CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214759Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214759
PDUFA Goal Date	August 11, 2021
OSE RCM #	2020-1686; 2020-1688
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Doris Auth, Pharm.D.
Review Completion Date	July 20, 2021
Subject	Review to determine if a REMS is necessary
Established Name	treosulfan
Trade Name	Grafapex
Name of Applicant	Medac Gesellschaft für klinische Spezialpräparate mbH
Therapeutic Class	Alkylating agent
Formulation(s)	1 g/vial and 5 g/vial treosulfan as a lyophilized powder in a single-dose vial for injection
Dosing Regimen	The recommended dose is 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) in conjunction with fludarabine before hematopoietic stem cell infusion (day 0).

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Grafapex (treosulfan) is necessary to ensure the benefits outweigh its risks. Medac Gesellschaft für klinische Spezialpräparate mbH (the applicant) submitted a New Drug Application (NDA) 214759 for treosulfan with the proposed indication as an alkylating drug as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The serious risks associated with the use of treosulfan are myelosuppression, seizures, skin disorders, injection site reactions and tissue necrosis, secondary malignancies, increased early morbidity and mortality at dosages higher than recommended and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information that includes a Boxed Warning, Warnings and Precautions, as well as information to be included in Patient Counseling Information.

The Division of Risk Management (DRM) and the Division of Hematology Malignancies 1 (DHM1) have determined that if approved, a REMS is not necessary to ensure the benefits of treosulfan outweigh its risks. HSCT is a potentially curative therapeutic approach for a variety of malignant and nonmalignant hematopoietic diseases. Refinement of standard regimens has led to a reduction of non-relapse mortality. Relapse post allo-HSCT remains an important issue, especially for patients who undergo transplant with residual or refractory disease. In these patients, pre- and post-transplant interventions need to be considered. There is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for patients. Treosulfan appeared efficacious in its primary outcomes and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of treosulfan as an alkylating drug indicated for:

- Use in combination with fludarabine as a preparative regimen for alloHSCT in adult and pediatric patients at least >1 year old with AML.
- Use in combination with fludarabine as a preparative regimen for alloHSCT in adult and pediatric patients at least >1 year old with MDS.

The most concerning adverse reactions observed with the use of treosulfan are myelosuppression, seizures, skin disorders, injection site reactions and tissue necrosis, secondary malignancies, increased early morbidity and mortality at dosages higher than recommended and embryo-fetal toxicity. If treosulfan is approved, similar to another alkylating agent, busulfan, the Prescribing Information, including a Boxed Warning, Warnings and Precautions and Patient Counseling Information, will be used to communicate the safety issues and management of toxicities associated with treosulfan.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the NME treosulfan is necessary to ensure the benefits outweigh its risks. Medac Gesellschaft für klinische Spezialpräparate mbH submitted a NDA 214759 for treosulfan with the proposed indication as an alkylating drug as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).[1] The applicant did not submit a REMS with this application but proposed describing the risks in the Prescribing Information that includes a Boxed Warning, Warnings and Precautions, as well as information to be included in Patient Counseling Information.

2 Background

2.1 Product Information

Treosulfan is an NME NDA type 505(b)(1) pathway application.[a] It is an alkylating agent. DNA alkylation is thought to be responsible for the cytotoxic activities of treosulfan. Treosulfan depleted hematopoietic stem cells and showed immunosuppressive and antitumor activity in mouse models of leukemia.[1] Treosulfan is available as lyophilized powder in 1 g/vial and 5 g/vial single-dose vials for injection. The recommended dose is 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) in conjunction with fludarabine before hematopoietic stem cell infusion (day 0).[b] Treosulfan was granted orphan drug designation as a conditioning treatment prior to HSCT in malignant and nonmalignant diseases in adults and pediatric patients on April 8, 2015. Treosulfan is currently approved in the European Union in combination with fludarabine as part of conditioning treatment prior to alloHSCT in adult patients with malignant and non-malignant diseases, and in pediatric patients older than one month with malignant diseases.

