



**TRANSMITTED BY FACSIMILE**

Stephanie H. Jameison, MBA, RAC  
Senior Manager, Labeling and Promotion Compliance  
Otsuka Pharmaceutical Development and Commercialization, Inc.  
2440 Research Boulevard  
Rockville, MD 20850

**RE: NDA #020954**  
Busulfex<sup>®</sup> (busulfan) Injection  
MA #77

Dear Ms. Jameison,

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the US Food and Drug Administration has reviewed the US product website (0608W-0013) for Busulfex<sup>®</sup> (busulfan) Injection (Busulfex) submitted by Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC) under cover of Form FDA-2253<sup>1</sup>. This website is misleading because it omits material facts, minimizes important risk information about Busulfex, makes unsubstantiated claims, overstates the efficacy of Busulfex, and makes a misleading claim. Therefore, the website misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a) & (n); 321(n). See 21 CFR 202.1(e)(5); (e)(6)(i); (e)(7)(i) & (iii).

**Background**

Below is the indication and summary of the most serious and most common risks associated with the use of Busulfex.<sup>2</sup>

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI):

BUSULFEX<sup>®</sup> (busulfan) Injection is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

The PI for Busulfex includes a Boxed Warning regarding the risk of profound myelosuppression at recommended doses and the need for supervision by a qualified physician experienced in allogeneic hematopoietic stem cell transplantation, the use of

<sup>1</sup> Last accessed October 3, 2011.

<sup>2</sup> This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

chemotherapeutic drugs, and the management of patients with severe pancytopenia. The PI for Busulfex also includes the following Warnings: seizures; hepatic veno-occlusive disease (HVD); cardiac tamponade in pediatric patients with thalassemia who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation; bronchopulmonary dysplasia with pulmonary fibrosis; and use in pregnancy. The PRECAUTIONS section of the PI also includes recommendations for monitoring serum transaminases, alkaline phosphatase, and bilirubin to detect hepatotoxicity.

The most common non-hematologic adverse reactions in adult patients treated with Busulfex were nausea, stomatitis (mucositis), vomiting, anorexia, diarrhea, insomnia, fever, hypomagnesemia, abdominal pain, and anxiety.

The PRECAUTIONS – Special Populations: Pediatric section of the PI discusses the use of Busulfex in pediatric patients participating in an open-label, uncontrolled study that evaluated the pharmacokinetics of Busulfex therapy when used as part of a conditioning regimen administered prior to hematopoietic progenitor cell transplantation for a variety of malignant hematologic or non-malignant diseases. Adverse events reported for these patients include vomiting, nausea, stomatitis, HVD, graft-versus host disease (GVHD), and pneumonia.

### **Omission of Material Facts**

Promotional materials are misleading if they fail to reveal material facts in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The Dosing and Straightforward IV Administration – Infusion Examples webpages of the Busulfex website present information regarding dosage and administration for pediatric patients, but omit important material information regarding the risks associated with the use of Busulfex in this patient population. Specifically, these presentations omit the risk of cardiac tamponade observed in pediatric patients receiving high doses of oral busulfan. The webpages also fail to include the adverse events reported for pediatric patients including vomiting (100%), nausea (83%), stomatitis (79%), GVHD (25%), HVD (21%), and pneumonia (21%). By failing to communicate this important risk information, the website misleadingly suggests that Busulfex is safer than has been demonstrated by substantial evidence or substantial clinical experience.

The Important Safety Information section on the bottom of each webpage and the Clinical Trial Results – Safety Profile webpage present some information regarding the risk of HVD, but omit material facts regarding HVD and hepatotoxicity. In particular, the WARNINGS – Hepatic section of the PI states, “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 HVD with the recommended BUSULFEX dose and regimen.” Moreover, the PRECAUTIONS section of the PI states, “To

detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase, and bilirubin should be evaluated daily through BMT Day +28.” Finally, the ADVERSE REACTIONS - Hepatic section of the PI indicates that hyperbilirubinemia occurred in 49% of patients, was grade 3/4 in 30% of patients, and was considered life-threatening in 5% of these patients. Hyperbilirubinemia was associated with both GVHD and HVOD. By omitting these material facts, the website suggests that Busulfex is safer than has been demonstrated by substantial evidence or substantial clinical experience.

