 mg MCFB	Tot. TEPADINA mg sold
CCI [redacted]				
GRAND TOTAL	**364640**	**537934**	**513**	**59468200**

(*) Including sales of TEPADINA in USA before the date of approval (e.g. during the shortage of thiotepa in USA)

Although it is impossible to know precisely how TEPADINA® was used in the hospital, estimates can be made assuming that:

- 80% of the drug was given to patients as part of a conditioning regimen (the remaining 20% remains in the distribution channel)
- 80% of transplant recipients were adult (considered weight is 60 kg for adults and 20 kg for pediatric patients, respectively)
- the following doses were used in the different approved indications:

  a. 10 mg/kg of TEPADINA® in allogeneic HSCT (both in adult and paediatric patients);
  b. 15 mg/kg of TEPADINA® in autologous HSCT in adult patients;
  c. 36 mg/kg of TEPADINA® in autologous HSCT in paediatric patients.

Finally, it is assumed that TEPADINA® has been used in different transplant conditions as follows:

  d. 10% in conditioning regimen prior to autologous HSCT in adult patients;
  e. 70% in conditioning regimen prior to allogeneic HSCT in adult patients;
  f. 10% in conditioning regimen prior to autologous HSCT in paediatric patients;
  g. 10% in conditioning regimen prior to allogeneic HSCT in paediatric patients.

SV.2.2 Exposure

Overall, on the basis of the above assumptions, it could be estimated that overall **91.185** subjects and in particular **60.790** adult and **30.395** pediatric patients have received TEPADINA® based conditioning before stem cell transplant during the period between IBD and 31 March 2023.

Table SV.2.2.1 – TEPADINA® cumulative patient exposure from 10 March 2010 (IBD) to 31 March 2023

Indication		Age	Dose for a complete treatment (mg/kg)	Mean body weight (kg)	Quantity of TEPADINA® to treat a patient (mg)	% incidence	Quantity of TEPADINA® totally used 15 Mar 2010 – 31 Mar 2023 (mg)	Number of patients treated
HSCT	Autologus	Adult	15	60	900	10%	4757456	5286
HSCT	Allogenic	Adult	10	60	600	70%	33302192	55504
HSCT	Autologus	Pediatric	36	20	720	10%	4757456	6608
HSCT	Allogenic	Pediatric	10	20	200	10%	4757456	23787
						TOTAL	**47574560**	**91185**

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

1. **Myelosuppression:**

Myelosuppression is the result of the pharmacological effect of thiotepa. Therefore all patients experienced profound myelosuppression. Generally myelosuppression is transient, so most of the symptoms resolved. In some cases death principally from infections and sepsis has occurred as a direct result of hematopoietic depression by the conditioning regimen (see "Identified risk: infection").

Frequency reported (95% CI) for myelosuppression and myelosupprossion-related conditions are as follows:
In Adults, autologous HSCT: from a minimum of 5% (1/20: Cairncross, 2000) to a maximum of 100% (100/100: Schrama 2003) of patients experienced cytopenia. From 24% (34/143: Coombes, 2005) to 100% (18/18: Papadopoulos, 1998) of patients reported febrile neutropenia.

In Adults, allogenics HSCT: from a minimum of 1.9% (1/53: Majoilino, 2007) to a maximum of 49% (63/154: Bacigalupo, 2009) of patients experienced cytopenia. 91% (64/70: Alessandrino, 2004; Grullich, 2008) of patients reported febrile neutropenia.
In children, autologous HSCT: Grade III-IV: pancytopenia: 100% (40/40: Dunkel 1998, Broniscer 2004), anemia: 100% (8/8: Grodman 2009); neutropenia: 100% (68/68: Dunkel 1998, Mason 1998, Grodman 2009); febrile neutropenia: 100% (37/ 37: Mason 1998); thrombocytopenia: 100% (45/45: Mason 1998, Grodman 2009).
Patients who have received prior chemotherapy with respect to treatment with thiotepa could be more susceptible to the myelotoxic effect. Patients who receive concomitant therapies are more likely to have myelosuppression. Appropriate aid of growth factors and transfusion support will help prevent subsequent cases, if medically indicated. Given the limited population in the target indication, their overall prognosis and the availability of growth factors and transfusion support, the public health concern is small.

2. Mucositis

Mucositis is reported as one of the most debilitating side effects in patients who underwent conditioning regimen and stem cell transplantation. There are no fatal cases in the selected clinical studies due to mucositis.

Frequencies reported (95% CI) are as follows:
In adults, autologous HSCT: from a minimum of 16,6% (6/23: Illerhaus 2006) to a maximum of 100% (18/18: Papadopoulos, 1998) of patients with mild (grade I-II) mucosal inflammation; from a minimum of 3% (3/180: Gutierrez-Delgado 2001 and Gutierrez-Delgado, 2003) to a maximum of 88% (110/125: Glossmann 2005) of patients with severe (grade III-IV) mucosal inflammation.
In adults, allogenic HSCT: From a minimum of 6,7% (2/30: Rosales, 1999) to a maximum of 64% (20/31: Bacigalupo, 1996) of patients with severe (grade III-IV) mucosal inflammation.
In children, autologous HSCT: mild mucosal inflammation with a maximum of 49% (17/35: Dupuis-Girod 1997, Valteau-Couanet 2005); from a minimum of 38,9% (7/18: Lafay-Cousin 2000) to a maximum of 100% (85/85: Dunkel 1998, Broniscer 2004, Mason 1998, Grodman 2009, Massimino 2006, Kushner 2001) of patients with severe mucosal inflammation.
In children, allogenic HSCT: from a minimum of 14,3% (2/14: Locatelli 2009) to a maximum of 100% (18/18: Locatelli 2009) of patients with mild mucosal inflammation. Generally mucositis prevalence ranges from 75%to 85% in patients who underwent conditioning regimen and stem cell transplantation.
The pathogenesis of mucositis depends on the damage to the epithelium and underlying tissue. The main pathological changes are increased vascular permeability, oedema, inflammation. Furthermore conditioning regimen provokes myelosuppression that leads to mucosal superinfection. Given the limited population in the target indication and their overall prognosis, the public health concern is small.

3. Venoocclusive liver disease

Hepatic veno-occlusive disease (VOD) is a life threatening complication of preparative-regimen-related toxicity for bone marrow transplantation. Potential mechanism not known. Probably related to the increase of thrombotic risk in case of tumoral diseases.
Deaths from VOD were the following:
In adults, autologous HSCT: 5,7% (11/194: Gutierrez-Delgado 2001; Gutierrez-Delgado 2003; Gopal 2001); 1,4% (2/143: Rodenhuis 2006); 3% (1/31: Holmberg, 1998)
In adults, allogenic HSCT: 2% (1/58: Aversa 1999); 3,7% (1/27: La Nasa 2005)
In children, autologous HSCT: 9% (1/11: Grovas, 1999); 4,4% (2/45: Finlay,1996); 6,6% (1/15: Valteau-Couanet 2005); 4,8% (1/21: Chan 1997); 6,3% (1/16: Hawkins 2000).
In children, allogenic HSCT: 3% (1/32: La Nasa 2002); 5% (1/19: Strahm 2007); 3,8% (1/26: Rosales 1999).

Frequencies reported (95% CI) are as follows:

In adults, autologous HSCT: from a minimum of 1,4% (2/143: Rodenhuis 2006) to a maximum of 5,7% (11/194: Gutierrez-Delgado 2001; Gutierrez-Delgado 2003; Gopal 2001) of patients experienced severe or fatal (grade III-IV) venoocclusive liver disease.
In adults, allogenic HSCT: from a minimum of 2% (1/58: Aversa 1999) to a maximum of 12% (2/17: Aversa 1994) of patients experienced severe or fatal venoocclusive liver disease.
*In children, autologous HSCT:*from a minimum of 4,5% (1/22: Lucidarme 1998) to a maximum of 27,1% (19/70: Grill 1996, Dupuis-Girod 1997, Valteau-Couanet 2005, Ridola 2007) of patients experienced grade I-II venoocclusive liver disease.
From a minimum of 4,4% (2/45: Finlay,1996) to a maximum of 14,9% (11/74: Dupuis-Girod 1997, Valteau-Couanet 2005, Ridola 2007, CNS TUMOURS – TT/BU) of patients experienced severe or fatal venoocclusive liver disease.
In children, allogenic HSCT: Fatal VOD was reported in two studies with a maximum frequency of 5% (1/19: Strahm 2007).
From literature VOD incidence and severity are shown to be reduced with the use of defibrotide. Given the limited population in the target indication and their overall prognosis, the public health concern is small.