2.2 Regulatory History

The following is a summary of the regulatory history for treosulfan (NDA 214759) relevant to this review:

- 06/29/2013: Investigation New Drug (IND) 054552 submission for treosulfan was received.
- 04/08/2015: Orphan Drug Designation granted
- 08/11/2020: NDA 214783 submission for treosulfan with the proposed indication as an alkylating drug as part of conditioning treatment prior to alloHSCT in adult patients with AML and MDS, received.
- 01/22/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for treosulfan.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

AML is a form of cancer that is characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system.[2] The pathophysiology in AML consists of a maturational arrest of bone marrow cells in the earliest stages of development. The mechanism of this arrest is under study, but in many cases, it involves the activation of abnormal genes through chromosomal translocations and other genetic abnormalities. This developmental arrest results in 2 disease processes. First, the production of normal blood cells markedly decreases, which results in varying degrees of anemia, thrombocytopenia, and neutropenia. Second, the rapid proliferation of these cells, along with a reduction in their ability to undergo programmed cell death, results in their accumulation in the bone marrow, the blood, the spleen, and the liver.[3,4] The expected number of new cases of AML in the United States in 2021 is

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[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

20,240[c], with 11,400 expected deaths due to the disease.[d] Five-year survival for patients diagnosed with AML is approximately 29.5%.[5] Acute myeloid leukemia is generally a disease of older people and is uncommon before the age of 45. The average age of a patient with AML is 68 years.[6]

MDS are myeloid neoplasms characterized by clonal proliferation of hematopoietic stem cells, recurrent genetic abnormalities, myelodysplasia, ineffective hematopoiesis, peripheral-blood cytopenia, and a high risk of evolution to AML.[7,d] Diagnostic evaluation of MDS relies on morphologic assessment of the peripheral blood and bone marrow, conventional cyto- genetics, and exclusion of secondary causes of dysplasia. The presence of at least 1 cytopenia is mandatory for a diagnosis of MDS. Symptoms and signs are usually related to the cytopenias and include weakness, pallor, fatigue, petechiae, and bleeding. Occasionally patients are asymptomatic and cytopenias are noted during a routine complete blood count or when increased blasts, dysplastic morphology, or clonal cytogenetic abnormalities are identified in studies of peripheral blood or bone marrow obtained for other purposes.[8] MDS are diagnosed in slightly more than 10,000 people in the United States (US) per year, corresponding to an age-adjusted incidence rate of 4.5 per 100,000 persons.[9,c] The median age at diagnosis of MDS is approximately 70 years, and prognosis is poor with median survival of 3 year and 0.8 year in patients with intermediate-2 and high-risk MDS, respectively.[10]

3.2 Description of Current Treatment Options

The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years. The standard treatment is intensive chemotherapy and an allogeneic stem cell transplant, which is based mainly on the patient's ability to tolerate intensive treatment. Treatment of AML has been divided into induction chemotherapy and postremission (e.g. consolidation) therapy.[2] Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent more intensive treatments during consolidation to achieve durable disease control. Patients who do not receive postremission therapy may experience relapse, usually within 6 to 9 months.[11] A complete response is achieved in 60 to 85% of adults who are 60 years of age or younger. In patients who are older than 60 years of age, complete response rates are inferior (40 to 60%).[2] Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, prognosis in the elderly, who account for the majority of new cases, remains poor.[4] Therefore, treatment results are generally analyzed separately for younger (18-60 years) patients and for older patients (>60 years). In patients who can tolerate intensive therapy, which may be limited by factors such as age and comorbid conditions, cytarabine and daunorubicin induction followed by high-dose cytarabine consolidation is frequently used. Intensifying induction therapy with a high daily dose of anthracycline plus intensive consolidation therapy resulted in a high complete-remission rate and prolonged overall survival in patients with AML. This regimen typically results in CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age.[12] Older patients fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20%.[13] Patients who are fit for intensive therapy should receive a salvage chemotherapy

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

regimen followed by hematopoietic stem cell transplant (HSCT). About half will achieve a second complete remission, and 5-year survival of patients who achieve a second remission is about 40%.[14]

Because outcomes for patients with MDS are varied, individual risk stratification using tools, such as Revised International Prognostic Scoring System (IPSS-R), is important in managing patients with MDS. The initial step is assessing a patient's eligibility for allogeneic stem-cell transplantation, which is the only potentially curative treatment, but which is also associated with substantial morbidity and mortality. Patients with good performance status and no or few coexisting conditions are the best candidates for transplantation, whereas those with poor performance status or multiple coexisting conditions should be preferentially considered for medical treatments.[7]

