GRAFAPEX™
(treosulfan) for Injection

INCREASED OVERALL SURVIVAL
STARTS HERE

The first and only FDA-approved alloHSCT preparative regimen for AML and MDS[1]

GRAFAPEX improved overall survival at 24 months compared to busulfan; HR 0.67 (95% CI: 0.51, 0.90).[1]

alloHSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; MDS, myelodysplastic syndrome.

Indications, Important Safety Information, Including Boxed Warning, for GRAFAPEX™ (treosulfan) for Injection

Indications and Usage

Acute Myeloid Leukemia: GRAFAPEX is an alkylating drug indicated in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients >1 year old with acute myeloid leukemia.

Myelodysplastic Syndrome: GRAFAPEX is an alkylating drug indicated in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients >1 year old with myelodysplastic syndrome.

This product includes the following Boxed Warning:

WARNING: MYELOSUPPRESSION

- **GRAFAPEX causes severe and prolonged myelosuppression at the recommended dosage.**
- **Hematopoietic stem cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression. Monitor hematologic laboratory parameters.**

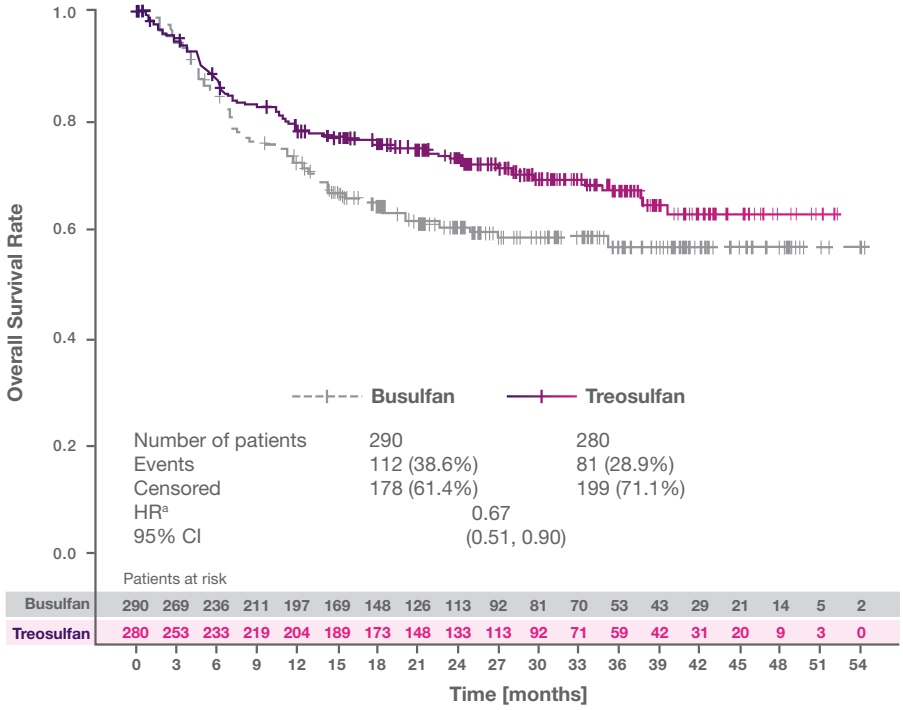
Please see enclosed Prescribing Information, including Boxed Warning for GRAFAPEX.

GRAFAPEX™ (treosulfan) for Injection HELPED MORE PATIENTS TO ACHIEVE OVERALL SURVIVAL[1]

GRAFAPEX was evaluated in a randomized active-controlled trial vs busulfan in combination with fludarabine as a preparative regimen for allogeneic transplantation[1]

- Adults aged 18 to 70 years old with AML or MDS
- Age ≥50 years or HCT-CI score >2 or both
- Karnofsky Performance Status ≥60%

Kaplan-Meier estimates of OS since time of randomization[1]



Event-free survival and non-relapse mortality were studied as part of the trial design.[2]

[a]Based on a Cox proportional hazards model stratified by donor type and risk group.