4. Hypersensitivity

Hypersensitivity reactions are a known pharmacologic class toxicity. The risk is potentially severe due to the nature of the possible adverse effects. Reactions are generally serious and life-threatening. In selected clinical studies for safety database there is no indication of death caused by hypersensitivity reactions. However the reaction is known for cytotoxic agents. In a literature research we found one article of hypersensitivity due to thiotepa were the patient recovered. The incidence of Hypersensitivity reactions should be higher for the combination of other cytotoxic agents (cyclophosphamide, fludarabine, melphalan, busulfan, etc).
Of note, hypersensitivity reactions includes events in addition to the MedDRA terms listed (for example cutaneous allergic manifestations, oedema): these adverse events are listed under the appropriate SOC, describing symptoms consistent with a hypersensitivity reaction were included. Patients who result to be hypersensitive to other alkylant drugs could be more susceptible to the hypersensitivity effect. Patients who receive concomitant therapies are more likely to have hypersensitivity reactions. Patients who experience a hypersensitivity reaction are not eligible for repeat exposure. Hypersensitivity to drugs is a contraindication to treatment. Given the low incidence in the target population, the generally prompt response to treatment and the use of subsequent pre-medication when appropriate, this does not represent a significant public health safety concern.

5. Graft Versus Host Disease

Acute and chronic graft-versus-host disease (GvHD) is a consequence of the conditioning regimen and transplant process and is considered the major cause of morbidity and mortality in allogeneic HPCT.
GvHD is firstly correlated to immunosuppressive therapy and compatibility donor/recipient.
Pathophysiology of acute GvHD:

h. The first phase involves damage to host tissues by inflammation from the preparative chemo- and/or radiotherapy regimen.
i. In the second phase, both recipient and donor antigen-presenting cells, as well as inflammatory cytokines trigger activation of donor-derived Tcells.
j. In the third (effector) phase, activated donor T cells mediate cytotoxicity against target host cells.

Deaths from GvHD in allogenic HPCT were the following:
Adults: 2,7% aGvHD (5/187) and 1,1% cGvHD (2/187: Corradini 2004, Corradini 2007); 0,5% aGvHD (3/625: Bacigalupo 2007, Raiola 2000, Di Grazia 2001); 6% cGvHD (15/251: Bacigalupo 2007, Raiola 2000, Di Grazia 2001); 3% aGvHD (4/150: Corradini 2005); 5% aGvHD (5/94: Alessandrino 2004, Grullich 2008, Alessandrino 2001, Picardi 2004); 1% CGvHD (1/88: Alessandrino 2004, Grullich 2008, Picardi 2004); 10% aGvHD (1/10: Bethge, 2006); 4% aGvHD (2/52: Jakubowski 2007); 13% aGvHD

(4/31: Bacigalupo 1996); 20% aGvHD (6/30) and 3,3% cGvHD (1/30: Rosales 1999); 2,4% aGvHD (1/42: Rigden 1996); 3,2% cGvHD (1/31: Papadopoulos 1998); 6% aGvHD (1/17: Aversa, 1994); 2,5% aGvHD (7/276: Aversa 1999, Aversa 2002, Aversa 2005, Aversa 2001); 7,4% aGvHD (2/27) and 3,7% cGvHD (1/27: La Nasa 2005).
Children: 6,2% aGvHD (6/97: Zecca 1999, Locatelli 2009); 2,5 aGvHD (1/40) and 2,5% cGvHD (1/40:Locatelli, 2009); 5,26% cGvHD (1/19: Locatelli 2009); 5% aGvHD (2/30: Bernardo 2008; Locatelli 2009); 1,5 % aGvHD (1/65: Locatelli 2009); 6,3% aGvHD (1/16) and 6,3% cGvHD (1/16: Locatelli, 2009); 3,8% aGvHD (1/26: Strahm 2007 =).

Frequencies reported (95% CI) are as follows:
In adults, allogenic HSCT: aGvHD: from a minimum of 6% (2/31: Papadopoulos, 1998) to a maximum of 89,4% (195/218: Bacigalupo, 2009, Bacigalupo, 2007, Raiola, 2000, Di Grazia, 2001) of patients with one or more epidosodes of grade I-II; from a minimum of 5,6% (6/107: Aversa 1999, Aversa 1994, Aversa 2001) to a maximum of 24% (17/78: Bacigalupo 2007, Bacigalupo 1996) of patients with one or more episodes of grade III-IV.
cGvHD: from a minimum of 19% (5/27: La Nasa, 2005) to a maximum of 28% (70/251: Bacigalupo, 2009, Raiola, 2000, Bacigalupo 2007, Di Grazia, 2001) of patients with one or more episodes of limited cGvHD; from a minimum of 0,9% (1/107: Aversa, 1999, Aversa 1994, Aversa, 2001) to a maximum of 55% (29/53: Majoilino 2007) of patients experienced one or more episodes of extensive cGvHD.
In children, allogenic HSCT: aGvHD: from a minimum of 10% (1/10: Locatelli 2009) to a maximum of 47,3% (9/19: Locatelli 2009) of patients with mild aGvHD; from a minimum of 7,5% (3/40: Locatelli 2009) to a maximum of 20% (3/15: Locatelli 2009) of patients with severe aGvHD.
cGvHD: from a minimum of 5,5% (1/18: Locatelli 2009) to a maximum of 26,6% (4/15: Locatelli 2009) of patients with limited cGvHD; from a minimum of 5,7% (2/35: Zecca 1999) to a maximum of 12,5% (1/8: Locatelli 2009) of patients with extensive cGvHD.
Many variables including stem cell source, age of donor and recipient, preparative regimen and prophylaxis can impact the incidence of GVHD.
Acute GVHD occurs within the first 100 days after BMT. It affects from 30 to 50 percent of allogeneic BMT recipients, depending on the presence of risk factors.
Chronic GVHD occurs in 30 to 40 percent of allogeneic BMT patients who survive more than 100 days after transplant.
Given the limited population in the target indication and their overall prognosis, the public health concern is small.

6. Infection

Most infections were low grade (I-II) and resolved. Respiratory infections were the common type of infection observed.
Deaths from infections were the following:
In Adults, autologous HSCT: 10% (20/194: Gutierrez-Delgado 2001; Gutierrez-Delgado 2003; Gopal 2001); 14,7% (5/34: Przepiorka 1995); 4,8%(2/42: Demirer 2004); 2,4%(3/125: Waheed 2004;Glossmann 2005); 10%(3/31: Papadopoulos K. 2005); 10%(3/29: Cumpston 2007); 1,5%(1/65: McCoy, 2004); 12,5%(2/16: Montemurro, 2007; 4,3% (11/257:Shimoni 2001, Anagnostopoulos 2004, Dimopoulos, 1993); 1% (6/566: Tallman 2003, Leonard 2004); 2,2% (4/177: Cheng 2004); 4% sepsis (1/25: Glossmann 2005); 0,5% sepsis (3/566: Tallman 2003, Leonard 2004); 0,5% sepsis (4/884: Rodenhuis 2006 , Rodenhuis 2003); *:* 0,3% toxic shock syndrome (1/296: Tallman 2003).
In Adults, allogenic HSCT: 6,9% (13/187: Corradini 2004, Corradini 2007); 11,3% (6/53: Majoilino 2007); 10% (25/251: Bacigalupo 2007, Raiola 2000, Bacigalupo 2007 P4956, Di Grazia 2001); 16% (14/88: Alessandrino 2004, Grullich 2008, Picardi 2004); 10% (1/10: Bethge, 2006); 15,4% (8/52: Jakubowski 2007); 3% sepsis (1/31: Bacigalupo 1996); 20% sepsis (6/30: Rosales 1999); 8,6% (7/81: Rigden 1996, Papadopoulos 1998); 6% (1/17: Aversa, 1994); 8,6% (5/58: Aversa 1999); 2% sepsis (1/58: Aversa 1999); 23,5% (65/276: Aversa 1999, Aversa 2002, Aversa 2005, Aversa 2001); 4,3% (10/233 Aversa 2002, Aversa 2005, Aversa 2001); 3,7% (1/27: La Nasa 2005).