HSCT is a potentially curative therapeutic approach for a variety of malignant and nonmalignant hematopoietic diseases. When HSCT is performed in patients with malignant disorders, preparative or conditioning regimens are administered as part of the procedure to achieve 2 goals: provide sufficient immunoablation to prevent graft rejection and reduce the tumor burden. Traditionally, these goals have been achieved by using otherwise supralethal doses of total body irradiation (TBI) and chemotherapeutic agents with nonoverlapping toxicities. However, as it was recognized that immunologic reactions of donor cells against malignant host cells (ie, graft-versus-tumor [GVT] effects) substantially contributed to the effectiveness of HCT, reduced-intensity and nonmyeloablative conditioning regimens have been developed, making HCT applicable to older and medically infirm patients.[15]Presently conditioning regimens are divided into three categories: (a) myeloablative conditioning (MA), (b) reduced intensity conditioning (RIC) and (c) non-myeloablative (NMA) conditioning. While MA regimens cause irreversible cytopenia and stem cell support is mandatory, NMA regimens cause minimal cytopenia and can be given also without stem cell support. RIC regimens do not fit criteria for MA or NMA regimens: they cause cytopenia of variable duration and should be given with stem cell support, although cytopenia may not be irreversible.[16] In the USA, the number of alloHSCTs performed after RIC has increased steadily over the last decade, particularly in patients age ≥ 50 years. In 2015, 66% of all RIC HSCTs were performed in this age group, compared with 44% in 2000. Among patients age < 50 years, the proportion of RIC HSCT also has increased slightly from 2000 to 2015. The use of RIC varies according to the indication for transplantation. MA is still used in the majority of patients with acute leukemias and MDS; however, there is a trend toward increased use of RIC over the last decade, reflecting the increasing age of HSCT recipients. Most commonly used MA regimens in the USA include full-dose busulfan (BU) plus cyclophosphamide (CY) ± others (28%), full-dose BU plus fludarabine (FLU) ± others (38%) and full dose total body irradiation (TBI) ± others (27%). Most commonly used RIC regimens in the USA include reduced-dose BU plus FLU ± others (33%), FLU plus melphalan (MEL) ± others (29%) and low dose TBI ± others (31%).[17] Young patients under the age of 45 will most likely benefit from a MAC transplant with full-dose TBI, although BU-CY is also an acceptable alternative. Between 45 and 65 years of age, BU-CY may be toxic, and FLU-BU would be the first choice. The serious risks associated with busulfan[18] are myelosuppression, seizures, hepatic veno-occlusive disease, embryo-fetal toxicity, cardiac tamponade, bronchopulmonary dysplasia and cellular dysplasia. Busulfan has a Boxed Warning in the label for myelosuppression, but a REMS was not required for approval.[18] Refinement of standard regimens has led to a reduction of non-relapse mortality, also in the older age group over 60 or 70 years of age. Relapse post allo-HSCT remains an important issue, especially for patients who undergo transplant with residual or refractory disease. In these patients, pre- and post-transplant interventions need to be considered.[16] There is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for patients.

4 Benefit Assessment

The efficacy of treosulfan was evaluated in a randomized active-controlled trial (MC-FludT.14/L Trial II; NCT00822393) comparing treosulfan to busulfan in combination with fludarabine as a preparative regimen for allogeneic transplantation. Eligible patients included adults 18 to 70 years old with AML or MDS, Karnofsky performance status $\geq$ 60%, and age ≥ 50 years or hematopoietic cell transplantation comorbidity index [HCT-CI] score > 2. Patients were excluded if the creatinine clearance was < 60 mL/min, forced expiratory volume (FEV1) < 50% or on supplemental oxygen, left ventricular ejection fraction (LVEF) < 40%, bilirubin > 3X ULN, or aminotransferases (ALT or AST) > 5X ULN. The patients were randomized to receive treosulfan 10 g/m^2 daily on day -4, -3 and -2 or to busulfan 0.8 mg/kg every 6 hours on day -4 and -3 in combination with fludarabine 30 mg/m^2 daily on day -6, -5, -4, -3 and -2, and hematopoietic stem cell transplantation on day 0. Antithymocyte globulin was administered as well in 97% and 95% on each arm, respectively, for patients with unrelated donors. Cyclosporine and methotrexate were used as graft-vs-host disease prophylaxis. There were 570 patients randomized to treosulfan (n=280) or busulfan (n=290). The population included 365 patients with AML and 205 patients with MDS: 536 patients received peripheral blood stem cells, 15 patients received marrow stem cells, and 19 patients were not transplanted.[1]

The following section is a summary of relevant efficacy information to date for treosulfan. The main efficacy was established on the basis of overall survival (OS), measured from the date of randomization until death by any cause. [redacted] (b) (4) .[1]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for treosulfan. The safety of treosulfan was evaluated in 553 adult patients in a randomized trial (MC-FludT.14/L Trial II; NCT00822393) comparing treosulfan to busulfan in combination with fludarabine as a preparative regimen for alloHSCT.[1]

The most common (≥20%) adverse reactions reported were musculoskeletal pain (39%), stomatitis (38%), pyrexia (34%), nausea (33%), edema (29%), infection (23%) and vomiting (22%). The most common (≥ 5%) Grade ≥ 3 adverse reactions were musculoskeletal pain (5%), stomatitis (6%).