Efficacy was established based on OS, which was defined as the time from randomization until death from any cause[1]

The HR for OS compared to busulfan was:

0.67
(95% CI: 0.51, 0.90)
in the randomized population

0.73
(95% CI: 0.51, 1.06)
in patients with AML

0.64
(95% CI: 0.40, 1.02)
in patients with MDS

AML, acute myeloid leukemia; CI, confidence interval; HCT-CI, hematopoietic cell transplantation comorbidity index; HR, hazard ratio; MDS, myelodysplastic syndrome; OS, overall survival.

Important Safety Information *(continued)*

Warnings and Precautions

Myelosuppression: Profound myelosuppression with pancytopenia is the desired therapeutic effect of a GRAFAPEX-based preparative regimen, occurring in all patients. Do not begin the preparative regimen if the stem cell donor is not available. Monitor blood cell counts at least daily until hematopoietic recovery. Provide standard supportive care for infections, anemia, and thrombocytopenia until there is adequate hematopoietic recovery.

Seizures: Monitor patients for signs of neurological adverse reactions, including seizure. Clonazepam prophylaxis may be considered for patients at higher risk for seizures, including infants.

Skin Disorders: An increase in skin disorders (eg, rash, dermatitis) was observed when patients received sodium bicarbonate–containing hydration in the course of treosulfan infusion. Keep skin clean and dry on days of GRAFAPEX infusion. Diaper dermatitis may occur because of excretion of treosulfan in the urine. Change diapers frequently during the 12 hours after each infusion of GRAFAPEX. Dermatitis may occur under occlusive dressings; change occlusive dressings after each infusion of GRAFAPEX.

GRAFAPEX OFFERS AN ALTERNATIVE CONDITIONING REGIMEN[1]

The safety of GRAFAPEX in pediatric patients is supported by evidence from adequate and well-controlled studies in adult and geriatric populations[1]

Table 1: Adverse Reactions in ≥10% of Patients Through Transplant Day +30[1]

Adverse Reaction[b]	All Grades		Grades 3 or 4	
	Treosulfan (n=270)	Busulfan (n=283)	Treosulfan (n=270)	Busulfan (n=283)
Musculoskeletal pain	39%	27%	5%	2%
Stomatitis	38%	48%	6%	7%
Pyrexia	34%	36%	1%	3%
Nausea	33%	41%	3%	6%
Edema	29%	18%	0.7%	1%
Infection[c]	23%	18%	12%	6%
Vomiting	22%	19%	1%	1%
Rash	17%	13%	1%	1%
Diarrhea	17%	18%	1%	1%
Headache	16%	18%	1%	1%
Febrile neutropenia	15%	11%	15%	11%
Abdominal pain	15%	13%	3%	2%
Hypertension	14%	21%	8%	10%
Hemorrhage	14%	14%	1%	1%
Fatigue	13%	15%	1%	0.4%
Constipation	12%	12%	0.4%	0%
Tachycardia	10%	5%	1%	2%
Hepatoxicity	10%	8%	4%	3%

[b]Includes grouped terms.

[c]Includes fatalities: n=6 in the GRAFAPEX arm and n=2 in the busulfan arm.

Grading is based on Common Terminology Criteria for Adverse Events version 4.03.

Recommended dosage[1]

The recommended dosage of GRAFAPEX is 10 g/m^2 by intravenous infusion given daily for three days, beginning on Day –4 prior to transplantation in combination with fludarabine as outlined in Table 2.