In Children, autologous HSCT: 6,5% (3/46: Broniscer 2004, Dhall 2008, Grodman 2009); 4,3% (1/23: Dunkel 1998); 3,7% (1/27; Fagioli,2004); 4,4% sepsis (2/45: Finlay,1996); 2,6% (1/39: Ridola 2007); 2,6% sepsis (1/39: Ridola 2007).
In Children, allogenic HSCT: 7,5% (3/40: Locatelli 2009); 3,5% sepsis (2/57: Locatelli 2009); 2,5% (1/40: Locatelli, 2009), 2,5% sepsis (1/40: Locatelli, 2009); 4,76% (1/21: (Locatelli, 2009); 6,7% (1/15: Locatelli 2009); 5% (1/19: Strahm 2007); 3,8% sepsis (1/26: Rosales 1999).

Frequencies reported (95% CI) are as follows:
In adults, autologous HSCT: From a minimum of 6,6% (Dimopoulos 1993) to a maximum of 82% (32/39: Ando 2000) of patients with one or more episodes of mild (grade I-II) infection. From a minimum of 5% (2/42: Chen 2004) to a maximum of 87% (109/125: Glossmann 2005) of patients with one or more episodes of severe (grade III-IV) infection.
In adults, allogenic HSCT: From a minimum of 23% (4/17: Aversa 1994) to a maximum of 71% (15/21: Alessandrino, 2004) of patients with one or more episodes of mild (grade I-II) infection. From a minimum of 6% (Aversa 1994) to a maximum of 52% (16/31: Bacigalupo, 1996) of patients with one or more episodes of severe (grade III-IV) infection.
In Children, autologous HSCT: From a minimum of 38,1% (8/21: Kushner 2001) to a maximum of 58,8% (30/51: Grill 1996, Dupuis-Girod 1997, Valteau-Couanet 2005) of patients with one or more episodes of mild (grade I-II) infection.
From a minimum of 2,2% (1/45: Finlay 1996) to a maximum of 33,3% (7/21: Chan 1997) of patients with one or more episodes of severe (grade III-IV) infection.
In Children, Allogenic HSCT: maximum frequency of 79% (15/19: Strahm 2007) of patients with severe infections.
Haematopoietic stem cell transplant patients are profoundly immunodeficient for several months following transplantation. Even after successful engraftment, patients do not have a fully functioning immune system until reconstitution is completely achieved.
The frequency and severity of infection are usually inversely proportional to the patient's neutrophil count. Bacterial infections occur most frequently in the first 30 days after transplant, whereas the onset of viral infections usually occurs later during the first three months posttransplant.
All patients in the target population are at risk for infection due to their immunodeficient status.
Increased risk of infection is likely related to concomitant myelosuppression. As for GvHD, infections are firstly correlated to immunosuppressive therapy and compatibility donor/recipient.
Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period.
Given the limited population in the target indication, their overall prognosis and the availability of growth factors and transfusion support, the public health concern is small.

7. Treatment related secondary malignancy

Secondary malignancies are medical terms "serious" for definition.
Deaths from secondary malignancies were the following:
In adults, autologous HSCT: 5% (5/100: Waheed 2004); 1,5 1,5%(1/65: McCoy, 2004); 0,5% (1/201: Nitz 2005).
In adults, allogenic HSCT: 0,5% (1/187: Bacigalupo 2007).

Frequencies reported (95% CI) are as follows:
In adults, autologous HSCT: Secondary malignancies have been reported in a minimum of 0,5% (1/201: Nitz, 2005) to a maximum of 9% of patients (9/100: Schrama 2003).
In adults, allogenic HSCT: Secondary malignancies have been reported in a minimum of 0,5% (1/187: Bacigalupo, 2009 and Bacigalupo 2007) to a maximum of 4.8% (2/42: Rigden, 1996).
In children, autologous HSCT: Secondary malignancies have been reported with a frequency of 9% (1/11: Grovas 1999).
Thiotepa is mutagenic and carcinogenic. On the basis of human data, it has been classified by the IARC as a human carcinogen. The available data on animals support the carcinogenic potential of thiotepa. These finding indicate that thiotepa could increase the risk of a second malignancy in patients. Given

the limited population in the target indication and their overall prognosis, the public health concern is small.

8. Nervous system disorders

Thiotepa is a lipophilic alkylating agents capable of penetrating the blood-brain barrier and of achieve cerebrospinal fluid (CSF) levels up to 100%.
In the selected clinical trials, deaths from nervous system disorders were the following:
In adults, autologous HSCT: Due to nervous system disorders: 0,8% (1/120: Shimoni 2001); 2% (1/39: Cairncross 2000); cerebral hemorrage: 0,4% (1/270: Tallman 2003).
In adults, allogenic HSCT: due to cerebral aneurism: 5,5% (1/18: Picardi 2004); encephalopathy: 2,1% (5/233: Aversa 2002, Aversa 2005, Aversa 2001); encephalitis: 0,4% (1/233: Aversa 2002, Aversa 2005, Aversa 2001).
In children, allogenic HSCT: due to cerebral haemorrhage: 2,5% (1/40: Locatelli, 2009) and 6,3% (1/16: Locatelli, 2009); cerebral hemorrhage (as complication of other occurrences): 6,25% (2/32: La Nasa 2002).

Frequencies reported (95% CI) are as follows:
*In adults, autologous HSCT: f*rom a minimum of 2,7% (8/296: Leonard, 2004) to a maximum of 7% (3/42: Demirer, 2004) of patients with mild (grade I-II) nervous system disorders.
From a minimum of 0,8% (1/120: Shimoni, 2001) to a maximum of 9% (9/100: Schrama 2003) of patients with severe (grade III-IV) nervous system disorders.
24% (15/62: Rick 2001) of mild paraesthesia and 3% 82:62: Rick 2001) of severe paraesthesia. 4,3% of severe cognitive disorders (1/23: Illerhaus, 2006). 6% extrapyramidal disorder (1/16: Montemurro 2007). Severe convulsion/seizure with a maximum incidence of 25% (3/12: Papadopoulos 1998). Severe encephalopathy with a maximum incidence of 10% (2/20: Cairncross 2000). Severe cerebral haemorrhage with a maximum incidence of 4,6% (3/65: McCoy 2004).
In adults, allogenic HSCT: 20% (6/30: Rosales 1999) of patients with mild (grade I-II) nervous system disorders and 3,3% (1/30: Rosales 1999) of patients with severe (grade III-IV) nervous system disorders.
Fatal encephalopathy with a maximum incidence of 2,1% (5/233: Aversa 2002, Aversa 2005, Aversa 2001).
In children, autologous HSCT: from a minimum of 2,7% (1/37: Mason 1998) to a maximum of 22,7 (5/22: Lucidarme 1998) of patients with mild (grade I-II) nervous system disorders.
From a minimum of 2,4% (1/42: Papadakis 2000) to a maximum of 53,3% (8/15: Valteau-Couanet 2005) of patients with severe (grade III-IV) nervous system disorders.
A maximum incidence of 32% (7/22: Bouffet 1997) of patients with severe headache.
Mild encephalophaty with a maximum incidence of 6,3% (1/16: Grill 1996); severe encephalophaty with an incidence of 11,4% (6/53: Papadakis, 2000; Grovas, 1999).
A maximum incidence of 45% (19/42: Papadakis 2000) of patients with severe intraparenchimal haemorrhage.
Mild convulsion with a maximum incidence of 10% (2/20: Dupuis-Girod 1997), severe convulsion with a maximum incidence of 20,7% (11/53: Papadakis, 2000; Grovas, 1999).
2,4% (1/42: Papadakis 2000) of patients with severe ataxia and 2,4% (1/42: Papadakis 2000) of patients with severe hemiparesis.
In children, allogenic HSCT: from a minimum of 2,5% (1/40: Locatelli 2009) to a maximum of 20% (3/15: Locatelli 2009) of patients with mild nervous system disorders.
From a minimum of 2,5% (1/40: Locatelli) to a maximum of 10,5% (2/19: Locatelli 2009) of patients with severe nervous system disorders.
Fatal cerebral haemorrhage was reported with a maximum frequency of 6,3% (1/16: Locatelli 2009).
Given the limited population in the target indication and their overall prognosis, the public health concern is small.

