Treosulfan (GRAFAPEX)
National Drug Mini-Monograph
June 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial; HCT-CI, hematopoietic stem cell transplant – comorbidity index, MAC myeloablative conditioning, RIC reduced-intensity conditioning; HSCT hematopoietic stem cell transplant; MRD matched related donor; MUD matched unrelated donor; HLA human leukocyte antigen

SUMMARY OF PRESCRIBING INFORMATION[1]	
Description / MOA	Alkylating agent
Indication Under Review	In combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation (alloHSCT) with acute myeloid leukemia (AML) In combination with fludarabine as a preparative regimen for alloHSCT with myelodysplastic syndrome (MDS)
Dosage Regimen	Treosulfan 10g/m2 IV daily x 3 days (day -4, -3, -2) with Fludarabine 30mg/m2/day IV daily x5 days (day -6, -5, -4, -3, -2)
Dosage Forms Under Review	1g/vial and 5g/vial treosulfan as a lyophilized powder in a single-dose vial
Boxed Warnings	Risk of severe and prolonged myelosuppression HSCT is required to prevent potentially fatal complications of prolonged myelosuppression
Contraindications	Hypersensitivity to any component of the drug product
Other Warnings	□ Seizures □ Skin disorders □ Injection site reactions and tissue necrosis □ Secondary malignancy □ Increased early morbidity and mortality at doses higher than recommended □ Embryo-fetal toxicity
Most Common AEs	≥ 20%: musculoskeletal pain, stomatitis, pyrexia, nausea, edema, injection, vomiting
Drug Interactions	Treosulfan is a CYP2C19 and CYP3A4 inhibitor; substrates of these enzyme systems with treosulfan is expected to result in increased exposure, which may increase their toxicity
Pregnancy	Expected to cause fetal harm with administered to a pregnant woman; Conduct pregnancy test in females of reproductive potential within 7 days of start; Advise females and males with partners of reproductive potential to use effective contraception during treatment and for 3 months following.
Lactation	Advise women not to breastfeed during treatment and for one week following.
Renal Impairment	No clinically significant differences in PK profile in mild renal impairment; unknown in moderate or severe renal impairment
Hepatic Impairment	No clinically significant differences in PK profile in mild hepatic impairment; unknown in moderate or severe hepatic impairment

CLINICAL EVIDENCE SUMMARY

Trial

Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic HSCT for older patients with AML or MDS (MC-FludT.14/L): a randomized, non-inferiority, phase 3 trial

Design

P3, multicenter, open-label, randomized, non-inferiority trial

Primary Endpoint

Event Free Survival (EFS) 2 years after HSCT

EFS = time from alloHSCT to relapse, disease progression, graft failure or death

Population

31 transplant centers in France, Germany, Hungary, Italy and Poland; n= 570 (ages 18-70)

Inclusion: Patients with AML in first or consecutive hematologic remission (blast count < 5% in marrow) or MDS (blast count < 20% in marrow); eligible for alloHSCT but increased mortality risk for MAC based on age ≥ 50 yrs, HCT-comorbidity index > 2 or both; Age 18-70 years; Karnofsky index ≥ 60% and availability of an HLA-identical MRD or HLA-identical MUD

Exclusion: prior alloHSCT, active and uncontrolled infection, CrCl < 60ml/min; FEV < 50% or supplemental oxygen, LVEF < 40%; Tbili > 3x ULN or ALT or AST > 5x ULN

Interventions

Treosulfan 10g/m2 IV daily x3 days (d-4 to d-2) + fludarabine 30mg/m2 IV daily x5 days (d-6 to d-2), a myeloablative conditioning regimen (MAC)

Vs.

Busulfan 0.8 mg/kg IV every 6 hrs on d-4 and d-3 + fludarabine, as above, a reduced-intensity conditioning regimen (RIC)

Efficacy Results

Median follow up 17.4 and 15.4 months (busulfan and treosulfan, respectively)

Endpoint	Busulfan + fludarabine (n=240)	Treosulfan + fludarabine (n=220)	HR [95% CI]; p value
2-yr EFS (1°)	50.4% (42.8-57.5)	64.0% (56-70.9)	HR 0.65 [95% CI 0.47-0.90]; p<0.0001 for non-inferiority; p=0.0051 for superiority (NS)
2-yr OS	56.4%	71.3%	HR 0.61 (0.42-0.88); p=0.0082
2-yr relapse	23.3%	24.6%	HR 0.87 (0.59-1.30); p=0.50
3-yr EFS	49.7%	59.5%	HR 0.64 (0.49-0.84); p=0.0006
3-yr OS	56.3%	66.8%	HR 0.64 (0.48-0.87); p=0.0037