Deaths

A total of 179 deaths (32.4%) were reported in MC-FludT.14/L Trial II in median 6.31 months (range, 0.4 to 24.1) after transplantation, 72 in the treosulfan group (33 transplant-related) and 107 (58 transplant-related) in the busulfan group. There were 41 deaths that occurred between 12 months and 24 months post-transplant, 28 in the busulfan group (16 transplant-related) and 13 in the treosulfan group (3 transplant-related). There were 14 deaths that occurred in the post-trial surveillance period, 5 in the busulfan treatment group and 9 in the treosulfan group.[19] The clinical reviewer noted that there were 11 treatment-related fatal adverse events that occurred in MC-FludT.14/L Trial II through day 30;8 in the treosulfan group and 3 in the busulfan group. Out of the 8 deaths in the treosulfan group, 6 (2.22%) were reported from infection, and 1 each was from both hemorrhage and respiratory failure (0.37%).

Out of the 3 deaths documented in the busulfan group, 2 (0.71%) were reported from infection, and one (0.37%) was from respiratory failure.[20]

Serious Adverse Events (SAE)

Fatal pulmonary regimen-related adverse reactions occurred within 30 days of transplantation in 1.5% of patients on the treosulfan arm.[1] There were no events that led to a substantial intervention (dose interruptions, reductions or discontinuation) in the study.[19,20]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 Myelosuppression

Profound myelosuppression with pancytopenia is the desired therapeutic effect of treosulfan-based preparative regimens, occurring in all patients. In the clinical trial, time to neutrophil count > 0.5 Gi/L occurred at a median of 18 days (range 7-42 days) after allogeneic hematopoietic stem cell transplantation in adult patients using treosulfan in combination with fludarabine as the preparative regimen. Labeling instructs not to begin the preparative regimen if the stem cell donor is not available. Labeling also instructs to monitor blood cell counts daily until hematopoietic recovery and to provide standard supportive care for infections, anemia and thrombocytopenia until there is adequate hematopoietic recovery. Similar to another alkylating agent, busulfan[18], labeling will include the risk of myelosuppression as a Boxed Warning.[1]

5.2 Seizures

There have been reports of seizures in patients following treatment with treosulfan. Labeling instructs to monitor patients for signs of neurological adverse reactions. Clonazepam prophylaxis may be considered for patients at higher risk for seizures, including infants.[1]

5.3 Skin Disorders

An increase of skin disorders (e.g. rash, dermatitis) was observed when patients received sodium bicarbonate-containing hydration in the course of treosulfan infusion, potentially because of acceleration of the pH-dependent formation of alkylating epoxides. Labeling instructs to keep skin clean and dry on days of treosulfan infusion. Diaper dermatitis may occur because of excretion of treosulfan in the urine. Labeling recommends changing diapers frequently during the 12 hours after each infusion of treosulfan. Dermatitis may occur under occlusive dressings; change occlusive dressings after each infusion of treosulfan.[1]

5.4 Injection Site Reactions and Tissue Necrosis

Treosulfan may cause local tissue necrosis and injection site reactions, including erythema, pain, and swelling, in case of extravasation. Labeling instructs to assure venous access patency prior to starting treosulfan infusion, and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of treosulfan. If extravasation occurs, stop the infusion immediately and manage medically as required. Labeling also instructs not to administer by the intramuscular or subcutaneous routes.[1]

5.5 SECONDARY MALIGNANCIES

There is an increased risk of a secondary malignancy with use of treosulfan. Treosulfan is carcinogenic and genotoxic. In a general toxicity study in rats, animals were treated with 5 or 50 mg/kg /day treosulfan orally for 7 months, 6 days a week. Spermatogenesis and ovarian function were significantly affected, starting at 5 mg/kg (0.003-fold the human dose based on BSA). Findings included reduced weight of the testicles, seminal vesicle, prostate, and uterus, as well as spermatogenesis reduction and arrest, uterine atrophy, and reduced or absent corpora lutea and follicles. No dedicated animal fertility studies were conducted. The risk of secondary malignancy is increased in patients with Fanconi anemia and other DNA breakage disorders.

5.6 INCREASED EARLY MORBIDITY AND MORTALITY AT DOSAGES HIGHER THAN RECOMMENDED

In the clinical trial, (b) (4) [redacted] adult patients were randomized to receive treosulfan at 14 g/m^2 (1.4 times the recommended dose) or busulfan, in combination with fludarabine as a preparative regimen for allogeneic transplantation. This trial was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in patients receiving treosulfan. Labeling instructs not to exceed the recommended treosulfan dosage of 10 g/m^2 daily for three days.