9. Confusion, Delirium,Hallucination

There are no fatal cases in the selected clinical studies due to confusion.

Frequencies reported (95% CI) are as follows:
In adults, autologous HSCT: 12% (8/65: McCoy 2004) of confusional state grade I-II; 33% (4/12: Papadopoulos 1998) of mental status changes grade III-IV.
In children, autologous HSCT: 33% (7/21: Massimino 2005) of mental status changes grade I-II.
A number of antineoplastics and immunosuppressant including alkylating agents have been associated with mental symptoms such as anxiety, depression, behavioural changes, delirium, and hallucination, in both adults and children. Patients receiving chemotherapy inevitably suffer emotional distress associated in part with the adverse effect of treatment.
Potential mechanisms are unknown. Neurologic and psychiatric complications (altered mental status, confusion) occur frequently in patients with cancer. After chemotherapy, these complications are very common.
Given the limited population in the target indication and their overall prognosis, the public health concern is small.

10. Pulmonary toxicity

Pulmonary toxicity is a potential life threatening or fatal event.
Deaths from pulmonary toxicity were the following:
In adults, autologous HSCT: due to idiopathic pneumonia syndrome: 6,8% (5/74: Gutierrez-Delgado 2003; Gopal 2001) and 2% (3/164: Wong 2003); pulmonary toxicity: 0,3% (2/566: Tallman 2003, Leonard 2004), 3% (1/31: Holmberg, 1998) and 0,2% (1/442: Rodenhuis 2006); interstitial pneumonitis: 0,5% (1/177; Cheng 2004).
In adults, allogenic HSCT: due to idiopathic pneumonia syndrome: 1% (1/10: Bethge, 2006); pulmonary toxicity: 1,88% (1/53: Majoilino 2007), 5,5% (1/18: Picardi 2004), 2,4% (1/42 Rigden 1996), 35% (6/17: Aversa, 1994) and 3,4% (4/119: Aversa 1999, Aversa 2001); interstitial pneumonia: 0,6% (1/154: Bacigalupo 2007) and 3% (1/31: Papadopoulos 1998).
In children, autologous HSCT: due to interstitial pneumonitis: 4,5% (1/22: Bouffet, 1997) and 6,3% (1/16; Hawkins 2000); pneumonitis: 5% (1/20: Dupuis-Girod 1997); pulmonary toxicity: 9,5% (2/21: Chan 1997).
In children, allogenic HSCT: due to idiopathic interstitial pneumonia: 2,5% (1/40: Locatelli 2009); pulmonary toxicity: 7% (4/57: Locatelli 2009); pneumonitis: 7,5% (3/40: Locatelli, 2009), 10% (1/10: Locatelli 2009) and 6,7% (1/15; Locatelli 2009).

Frequencies reported (95% CI) are as follows:
In adults, autologous HSCT: from a minimum of 5% (5/100: Schrama 2003) to a maximum of 13% (4/31: Holmberg, 1998) of patients with grade I-II pulmonary toxicity.
From a minimum of 0,5% (1/177: Cheng 2004) to a maximum of 11% (20/177: Cheng 2004) of patients with severe and fatal pulmonary toxicity (idiopathic interstitial pneumonia).
In adults, allogenic HSCT: from a minimum of 0,6% (1/154: Bacigalupo 2007) to a maximum of 35% (6/17: Aversa, 1994) of patients with grade III-IV pulmonary toxicity.
In children, autologous HSCT: 12,9% (4/31: Grill 1996, Valteau-Couanet 2005) of patients with grade I-II pneumonitis; from a minimum of 4,5% (1/22: Bouffet, 1997) to a maximum of 27% (3/11: Grovas, 1999) of patients with severe or fatal interstitial pneumonitis.
In children, allogenic HSCT: from a minimum of 2,1% (2/97: Zecca 1999, Locatelli 2009) to a maximum of 23,2% (6/26: Rosales 1999) of patients with grade I-II pulmonary toxicity.
From a minimum of 3,1% (3/97: Zecca 1999, Locatelli 2009) to a maximum of 10% (1/10: Locatelli 2009) of patients with grade III-IV pulmonary toxicity.
Various mechanisms have been postulate. For example, chemotherapy may induce immunomodulation that indirectly contributes to lung injury. The interstitial pneumonitis was also reversible with steroids.
Given the limited population in the target indication and their overall prognosis, the public health concern is small.

Missing Informations

1. **Pregnant or lactating women**

The findings of dose toxicity studies indicated that thiotepa may have a negative effect on both female and male fertility. Gestational studies in mouse, rats and rabbits demonstrated toxicity to embryo-fetal development as well as maternal toxicity. These finding indicate that thiotepa should not be given to patients who are pregnant or plan to become pregnant.

2. **Elderly patients (unknown number of patient treated).**
Despite exclusion criteria for many clinical studies, elderly patients were treated with thiotepa in the current indications, but not separately from other "adults" patients.

3. **Patients with clinically significant renal disease.**
Patients with clinically significant renal disease were generally excluded from studies.

4. **Patients with clinically significant hepatic disease.**
Patients with clinically significant hepatic disease were generally excluded from studies.

5. **Patients with impaired cardiac function (limited experience).**
Patient with impaired cardiac function were generally excluded from many studies. Concerning patients with impaired cardiac function, in one clinical study (Rose, 2000) of the safety database twelve patients were found to have a reduced left ventricular ejection fraction (LVEF <50%) at least once during treatment. Although two of these 12 patients developed symptomatic heart failure, their cardiac symptoms were easily treated and there were no cardiac deaths. Conclusion were that the protocol has acceptable cardiac toxicity and breast cancer patients with impaired LV function should not be denied high-dose chemotherapy if otherwise indicated.

6. **Patients with impaired pulmonary function.**
Patient with impaired pulmonary function were generally excluded from many studies.

7. **Patients with previous brain or craniospinal irradiation.**
In most clinical studies patients were previously treated with brain or craniospinal radiotherapy, but contribution to the onset of severe toxic reactions is poorly known.

8. **Data on ethnicity/race.**
We presume that most patients were Caucasians, but data on ethnicity are not stated in most of clinical studies.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Introduction of Infertility, Haemorrhage (including cerebral haemorrhage), embolism, cardiac failure, renal failure and paediatric hepatic failure as new important identified risks CCI [redacted].

CCI [redacted] Delirium and hallucination were added to the risk of "confusion". "Infertility" was added as important identified risk. Haemorrhage (including cerebral haemorrhage), embolism, cardiac failure, renal failure and paediatric hepatic failure were added as important identified risks.