Table 2: Dosage Regimen for GRAFAPEX-Based Allogeneic HSCT[1]

Treatment	Day –6	Day –5	Day –4	Day –3	Day –2	Day –1	Day 0
GRAFAPEX 10 g/m^2/day intravenously			X	X	X		
Fludarabine 30 mg/m^2/day intravenously	X	X	X	X	X		
Allogeneic hematopoietic stem cell infusion							X

1. **Premedicate patients** with antiemetics prior to the first dose of GRAFAPEX and continue antiemetics on a fixed schedule through completion of treosulfan administration
2. **Confirm patency** of the intravenous line prior to infusion
3. **Infuse GRAFAPEX** intravenously over 2 hours
4. **Monitor for extravasation**; if extravasation occurs, stop the infusion

Important Safety Information *(continued)*

Warnings and Precautions (*continued*)

Injection Site Reactions and Tissue Necrosis: Treosulfan may cause local tissue necrosis and injection site reactions, including erythema, pain, and swelling, in cases of extravasation. Assure venous access patency prior to starting GRAFAPEX infusion, and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of GRAFAPEX. If extravasation occurs, stop the infusion immediately and manage medically as required. Do not administer by intramuscular or subcutaneous routes.

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Important Safety Information *(continued)*

Warnings and Precautions (*continued*)

Secondary Malignancies: There is an increased risk of a secondary malignancy with the use of GRAFAPEX. Treosulfan is carcinogenic and genotoxic.

The risk of secondary malignancy is increased in patients with Fanconi anemia and other DNA breakage disorders. The safety of GRAFAPEX has not been established for patients with these disorders.

Increased Early Morbidity and Mortality at Dosages Higher Than Recommended: A higher incidence of early fatal and/or serious adverse reactions has been observed in patients receiving treosulfan at dosages of 14 g/m^2 (1.4 times the recommended dose). Avoid exceeding the recommended GRAFAPEX dosage of 10 g/m^2 daily for three consecutive days.

Embryo-Fetal Toxicity: GRAFAPEX can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception.

Adverse Reactions

The most common adverse reactions (≥20%) in patients treated with GRAFAPEX were musculoskeletal pain, stomatitis, pyrexia, nausea, edema, infection, and vomiting. Select Grade 3 or 4 nonhematological laboratory abnormalities were increased GGT, increased bilirubin, increased ALT, increased AST, and increased creatinine.

Drug Interactions

Effect of GRAFAPEX on Other Drugs (Certain CYP2C19 and CYP3A Substrates): Concomitant use of GRAFAPEX is predicted to increase the exposure of CYP2C19 and CYP3A4 substrates based on a mechanistic understanding of treosulfan metabolism, which may increase the risk of adverse reactions.

Use in Specific Populations

- **Pregnancy:** GRAFAPEX can cause fetal harm. There are no available human clinical data on the use of treosulfan in pregnant women to support an estimation of a drug-associated risk. Specific embryo-fetal developmental toxicity studies with treosulfan in animals were not conducted.
- **Lactation:** There is no data on the presence of treosulfan or its metabolites in human milk, its effects on milk production, or the effects of treosulfan on the breastfed child. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with GRAFAPEX and for at least 1 week after the last dose.
- **Patients With Renal Impairment:** No dosage adjustment is recommended for patients with mild renal impairment (creatinine clearance [CLcr] 60–89 mL/min). The effect of moderate or severe renal impairment and age >65 years on GRAFAPEX pharmacokinetics is unknown.
- **Pediatric Use:** The safety profile in children 1 year of age and older is comparable to that seen in adult patients, except that the incidence of hepatic and gastrointestinal toxicities was higher in pediatric patients than in adults.
- **Geriatric Use:** No significant differences in safety or effectiveness were observed between elderly subjects and younger subjects.
- **Hepatic Impairment:** No dosage adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] with aspartate aminotransferase [AST] greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). The effect of moderate or severe hepatic impairment and age >65 years on GRAFAPEX pharmacokinetics is unknown.

For adverse events, medical inquiries, and GRAFAPEX product-related concerns, please call 1-855-336-3322.

Please see enclosed Prescribing Information, including Boxed Warning for GRAFAPEX.

References: 1. GRAFAPEX (treosulfan) for Injection Prescribing Information. Medexus Pharma, Inc. 2025. **2.** Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. *Lancet Haematol*. 2020;7(1):e28-e39.

CORE CONNECTIONS

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1-84-GRAFAPEX (844-723-2739)

9:00 AM to 6:00 PM EST Monday through Friday (excluding holidays)

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MEDEXUS PHARMA

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