5.7 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, treosulfan can cause fetal harm when administered to a pregnant woman because it is genotoxic and affects dividing cells. Animal reproductive or developmental toxicity studies were not conducted with treosulfan. (b) (4) [redacted]. If treosulfan is used during pregnancy, or if the patient becomes pregnant while taking treosulfan, labeling also instructs to inform the patient of the potential risk to the fetus. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential during the treatment with treosulfan and for at least 6 months after the last dose, and for males with female partners of reproductive potential during the treatment and for 3 months after the last dose will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

According to the current proposed indication, if approved, treosulfan will be used in both inpatient and outpatient settings. It is expected that oncologists, familiar with the management of toxicities such as myelosuppression, injection site reactions and tissue necrosis, secondary malignancies, and embryo-fetal toxicity, will be the likely prescribers.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for treosulfan beyond routine pharmacovigilance and labeling. The applicant proposed describing these risks in the Prescribing Information that includes a Boxed Warning, Warnings and Precautions, as well as information to be included in Patient Counseling Information, to address the risks of myelosuppression, seizures, skin disorders, injection site reactions and tissue necrosis, secondary malignancies, increased early morbidity and mortality at dosages higher than recommended and embryo-fetal toxicity.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for treosulfan, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Treosulfan is an alkylating agent, with the proposed indication as an alkylating drug as part of conditioning treatment prior to alloHSCT in adult patients with AML and MDS. Based on the efficacy and safety information currently available, the clinical reviewers stated that treosulfan shows clinically meaningful benefit, and recommend approval of treosulfan as an alkylating drug indicated for:

- Use in combination with fludarabine as a preparative regimen for alloHSCT in adult and pediatric patients at least >1 year old with AML.
- Use in combination with fludarabine as a preparative regimen for alloHSCT in adult and pediatric patients at least >1 year old with MDS.[1,20]

AML is a form of cancer that is characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system. MDS are myeloid neoplasms characterized by clonal proliferation of hematopoietic stem cells, recurrent genetic abnormalities, myelodysplasia, ineffective hematopoiesis, peripheral blood cytopenia, and a high risk of evolution to AML. The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years. The standard treatment is intensive chemotherapy and an allogeneic stem cell transplant, which is based mainly on the patient's ability to tolerate intensive treatment. The initial step is assessing a MDS patient's eligibility for allogeneic stem-cell transplantation, which is the only potentially curative treatment but is associated with substantial morbidity and mortality. HSCT is a potentially curative therapeutic approach for a variety of malignant and nonmalignant hematopoietic diseases. Refinement of standard regimens has led to a reduction of non-relapse mortality. Relapse post allo-HSCT remains an important issue, especially for patients who undergo transplant with residual or refractory disease. In these patients, pre- and post-transplant interventions need to be considered. There is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for patients. Treosulfan appeared efficacious in its primary outcomes and its risks can be communicated and managed through labeling.[1,20,21] The likely prescribers for treosulfan will be oncologists. The risks identified are risks that these providers have likely encountered in their practice experience and can manage without additional risk mitigation measures.

DRM and DHM1 have determined that if approved, a REMS is not necessary to ensure the benefits of treosulfan outweigh its risks. The most concerning adverse reactions observed with the use of treosulfan include myelosuppression, seizures, skin disorders, injection site reactions and tissue necrosis, secondary malignancies, increased early morbidity and mortality at dosages higher than recommended and embryo-fetal toxicity. Embryo-fetal toxicity is based on nonclinical data. The serious risks associated with a previously approved alkylating agent, bulsulfan are myelosuppression, seizures, hepatic veno-occlusive disease, embryo-fetal toxicity, cardiac tamponade, bronchopulmonary dysplasia and cellular dysplasia and has a Boxed Warning in their label for myelosuppression, but a REMS was not required for approval. At the time this review was completed, labeling negotiations were still ongoing with the Applicant; however, similar to the other alkylating agent, busulfan, if treosulfan is approved, labeling including a Boxed Warning and Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with treosulfan, as well as information to be included in Patient Counseling Information.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of treosulfan. The management of the risks associated with treosulfan treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

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[18] Busulfex. Prescribing Information (last updated 03/2020).

[19] Medac Gesellschaft für klinische Spezialpräparate mbH. Summary of Clinical Safety for treosulfan, dated August 11, 2020

[20] Rabik C. Clinical Safety Review Presentation. Mid-Cycle Meeting, dated January 8, 2021.

[21] Gu W. Efficacy-Statistical Review Presentation. Mid-Cycle Meeting, dated January 8, 2021.

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