1	**SOC – Reproductive system and breast disorders**
Identified Risk	**Infertility**

	Infertility Infertility female Infertility male
Seriousness/outcomes	Serious long-term toxicities related to conditioning regimens used for BMT include toxic effects on male and female reproductive systems. As most alkylating agents, thiotepa might impair male and female fertility, causing an often permanent amenorrhea, particularly in perimenopausal women and an irreversible azoospermia in men. The amenorrhea risk is strongly influenced by patient age and type and duration of therapeutic regimen (Spinelli 1994). Younger women of childbearing age are confronted with the risk of compromising their fertility by therapy-induced temporary or permanent amenorrhea.
Severity and nature of risk	Severity observed is high.
Frequency with 95 % CI	The highest incidence of azoospermia following BMT was found in patients prepared with CY plus TBI or TAI (85.4%). Among patients conditioned with CY plus BU or thiotepa 50% remained azoospermic. The trend toward a higher spermatogenesis recovery rate recorded after these regimens in comparison with CY-TBI (P <0.069), if confirmed in larger studies, would favor the choice of BU or thiotepa for conditioning young male patients (Anserini 2002).
Background incidence/prevalence	The negative impact on spermatogenesis of the conditioning regimen cyclophosphamide +TBI for allogeneic BMT on sperm count was demonstrated about 20 years ago (Sanders 1983) and a more recent publication evaluated the effect of the busulfan-cyclophosphamide conditioning regimen for BMT (Grigg 2000). For alkilating agents estimated risk of permanent amenorrhea resulting from single-agent chemotherapy and combination regimens used as adjuvant treatment for breast cancer is reported as higher than 80% (Lee 2006).
Risk groups or risk factors	Males and females of childbearing age.
Potential mechanisms	Thiotepa 400 mg/mq can be additive with other agents in causing prolonged azoospermia, but cause only temporary reductions in sperm count when not combined with other agents (K Oktay – 2007 Vol. 5, No. 1 srm Fertility) Thiotepa can causes temporary reductions in sperm count when given alone; additive with other agents (K Oktay – 2007 Vol. 5, No. 1 srm Fertility)
Preventability	Male patients should seek for sperm cryopreservation before therapy is started.
Potential public health impact of safety concern	Given the limited population in the target indication and their overall prognosis, the public health concern is small.
Evidence source	See selected clinical studies in the safety database. See also K Oktay – 2007 Vol. 5, No. 1 srm Fertility
MedDRA terms	PT: Infertility

2	**SOC - Vascular disorders**
Identified Risk	**Haemorrhage** **Cerebral haemorrhage** (see also Risk#10 in section SVII.3 Nervous System Disorders) **Embolism**

Seriousness/outcomes	Reactions are generally serious and life-threatening.
Severity and nature of risk	Severity observed is high.
Frequency with 95 % CI	Adults: TT/BU/CY: Deaths for haemorrhage = 2,9%(1/34) (Przepiorka 1995 Study 5.3.4.2.4) TT/CY: haemorrages = 1% (2/185) (Bacigalupo 2009, Di Grazia 2001); TT/CY: haemorrage = 3% (1/31) (Bacigalupo 1996); TT/BU/CY: death for haemorrhage 2.5% (1/40) (Dimopoulos 1993); TT/MITOX/CARB: haemorrhages = 1% (1/100) (Waheed 2004); TT/CARB/VP16: haemorrhages = 6,4% (2/31) Papadopoulos 2005 (Study 5.3.5.2.48); TT/VP16: CNS haemorrhages = 4,6% (3/65) Mc Coy 2004; TT/BU/CY: haemorrhages = 2,2% (3/137)(Anagnostopoulos 2004, Dimopoulos, 1993); Pediatric patients: TT/CY/ALG/TBI: deaths for cerebral haemorrage = 6,3% (1/16) (Locatelli 2009); TT/BU: GI haemorrhage = 10% (2/20) (Dupuis-Girod 1997); TT/BU/FLU/ALG: 1 death for cerebral haemorrhage (6,25%) (Locatelli 2009).
Background incidence/prevalence	Not applicable
Risk groups or risk factors	None identified
Potential mechanisms	The consequence of the myelosuppression and of the direct injury on produced by Thiotepa on endothelial cells may be a possible mechanism causing hemorrhagic events. Thiotepa is a lipophilic alkylating agents capable of penetrating the blood-brain barrier and this may explain cerebral/intracranial hemorrhages.
Preventability	Platelet counts should be maintained above 50 000/mm^3, if possible, to minimize the risk of intracranial (intratumoral) hemorrhage.
Potential public health impact of safety concern	Given the limited population in the target indication and their overall prognosis, the public health concern is small.
Evidence source	See selected clinical studies in the safety database.
MedDRA terms	HLGT: Vascular haemorrhagic disorders; HLGT: Embolism and thrombosis

3	**SOC - Cardiac disorders**
Identified Risk	**<u>Cardiac failure</u>**
Seriousness/outcomes	Heart failure is a disorder in which the cardiac muscle is unable to pump enough blood through to meet the body's needs for blood and oxygen. Heart failure can be both debilitating and life-threatening.
Severity and nature of risk	The risk is severe.
Frequency with 95 % CI	In Adults: A frequency equal to 4% (4/94) was calculated form the following papers: Alessandrino 2004, Grullich 2008 and Picardi 2004; In children: Thiotepa in association with fludarabine and TBI, following allogeneic HPCT for treating leukemia in Locatelli 2009 (Stiu revealed 2 patients (10,5%) with cardiac failure.

Background incidence/prevalence	Cardiotoxicity is a recognised chemotherapy induced adverse event. As early as 1967, there were reports of heart failure in children treated with doxorubicin. Drugs associated with congestive heart failure (CHF) are anthracyclines/anthraquinolones, cyclophosphamide, trastuzumab and other monoclonal antibody-based tyrosine kinase inhibitors.Cardiac events associated with chemotherapy vary from mild transient blood pressure and or electrocardiographic (ECG). changes to more serious arrhythmias, myocarditis, pericarditis, myocardial infarction and cardiomyopathy, which may end in left ventricular dysfunction (LVD) or congestive heart failure (CHF). The incidence of cardiotoxicity depends on different factors related to oncological therapies (type of drug, dose administered during each cycle, cumulative dose, schedule of administration, route of administration, combination of other cardiotoxic drugs or association with radiotherapy) and to patient [age, presence of cardiovascular (CV) risk factors, previous cardiovascular disease (CVD), prior mediastinal radiation therapy]. The incidence of heart failure reported with the alkylating agent cyclophosphamide therapy ranges from 7% to 28%, the risk of cardiotoxicity being dose related (Bovelli 2010).
Risk groups or risk factors	Both adult and pediatric patients
Potential mechanisms	It may be assumed that the potential mechanism of action for thiotepa is similar to that of cyclophosphamide. Cyclophosphamide rapidly impairs cellular respiration and also damages the inner mitochondrial membrane of heart leading to the permeability of calcium ions mediated by oxidative stress (Souid 2003). Cyclophosphamide induced cardiotoxicity has been implicated to increase the generation of superoxide radicals and hydrogen peroxide. These reactive oxygen species (ROS) damage the heart by exceeding the oxygen radical detoxifying capacity of cardiac mitochondria (Mythili 2005).
Preventability	Careful clinical evaluation and assessment of cardiovascular risk factors.
Potential public health impact of safety concern	Given the limited population in the target indication and their overall prognosis, the public health concern is small.
Evidence source	See selected clinical studies in the safety database.
MedDRA terms	PT: Cardiac failure

4	**SOC – Renal and urinary disorders**
Identified Risk	**Renal failure**
Seriousness/outcomes	Serious and potentially life-threatening condition. Acute renal failure is associated with high early mortality rate post-BMT (Noel 1998). In Pediatric Transplantation 2006 Vol.10, Issue 7 Termuhlen demonstrates that it is feasible and safe to perform HSCT in pediatric patients with low nGFR using melphalan and thiotepa-based preparative therapy.
Severity and nature of risk	The risk is severe. Serious and fatal events are reported in "Frequency".