EFS stratification favors treosulfan for most risk groups; groups where the confidence interval crosses the value of 1, suggesting possibly no difference between the treatment arms, includes MRD donor type, RG I (risk group 1), age < 50 years and HCT-CI score > 2

Safety Results

Summary of Safety in MC-FludT.14/L

Adverse Event	Busulfan + fludarabine (n=240)	Treosulfan + fludarabine (n=220)	HR (95% CI); p-value
Deaths	1%	3%	
Serious Adverse Event	8%	7%	
Drug-related SAE	3%	3%	
Discontinuation Due to AE	0	0	
Any AE (Grade 3/4)	53%	50%	
GI disorders (Grade 1-2/3)	**58/14%**	57/9%	
Cardiac disorders (Grade 1-2/3)	5/3%	**12/3%**	
Eye disorders (Grade 1-2/3)	**10/0%**	4/0%	
Ear and labyrinth disorders (Grade 1-2/3)	8/<1%	5/0%	
GGT increases	**28%**	16%	
AST and ALT increases	5%	**10%**	
2-yr transplant-related mortality	28.2%	12.1%	HR 0.54 (0.32-0.91); p=0.02
2-yr non-relapse mortality	22.6%	11.4%	HR 0.60 (0.36-1.01); p=0.05

Authors' Conclusions	• Treosulfan/fludarabine, was non-inferior to busulfan/fludarabine as a conditioning regimen for alloHSCT for AML or MDS in older, comorbid patients. • Treosulfan/fludarabine could be used as the preferred standard preparative regimen in these settings. • Benefit in OS thought to be driven by the reduction in transplant-related mortality
Trial limitations	Open-label design Eligibility criterion limits the study to patients with AML or MDS at increased mortality risk for myeloablative conditioning: age > 50 years and/or HCT-CI > 2, therefore the results apply only to this population Comparison of a MAC regimen to a RIC regimen and not another MAC regimen, which is the standard in a fit population

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	VA Restrictions	FDA Labeling for Adults	NCCN GUIDELINES
treosulfan	tbd	n/a	In combo with fludarabine as a preparative regimen for alloHSCT in AML or MDS	Myeloablative regimens treosulfan + fludarabine (cat 2A)
busulfan inj	PA-F	Restrict to hem/onc	FDA-approved since 1999 in combo with cyclophosphamide as a conditioning regimen prior to alloHSCT for CML; Off-label uses (e.g. HSCT conditioning in other non-CML malignancies; polycythemia vera, essential thrombocythemia)	Busulfan + fludarabine (cat 2A) VA Clinical Pathway for AML and MDS refers to transplant but does not specify transplant-related therapies.

POTENTIAL PLACE IN THERAPY

Summary of Evidence

- Preparative regimens for HSCT can be separated into MAC or RIC. RIC regimens are associated with less transplant-related toxicities for the older transplant population and/or those with multiple comorbidities.
- MC-FludT.14/L was a non-inferiority study designed to compare a MAC regimen, treosulfan/fludarabine, to a RIC regimen, busulfan/fludarabine.
- Treosulfan/fludarabine was found to be non-inferior to busulfan/fludarabine as a conditioning regimen for alloHSCT for AML or MDS in older, comorbid patients.
- The authors conclude that treosulfan/fludarabine could be used as the preferred standard preparative regimen in these settings.
- Benefit in OS, a secondary endpoint, is thought to be driven by the reduction in transplant-related mortality (TRM) as relapse rates between treatment arms were comparable.
- Overall, the toxicity profiles between the treatment arms were comparable, with some variability. Treosulfan patients experienced more cardiac disorders and AST/ALT elevations while busulfan patients experienced more GI, eye effects and GGT elevations.
- 2-yr transplant-related mortality and non-relapse mortality favored the treosulfan patients

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References

1 Treosulfan (GRAFAPEX) formulation Chicago, Illinois: Medexus. Jan 2025. Available at: Treosulfan GRAFAPEX Prescribing Information

2 Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic hematopoietic stem cell transplantation for older patients with AML or MDS (MD-FludT.14/L). Lancet Hematol 2020; 7: e28-39.

3 Beelen DW, Stelljes M, Remenyi P, et al. Treosulfan compared with reduced-intensity busulfan improves allogeneic hematopoietic cell transplantation outcomes of older AML and MDS patients: final analysis of a prospective randomized trial. Am J Hematol 2022; 97: 1023-1034.