For Immediate Release

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American Regent announces the commercial availability of Busulfan Injection, the first and only AP-rated therapeutically equivalent generic to Busulfex®[1*]

Shirley, NY (March 1, 2017) - American Regent today announced the launch of Busulfan Injection which had been previously approved by the U.S. Food and Drug Administration. Busulfan Injection is an alkylating drug indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia (CML).[2] **Busulfan Injection is available for shipment on April 7th. Customers can order Busulfan Injection through their wholesaler/distributor or by contacting our Customer Support Group at 1-800-645-1706.**

Busulfan Injection is supplied as a clear, colorless, sterile solution in 10 mL single-use vials. Each vial contains 60 mg of busulfan at a concentration of 6 mg per mL for intravenous use. Busulfan 10 mL vials are distributed in a package of eight with an NDC number of 0517-0920-08.

Busulfan is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia (CML).[2] **Busulfan Injection causes severe and prolonged myelosuppression at the recommended dosage. Hematopoietic progenitor cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression.** See the Important Safety Information, including BOXED WARNING, at the end of this press release in addition to the Full Prescribing Information.

INDICATIONS AND USAGE

Busulfan injection is an alkylating drug indicated for:
Use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia (CML).

IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING

WARNING: MYELOSUPPRESSION

Busulfan Injection causes severe and prolonged myelosuppression at the recommended dosage. Hematopoietic progenitor cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression.

CONTRAINDICATIONS

Busulfan injection is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS AND PRECAUTIONS

The following warnings pertain to different physiologic effects of busulfan injection in the setting of allogeneic transplantation.

Myelosuppression

The most frequent serious consequence of treatment with busulfan injection at the recommended dose and schedule is prolonged myelosuppression, occurring in all patients (100%). Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Hematopoietic progenitor cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression. Monitor complete blood counts, including white blood cell differentials, and quantitative platelet counts daily during treatment and until engraftment is demonstrated. Absolute neutrophil counts dropped below $0.5x10^9$/L at a median of 4 days post-transplant in 100% of patients treated in the busulfan injection clinical trial. The absolute neutrophil count recovered at a median of 13 days following allogeneic transplantation when prophylactic G-CSF was used in the majority of patients. Thrombocytopenia (less than 25,000/mm^3 or requiring platelet transfusion) occurred at a median of 5 to 6 days in 98% of patients. Anemia (hemoglobin less than 8 g/dL) occurred in 69% of patients. Use antibiotic therapy and platelet and red blood cell support when medically indicated.

Seizures

Seizures have been reported in patients receiving high-dose oral busulfan at doses producing plasma drug levels similar to those achieved following the recommended dosage of busulfan injection. Despite prophylactic therapy with phenytoin, one seizure (1/42 patients) was reported during an autologous transplantation clinical trial of busulfan injection. This episode occurred during the cyclophosphamide portion of the conditioning regimen, 36 hours after the last busulfan injection dose. Initiate phenytoin therapy or any other alternative anti-convulsant prophylactic therapy (e.g., benzodiazepines, valproic acid or levetiracetam) prior to busulfan injection treatment. Use caution when administering the recommended dose of busulfan injection to patients with a history of a seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs.

Hepatic Veno-Occlusive Disease (HVOD)

Current literature suggests that high busulfan area under the plasma concentration verses time curve (AUC) values (greater than 1,500 µM•min) may be associated with an increased risk of developing HVOD. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing HVOD with the recommended busulfan injection dose and regimen. Based on clinical examination and laboratory findings, HVOD was diagnosed in 8% (5/61) of patients treated with busulfan injection in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three of the five patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria. The incidence of HVOD reported in the literature from the randomized, controlled trials was 7.7% to 12%. Monitor serum transaminases, alkaline phosphatase, and bilirubin daily through BMT Day +28 to detect hepatotoxicity, which may herald the onset of HVOD.