Frequency with 95 % CI	Adults: TT/CY/CISP: renal failure 2 (8%) (Stiff 2004 Study 5.3.5.1.8); TT/CARB/ETOP: renal failure = 2% (1/62) Rick 2001; TT/FLU: renal failure = 1% (1/88) (Grullich 2008). Paediatric patients: TT/CARB/VP16: Acute hepato-renal failure = 2,7% (1/37) (Mason 1998); TT/BU: Renal failure=6,25% (1/16)(Grill 1996).
Background incidence/prevalence	Different conditioning treatment regimens containing thiotepa are used as preparative to bone marrow transplantation (BMT) that is currently a treatment modality for a wide range of malignant and non-malignant disorders. Patients receiving conditioning regimen and BMT may develop some degree of acute renal insufficiency, which may progress to renal failure requiring dialysis.
Risk groups or risk factors	Several antineoplastic agents are potentially nephrotoxic and previous renal impairment as well as combinations with other nephrotoxic drugs may increase the risk of nephrotoxicity. Risk factors for renal failure also include veno-occlusive disease (VOD), graft-versus-host disease (GvHD) and the combined use with radiation.
Potential mechanisms	Potential mechanism for thiotepa to cause renal failure is not known. Nephrotoxic agents can cause renal failure through different mechanisms for instance by direct tubular toxicity (e.g. cisplatin and ifosfamide). High doses of methotrexate are associated to a high risk of acute renal failure caused by intra-renal obstruction due to precipitation of methotrexate or its metabolite, 7-OHmethotrexate, within the renal tubules.
Preventability	Not applicable
Potential public health impact of safety concern	Given the limited population in the target indication and their overall prognosis, the public health concern is small.
Evidence source	See selected clinical studies in the safety database.
MedDRA terms	PT: Renal failure

5	**SOC – Hepatobiliary disorders**
Identified Risk	**Hepatic failure** in pediatric patients
	Hepatic failure Liver failure Venoocclusive liver disease (see SOC Vascular Disorder)

Seriousness/outcomes	Elevations in alkaline phosphatase, alanine aminotransferase and bilirubin are reported as "very common" or "common" events associated with thiotepa (SmPC, section 4.8). These are generally mild and self limited. Rare instances of clinically apparent acute liver injury attributed to thiotepa have been reported, particularly with high doses. In most instances, thiotepa is administered in combination with other agents known to cause liver injury and the specific role of thiotepa is not clear. In addition, thiotepa is often used in combination with other alkylating agents in conditioning regimens for bone marrow ablation in preparation for hematopoietic cell transplantation and as such has been linked to instances of sinusoidal obstruction syndrome. Onset of sinusoidal obstruction syndrome is usually within 1 to 3 weeks of myeloablative or high dose therapy and is characterized by the sudden development of abdominal pain, hepatomegaly, weight gain and ascites followed by jaundice. The pattern of serum enzyme elevations is usually hepatocellular, with marked increases in serum aminotransferase and lactic dehydrogenase levels and minimal increase in alkaline phosphatase. In severe instances, there are elevations in prothrombin time and progressive hepatic failure. Immunoallergic and autoimmune features are uncommon. The fatality rate is high. Liver biopsy shows centrolobular necrosis and congestion with occlusion of small veins and red cells in sinusoids.
Severity and nature of risk	The risk is severe. Liver injury is not uncommon with high doses of thiotepa the severity of injury being reported as mild-to-moderate and self limiting, although fatalities attributed to hepatotoxicity of thiotepa and cyclophosphamide have been reported (Bacigalupo 1996). The sinusoidal obstruction syndrome associated with thiotepa and other alkylating agents can be severe and lead to acute liver failure. Since thiotepa is mainly metabolized through the liver, caution needs to be observed when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment.
Frequency with 95 % CI	Adults: TT/CY/CARM: hepatic failure = 0,5%(1/177)(Cheng 2004); TT/CY: hepatic failure = 2% (3/187) (Bacigalupo 2009, Raiola 2000); TT/CY/BU: Liver failure 1 (3,7%) (La Nasa 2005 Study 5.3.5.2.81) CARM/TT: One patient died from liver failure after metotrexate (Illheraus 2006 Study 5.3.5.2.23); TT/CY: Bacigalupo A. et al. (1996): liver failure (n = 1). Paediatric patients: TT/BU/CY: cerebral hemorrhage related to liver failure= 3% (1/32), liver failure due to chronic GvHD = 3% (1/32) (La Nasa 2002).
Background incidence/prevalence	Chemotherapeutic agents, alone or in combination, may cause hypersensitivity reactions or direct hepatic toxicity, and altered liver function may alter drug metabolism and cause an increased risk of non hepatic toxicity. Combination chemotherapy uses several chemotherapeutic agents, each with a different mechanism of action and toxicity profile. The development of combination chemotherapy treatment regimens produced new evidence of hepatotoxicity or enhanced toxicity along with the potential for greater efficacy. Bone marrow transplantation commonly uses very high doses of chemotherapeutic agents, total body irradiation, and combination chemotherapy which may result in hepatotoxicity.
Risk groups or risk factors	Both adult and paediatric patients
Potential mechanisms	The potential mechanism of hepatotoxicity from thiotepa is probably similar to that of other alkylating agents, a direct cytotoxic injury to rapidly dividing cells. High doses are likely to injure other cells such as sinusoidal endothelial cells and hepatocytes. The cause of the

	idiosyncratic liver injury associated with thiotepa is not known.
Preventability	Caution needs to be observed when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. Serum transaminase, alkaline phosphatase and bilirubin should be monitored regularly following transplant, for early detection of hepatotoxicity.
Potential public health impact of safety concern	Given the limited population in the target indication and their overall prognosis, the public health concern is small.
Evidence source	See selected clinical studies in the safety database.
MedDRA terms	PT: Hepatic failure

Addition of Pulmonary Arterial Hypertension as new important potential risk CCI [redacted].

CCI [redacted]

Safety concern	
New important potential risk	**Pulmonary hypertension**
Details	Pulmonary arterial hypertension Pulmonary arteriopathy
Source	Schechter T, Leucht S, Bouffet E et al. Pulmonary hypertensive vasculopathy following tandem autologous transplantation in pediatric patients with central nervous system tumors. Biol Blood Marrow Transplant. 2013 Feb;19(2):235-9 PRAC Request for Supplementary Information - Thiotepa (Tepadina) - Pulmonary arterial hypertension (EPITT ref. No 18046)
New studies proposed in pharmacovigilance plan? Yes/No	No
New risk minimisation actions proposed? Yes/No	No

Addition of Toxic skin reactions (including Stevens-Johnson syndrome and Toxic epidermal necrolysis) as new important potential risk CCI [redacted].

CCI [redacted]

Safety concern	
New important potential risk	**Toxic skin reactions (including Stevens-Johnson syndrome and Toxic epidermal necrolysis)**
Details	Toxic epidermal necrolysis (TEN) Stevens-Johnson syndrome Bullous eanthematic drug eruption Toxic skin eruption Bullous eruption
Source	Ferreri AJ, Ciceri F, Brandes AA et al. MATILDE chemotherapy regimen for primary CNS lymphoma: results at a median follow-up of 12 years.Neurology 2014; 82(15): 1370-3 Omuro A, Correa DD, DeAngelis LM ert al. R.MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood 2015; 125(9): 1403-10 Spontaneous reports.
New studies proposed in pharmacovigilance plan? Yes/No	No
New risk minimisation actions proposed? Yes/No	No

Addition of leukoencephalopathy as new important potential risk CCI [redacted].

CCI [redacted]

Safety concern	
New important potential risk	**Leukoencephalopathy**
Details	Leukoencephalopathy White matter lesion
Source	Thust SC, Blanco E, Michalski AJ et al. MRI abnormalities in children following sequential chemotherapy, hyperfractionated accelerated radiotherapy and high-dose thiotepa for high-risk primitive neuroectodermal tumours of the central nervous system. J Med Imaging Radiat Oncol 2014;

Safety concern	
New important potential risk	**Leukoencephalopathy**
	58(6):683-90 Hasan A, Palumbo M, Atkinson J, Carret AS, Farmer JP, Montes J, Albrecht S, Saint-Martin C, Freeman CR Treatment- related morbidity in atypical teratoid/rhabdoid tumor: multifocal necrotizing leukoencephalopathy. Pediatr Neurosurg. 2011;47(1):7-14. Wells EM, Kinlburn L, Rood B, Crozier F Fatal necrotizing leukoencephalopathy associated with proton beam radiation therapy and intensive chemotherapy in young children with brainstem region tumors. Annals of Neurology Vol 74 (suppl 17) 2013. Spontaneous reports.
New studies proposed in pharmacovigilance plan? Yes/No	No
New risk minimisation actions proposed? Yes/No	No

On the basis of data collected from the different sources during the post-marketing experience with TEPADINA, it is deemed appropriate the removal of all important indentified risks from the list of safety concerns since well characterized and thus not necessitating for further evaluation in the pharmacovigilance plan.

Risk 1 "Myelosuppression" previously classified as important identified risk is removed from the list of safety concerns. Myelosuppression is a well known and appropriately managed complication occurring in patients receiving TEPADINA as reported in diffent sections of the labelling. Further evaluation in the pharmacovigilance plan is not warranted since expected to produce results not varying the benefit/risk profile of the medicinal product.

Risk 2 "Cardiac failure" previously classified as important identified risk is removed from the list of safety concerns. Cardiotoxicity is a recognised chemotherapy induced adverse event. It is a well characterized risk and relating information concerning its occurrence are reported in the SmPC of TEPADINA. Adoption of further evaluation in the pharmacovigilance plan is deemed uneccessary since expected to produce results not impacting the benefit/risk profile of the medicinal product.

Risk 3 "Mucositis" previously classified as important identified risk is removed from the list of safety concerns. This is a well-known, common complication occurring in patients receiveing

chemotherapeutic agents, including thiotepa. This risk is well characterized and does not require further evaluation as part of the pharmacovigilance plan.

Risk 4 "Hepatic failure" previously classified as important identified risk is removed from the list of safety concerns. Elevations in alkaline phosphatase, alanine aminotransferase and bilirubin are reported as complications occurring with thiotepa in the concerned labelling. This risk is well characterized and does not require further evaluation as part of the pharmacovigilance plan.

Risk 5 "Venoocclusive liver disease" previously classified as important identified risk is removed from the list of safety concerns. This is a life threatening complication of preparative-regimen-related toxicity for bone marrow transplantation. It is a known complication which may occur following administration of thiotepa as stated in the labelling of TEPADINA. Further evaluation in the pharmacovigilance plan would not change the benefit/risk profile.

Risk 6 "Hypersensitivity" previously classified as important identified risk is removed from the list of safety concerns since well known pharmacologic class toxicity which may occur following administration of TEPADINA. Hypersensitivity to drugs is a contraindication to treatment, as stated in the SmPC of TEPADINA. This risk does not require further evaluation as part of the pharmacovigilance plan.

Risk 7 "Graft Versus Host Disease" previously classified as important identified risk is removed from the list of safety concerns. Acute and chronic graft-versus-host disease (GvHD) is a consequence of the conditioning regimen and transplant process and it is considered the major cause of morbidity and mortality in the context of allogeneic stem cell transplantation. It is mainly the consequence of the damage to host tissues by inflammation from the preparative chemo- and/or radiotherapy regimen. The severity of GvHD may vary from mild to fatal in the most severe manifestations of the disease with chronic manifistations that could be limited to certain organs or extensive. GvHD is a well-known complication occurring in the setting of allo-HSCT. In this setting, the population being treated is at high risk of mortality and thus the occurrence GvHD is accepted as a risk that does not negatively affect the benefit risk balance. Further evaluation through a pharmacovigilance plan is thus considered not appropriate for this risk.

Risk 8 "Infection" previously classified as important identified risk is removed from the list of safety concerns. All patients in the target population are at risk for infections due to their immunodeficient status. The immunosuppressive effect induced by thiotepa may facilitate the development of infections. This is a complication well-known to health care professionals operating in the hematopoietic stem cell transplant setting. This risk is well characterized and relating information concerning its occurrence and adoption of prohylactic measures such as the administration of anti-infective agents are reported in the SmPC. This risk does not require further evaluation as part of the pharmacovigilance plan.

Risk 9 "Treatment related secondary malignancy" previously classified as important identified risk is removed from the list of safety concerns. Thiotepa is mutagenic and carcinogenic. This risk is well

characterized and relating information concerning its occurrence are reported in the SmPC. It does not require further evaluation as part of the pharmacovigilance plan.

Risk 10 "Nervous system disorder" previously classified as important identified risk is removed from the list of safety concerns. Thiotepa is a lipophilic alkylating agents capable of penetrating the blood-brain barrier and of achieve cerebrospinal fluid (CSF) levels up to 100%. Due to its intrinsic cytotoxic nature, thiotepa may directly cause damages to neurons. Patients with a prior radiation therapy are more susceptible to develop nervous system disorders following administration of thiotepa. This risk is well characterized and does not require further evaluation as part of the pharmacovigilance plan.

Risk 11 "Confusion, Delirium, Hallucination" previously classified as important identified risk is removed from the list of safety concerns. Neurologic and psychiatric complications (altered mental status, confusion) occur frequently in patients with cancer since patients receiving chemotherapy inevitably suffer emotional distress associated in part with the adverse effect of treatment. This risk is well characterized and does not require further evaluation as part of the pharmacovigilance plan.

Risk 12 "Renal failure" previously classified as important identified risk is removed from the list of safety concerns. Several antineoplastic agents are potentially nephrotoxic and previous renal impairment as well as combinations with other nephrotoxic drugs may increase the risk of nephrotoxicity. Thiotepa is cytotoxic and as such can produce direct tubular toxicity. This risk is well characterized does not require further evaluation as part of the pharmacovigilance plan.

Risk 13 "Infertility" previously classified as important identified risk is removed from the list of safety concerns. As most alkylating agents, thiotepa might impair male and female fertility, causing an often permanent amenorrhea, particularly in perimenopausal women and an irreversible azoospermia in men. This risk is well characterized and relating information concerning its occurrence are reported in the SmPC. It does not require further evaluation as part of the pharmacovigilance plan.

Risk 14 "Pulmonary toxicity" previously classified as important identified risk is removed from the list of safety concerns. Chemotherapy may induce immunomodulation that indirectly contributes to lung injury. Pulmonary toxicity is a potential life threatening or fatal event. This risk is well characterized and relating information concerning its occurrence are reported in the SmPC. It does not require further evaluation as part of the pharmacovigilance plan.

Risk 15 "Haemorrage, Embolism" previously classified as important identified risk is removed from the list of safety concerns. This risk is well characterized and relating information concerning its occurrence are reported in the SmPC. It does not require further evaluation as part of the pharmacovigilance plan.

On the basis of the data collected during the post-marketing experience there have been no data confirming a causal relationship between TEPADINA and the potential risks pulmonary arterial hypertention, toxic skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) and leukoencephalopathy. Moreover, even in case data allowing further characterisation of

these risks should become available during the post-marketing period, taking into account the medical context in which TEPADINA is being used (patients with poor prognosis suffering life-threatening diseases) it is expected that the benefit-risk profile of the medicinal product would not change in the labelled indications. For these reasons the important potential risks have been removed from the list of safety concerns.

Risk 1 "Pulmonary arterial hypertension" previously classified as important potential risk is removed from the list of safety concerns. Pulmonary arterial hypertension should be considered in paediatric patients who develop respiratory symptoms after receiving a combination therapy because early diagnosis might improve outcomes. Since the time this risk was first detected, few other cases of pulmonary arterial hypertension suspected to be related to TEPADINA have been identified from the screening of the published literature. Relating information concerning its occurrence and adoption of prohylactic measures are reported in the labelling of TEPADINA. The risk can be considered as appropriately managed with no impact on the risk-benefit profile of TEPADINA.

Risk 2 "Toxic skin reactions (including Stevens-Johnson syndrome and Toxic epidermal necrolysis)" previously classified as important potential risk is removed from the list of safety concerns. The life-threatening forms of skin damage (including the so called Stevens-Johnson syndrome and Toxic epidermal necrolysis) are rare complications reported following administration of chemotherapeutic agents (6 cases per million people per year) which may appear with some delay following start of therapy (in general from 7 to 21 days from onset of therapy) and that in about the 50% of cases result in death. As many chemotherapeutic drugs, thiotepa may cause skin damage (e.g. severe lesions, bullae, etc.) which in the most severe forms can involve the full body surface, can be extremely painful, can reduce the patient's ability to eat and drink and can result in several other complications putting the patient's life at risk. Considering the rarity of this undesiderable event, there is no reasonable expectation that any pharmacovigilance activity can further characterize this risk in the context of rare diseases. Moreover, in the remote instance data allowing a further characterization of this risk should become available, the risk-benefit balance of TEPADINA would remain unchanged.