Embryo-fetal Toxicity

Busulfan injection can cause fetal harm when administered to a pregnant woman based on animal data. Busulfan was teratogenic in mice, rats, and rabbits. The solvent, DMA, may also cause fetal harm when administered to a pregnant woman based on findings in animals. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during and after treatment with busulfan injection.

Cardiac Tamponade

Cardiac tamponade has been reported in pediatric patients with thalassemia (8/400 or 2% in one series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children died and two were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. Monitor for signs and symptoms, promptly evaluate and treat if cardiac tamponade is suspected.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).

Cellular Dysplasia

Busulfan may cause cellular dysplasia in many organs. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes, pancreas, thyroid, adrenal glands, liver, lungs and bone marrow. This cytologic dysplasia may be severe enough to cause difficulty in the interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling: Myelosuppression, seizures, HVOD, embryo-fetal toxicity, cardiac tamponade, bronchopulmonary dysplasia and cellular dysplasia.

Table 1: Summary of the Incidence (greater than or equal to 20%) of Non-Hematologic Adverse Reactions through BMT Day +28 in Patients who Received Busulfan Injection Prior to Allogeneic Hematopoietic Progenitor Cell Transplantation

Non-Hematological Adverse Reactions[1]	**Percent Incidence**
BODY AS A WHOLE	
Fever	80
Headache	69
Asthenia	51
Chills	46
Pain	44
Edema General	28
Allergic Reaction	26
Chest Pain	26
Inflammation at Injection Site	25
Back Pain	23

CARDIOVASCULAR SYSTEM	
Tachycardia	44
Hypertension	36
Thrombosis	33
Vasodilation	25
DIGESTIVE SYSTEM	
Nausea	98
Stomatitis (Mucositis)	97
Vomiting	95
Anorexia	85
Diarrhea	84
Abdominal Pain	72
Dyspepsia	44
Constipation	38
Dry Mouth	26
Rectal Disorder	25
Abdominal Enlargement	23
METABOLIC AND NUTRITIONAL SYSTEM	
Hypomagnesemia	77
Hyperglycemia	66
Hypokalemia	64
Hypocalcemia	49
Hyperbilirubinemia	49
Edema	36

SGPT Elevation	31
Creatinine Increased	21
NERVOUS SYSTEM	
Insomnia	84
Anxiety	72
Dizziness	30
Depression	23
RESPIRATORY SYSTEM	
Rhinitis	44
Lung Disorder	34
Cough	28
Epistaxis	25
Dyspnea	25
SKIN AND APPENDAGES	
Rash	57
Pruritus	28

1. Includes all reported adverse reactions regardless of severity (toxicity grades 1 to 4)

Additional Adverse Reactions by Body System

Hematologic: Prolonged prothrombin time

Gastrointestinal: Esophagitis, ileus, hematemesis, pancreatitis, rectal discomfort

Hepatic: Alkaline phosphatase increases, jaundice, hepatomegaly

Graft-versus-host disease: Graft-versus-host disease. There were 3 deaths (5%) attributed to GVHD.

Edema: Hypervolemia, or documented weight increase

Infection: Infection, pneumonia (fatal in one patient and life-threatening in 3% of patients)

Cardiovascular: Arrhythmia, atrial fibrillation, ventricular extrasystoles, third degree heart block, thrombosis (all episodes were associated with the central venous catheter), hypotension, flushing and hot flashes, cardiomegaly, ECG abnormality, left-sided heart failure, and pericardial effusion

Pulmonary: Hyperventilation, alveolar hemorrhage (fatal in 3%), pharyngitis, hiccup, asthma, atelectasis, pleural effusion, hypoxia, hemoptysis, sinusitis, and interstitial fibrosis (fatal in a single case)

Neurologic: Cerebral hemorrhage, coma, delirium, agitation, encephalopathy, confusion, hallucinations, lethargy, somnolence

Renal: BUN increased, dysuria, oliguria, hematuria, hemorrhagic cystitis

Skin: Alopecia, vesicular rash, maculopapular rash, vesiculo-bullous rash, exfoliative dermatitis, erythema nodosum, acne, skin discoloration

Metabolic: Hypophosphatemia, hyponatremia

Other Events: Injection site pain, myalgia, arthralgia, ear disorder

DRUG INTERACTIONS

Itraconazole decreases busulfan clearance by up to 25%, and may produce an AUC greater than 1500 μM•min in some patients. Fluconazole (200 mg) has been used with busulfan injection.

Phenytoin increases the clearance of busulfan by 15% or more. Use of acetaminophen prior to dose less than 72 hours or concurrent with busulfan may result in reduced busulfan clearance. Caution should be exercised in these cases.

USE IN SPECIFIC POPULATIONS

Pregnancy

Busulfan can cause fetal harm when administered to a pregnant woman. Ovarian suppression and amenorrhea commonly occur in premenopausal woman undergoing chronic, low-dose busulfan therapy. In males, busulfan may damage spermatozoa and testicular tissue resulting in possible genetic fetal abnormalities. Sterility, azoospermia and testicular atrophy have been reported.

Pediatric Use

The effectiveness of busulfan injection in the treatment of CML has not been specifically studied in pediatric patients. An open-label, uncontrolled study evaluated the pharmacokinetics of busulfan injection in 24 pediatric patients receiving busulfan injection as part of a conditioning regimen administered prior to hematopoietic progenitor cell transplantation for a variety of malignant hematologic (N=15) or non-malignant diseases (N=9). Patients ranged in age from 5 months to 16 years (median 3 years). Busulfan injection dosing was targeted to achieve an area under the plasma concentration curve (AUC) of 900 to 1350 µM•min with an initial dose of 0.8 mg per kg or 1 mg per kg (based on ABW) if the patient was greater than 4 or less than or equal to 4 years, respectively. The dose was adjusted based on plasma concentration after completion of dose 1.

Four (17%) patients died during the study. Two patients died within 28 days of transplant; one with pneumonia and capillary leak syndrome, and the other with pneumonia and veno-occlusive disease. Two patients died prior to day 100; one due to progressive disease and one due to multi-organ failure.

Adverse reactions were reported in all 24 patients during the study period (BMT day -10 through BMT day +28) or post-study surveillance period (day +29 through +100). These included vomiting (100%), nausea (83%), stomatitis (79%), HVOD (21%), graft-versus host disease (GVHD) (25%), and pneumonia (21%).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Busulfan is a mutagen and a clastogen.

For additional Safety Information, including BOXED WARNING please see Full Prescribing Information.

You are encouraged to report side effects to American Regent Inc. at 1-800-734-9236 or to the FDA by visiting www.fda.gov/safety/medwatch or calling 1-800-FDA-1088.

About American Regent

Celebrating 50 years as a manufacturer and marketer of branded and generic specialty injectables, American Regent, a Daiichi Sankyo Group Company, is proud of its reputation as a consistent and reliable source of high quality pharmaceuticals. Through our multiple US based manufacturing facilities, American Regent is able to maintain strict control of the manufacturing process to help provide a steady supply of products that our customers can depend on.

For more information, please visit www.americanregent.com.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for hypertension and thrombotic disorders, under the Group's 2025 Vision to become a "Global Pharma Innovator with a Competitive Advantage in Oncology," Daiichi Sankyo research and development is primarily focused on bringing forth novel therapies in oncology, including immuno-oncology, with additional focus on new horizon areas, such as pain management, neurodegenerative diseases, heart and kidney diseases, and other rare diseases. For more information, please visit: www.daiichisankyo.com. Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit: www.dsi.com.

To Report Adverse Drug Events (ADEs):
Email: pv@luitpold.com;
Fax: 1-610-650-0170; Phone: 1-800-734-9236

***** Busulfex is a trademark of Otsuka Pharmaceutical Co., Ltd.

References: 1. US Food and Drug Administration, Center for Drug Evaluation and Research. Busulfan Injection ANDA 202259 Approval Letter. **2.** Busulfan Injection [Package Insert]. American Regent, Inc.; 2016: Shirley, NY.