Risk 3 "Leukoencephalopathy" previously classified as important potential risk is removed from the list of safety concerns. As other drugs used in chemotherapy, thiotepa has shown increased risk of cancer patients developing damage to a component of the brain, called white matter. This damage may result in symptoms that may vary widely depending on different factors such as the dosage used, the length of time the patient has been exposed to the drug and the patient's clinical history (e.g. previous irradiation therapy, etc.). In case data allowing a furher characterisation should become available during the post marketing period, these data would no change the risk-benefit balance of the medicinal product.

However, the safety profile (including those risks no longer considered as safety concerns) of TEPADINA will continue to be monitored by mean of routine pharmacovigilance activities (e.g. signal detection, PSURs).

On the basis of the post-marketing experience it is not expected that pharmacovigilance activities would allow a further characterization with respect to the areas of missing information for TEPADINA.

Moreover, even in case data allowing a characterisation of missing information should become available, considering the medical context in which TEPADINA is being used, it is expected that the benefit-risk profile of TEPADINA would not differ from that characterized so far. For these reasons missing information have been removed from the list of safety concerns.

Missing information 1 "Pregnant or lactating women" previously classified as missing information is removed from the list of safety concerns. There is no reasonable expectation that any pharmacovigilance activity can provide data allowing a further characterization about the use of TEPADINA in this population. According to the labelling of the medicinal product, the use of TEPADINA is contraindicated during pregnancy and breastfeeding. Women of childbearing potential have to use effective contraception during treatment and a pregnancy test should be performed before treatment with TEPADINA is started. This missing information can be considered as appropriately managed and further data would no impact the risk-benefit profile of TEPADINA.

Missing information 2 "Elderly patients (unknown number of patient treated)" previously classified as missing information is removed from the list of safety concerns. There is no reasonable expectation that any pharmacovigilance activity can provide data that could further characterize the safety profile of TEPADINA in this population. According to the labelling of TEPADINA, though the administration of thiotepa has not been specifically investigated in elderly patients, a proportion of patients over the age of 65 years received the same cumulative dose as the adult population thus not requiring a dose adjustment.

Missing information 3 "Patients with clinically significant renal disease" previously classified as missing information is removed from the list of safety concerns. There is no reasonable expectation that further data collected during the post-marketing could have an impact on the safety profile of TEPADINA in this population. As reported in the labelling of TEPADINA, since thiotepa and its metabolites are poorly excreted in the urine, dose modification is not recommended in patients with mild or moderate renal insufficiency. According to the labelling of the medicinal product, it is recommended caution in patients with history of renal diseases and periodic monitoring of renal function should be considered during therapy with thiotepa. This missing information can be considered as appropriately managed and further data would no impact the risk-benefit profile of TEPADINA.

Missing information 4 "Patients with clinically significant hepatic disease" previously classified as missing information is removed from the list of safety concerns. There is no reasonable expectation that further data collected during the post-marketing could have an impact on the safety profile of TEPADINA in this population. As reported in the labelling of TEPADINA, since thiotepa is mainly metabolized through the liver, caution needs to be exercised when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. Dose modification is not recommended for transient alterations of hepatic parameters. It is recommended that serum transaminase, alkaline phosphatase and bilirubin are monitored regularly following transplant, for early detection of hepatotoxicity. This missing information can be considered as appropriately managed and further data would no impact the risk-benefit profile of TEPADINA.

Missing information 5 "Patients with impaired cardiac function (limited experience)" previously classified as missing information is removed from the list of safety concerns. There is no reasonable expectation that further data collected during the post-marketing could have an impact on the safety

profile of TEPADINA in this population. As reported in the labelling of TEPADINA, caution must be used in patients with history of cardiac diseases, and cardiac function must be monitored regularly in patients receiving thiotepa. This missing information can be considered as appropriately managed and further data would no impact the risk-benefit profile of TEPADINA.

Missing information 6 "Patients with impaired pulmonary function" previously classified as missing information is removed from the list of safety concerns. Thiotepa might induce pulmonary toxicity that may be additive to pre-existing impaired pulmonary functions. There is no reasonable expectation that further data collected during the post-marketing could have an impact on the safety profile of TEPADINA in this population. This missing information can be considered as appropriately managed and further data would no impact the risk-benefit profile of TEPADINA.

Missing information 7 "Patients with previous brain or craniospinal irradiation" previously classified as missing information is removed from the list of safety concerns. As reported in the labelling of TEPADINA, previous brain irradiation or craniospinal irradiation may contribute to severe toxic reactions (e.g. encephalopathy). There is no reasonable expectation that further data collected during the post-marketing could have an impact on the safety profile of TEPADINA in this population. This missing information can be considered as appropriately managed and further data would no impact the risk-benefit profile of TEPADINA.

Missing information 8 "Data on ethnicity/race" previously classified as missing information is removed from the list of safety concerns. On the basis of post-marketing experience, it is not expected that pharmacovigilance activities could allow a further characterization of the safety profile of TEPADINA by ethnicity/race.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

None.

Part II: Module SVIII - Summary of the safety concerns

Table 1. Summary of safety concerns

Important Identified Risks	None
Important Potential Risks	None
Missing information	None

Part III: Pharmacovigilance Plan

Please refer to Module 1.8.1 for a more detailed description of the routine pharmacovigilance practices carried out by ADIENNE S.r.l. S.U.

In terms of pharmacovigilance activities, ADIENNE S.r.l. S.U has a Pharmacovigilance Division site in Italy, Caponago (MB).

The portfolio of products is divided in terms of pharmacovigilance duties in Proprietary Product and Non Proprietary Product.

The Product TEPADINA is under Pharmacovigilance Surveillance by ADIENNE's headquarter.

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Regarding the Approved Product TEPADINA, headquarter performs Pharmacovigilance activities such as data entry of Adverse drug reaction (ADR) reports, preparation of Periodic safety Update reports (PSURs), signal detection, answering safety-related enquiries from competent authorities, preparation of Risk Management Plans (RMSs). In addition, headquarter performs electronic expedited submissions to EMA and to other European competent authorities. Finally, headquarter monitors compliance with reporting timeframes.

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are required.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are deemed necessary.

III.3 Summary Table of additional Pharmacovigilance activities

Neither current study, nor additional pharmacovigilance plan is planned at this time.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The important identified risks associated with thiotepa treatment are similar to those observed with other medicinal products in the alkylating pharmacologic class.

Labelling risk minimisation activities beyond the routine pharmacovigilance activities described below are not warranted.

V.1 Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary table of risk minimisation measures

Not applicable. No safety concerns have been identified for the product.

Part VI: Summary of the risk management plan

Summary of risk management plan for TEPADINA (thiotepa)

This is a summary of the risk management plan (RMP) for TEPADINA. The RMP details important risks of TEPADINA, how these risks can be minimised, and how more information will be obtained about TEPADINA's risks and uncertainties (missing information).

TEPADINA 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TEPADINA should be used.

This summary of the RMP for TEPADINA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

I. The medicine and what it is used for

TEPADINA is authorised (see SmPC for the full indication) in combination with other chemotherapy medicinal products:

- 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;
- when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

It contains thiotepa as the active substance and it is given by intravenous route.

Further information about the evaluation of TEPADINA’s benefits can be found in TEPADINA’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/tepadina.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TEPADINA together with measures to minimise such risks and the proposed studies for learning more about TEPADINA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of TEPADINA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TEPADINA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TEPADINA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary table of Safety concerns

Summary of safety concerns	
Important Identified Risks	None
Important Potential Risks	None
Missing information	None

II.B Summary of important risks

Not applicable.

II.C Post authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TEPADINA.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for TEPADINA.

Part VII: Annexes

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Annex 4 – Specific adverse drug reaction follow-up forms

Not Applicable.

[redacted]

[redacted]

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not Applicable

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]

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