The Dosing webpage and Straightforward IV Administration – Infusion Examples webpage present information on the dosage and administration of Busulfex. However, these presentations omit material facts regarding the need to pre-medicate patients with antiemetics prior to the first dose of Busulfex therapy and on a fixed schedule for the duration of Busulfex treatment. This treatment recommendation is particularly relevant in light of the fact that nausea and vomiting occurred in 98% and 95% of patients, respectively, in the pivotal clinical trial.

### **Minimization of Risk/Unsubstantiated Claims**

Promotional materials are misleading if they contain a representation or suggestion that a drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Several pages of the Busulfex product website contain the claim, “**Low incidence of severe toxicities**” (emphasis original). The PI contains a BOXED WARNING which indicates that Busulfex is a cytotoxic drug associated with profound myelosuppression that occurs in **all** patients as well as other significant warnings and precautions. For example, some of the most common adverse events include nausea (98%), stomatitis (mucositis) (97%), vomiting (95%), anorexia (85%), diarrhea (84%), insomnia (84%), and fever (80%). Given the frequency and severity of profound myelosuppression, and the potential for other serious and significant adverse events with Busulfex therapy, the claim, “Low incidence of severe toxicities” is misleading and significantly minimizes the risks associated with the drug. We note that this presentation includes the claim that, “100% (61/61) completed the 16-dose regimen.” Although it is true that 61/61 patients completed the 16-dose regimen, the inclusion of this statement does not mitigate the misleading impression created by this claim.

The Straightforward IV Administration - Concomitant Medications webpage claims:

- “In a retrospective review, 29 pediatric patients (ages 6 months to 19 years) who received lorazepam for seizure prophylaxis did not develop seizures while receiving or within 48 hours of last dose of IV BUSULFEX<sup>[3]</sup>”

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<sup>3</sup> Chan KW, Mullen CA, Worth LL, et al. Lorazepam for seizure prophylaxis during high-dose busulfan administration. *Bone Marrow Transplant*. 2002;29:963-965.

- “During high dose IV BUSULFEX treatment, PK data showed no alteration in absorption and clearance of busulfan during concomitant administration of lorazepam<sup>[3]</sup>”

This presentation is misleading because it suggests that the use of lorazepam for seizure prophylaxis eliminates the risk of seizures with Busulfex therapy, when this has not been demonstrated by substantial evidence or substantial clinical experience. The reference cited (Chan, et al.) to support the above presentation is a retrospective review of the use of variable doses of lorazepam for seizure prophylaxis in 29 pediatric patients receiving busulfan as part of a conditioning regimen for hematopoietic stem cell transplantation (HSCT). A retrospective analysis of a study in a limited pediatric population does not constitute substantial evidence or substantial clinical experience to support claims implying that lorazepam eliminates the risk of seizures associated with Busulfex therapy. We note that the DOSAGE AND ADMINISTRATION section of the PI specifically states that “[a]ll patients should be premedicated with **phenytoin** as busulfan is known to cross the blood brain barrier and induce seizures. . . . Use of other anticonvulsants may result in higher busulfan plasma AUCs, **and an increased risk of VOD or seizures**. In cases where other anticonvulsants must be used, plasma busulfan exposure should be monitored . . .” (emphasis added). Furthermore, the totality of this presentation is particularly concerning given that the Busulfex PI contains a warning regarding the risk of seizures. In fact, one seizure (1/42 patients) was reported during an autologous transplantation clinical trial of Busulfex, despite prophylactic therapy with phenytoin.

### Unsubstantiated Claims

The Busulfex website includes claims and presentations such as the following (underlined emphasis added):

- “Begin with **Precision**”
- “For **optimal** HSCT conditioning”
- “Outcomes through **accuracy**”
- “**Predictable** pharmacokinetics”
- “**Predictable** pharmacokinetic profile<sup>[4]</sup>”
- “**Controlled** Myeloablation”
- “**Predictable** and **consistent** inpatient and outpatient AUC values<sup>[4]</sup>”
- “Excellent interdose reproducibility ( $C_{max}$  at dose 1 accurately predicted  $C_{max}$  at dose 9)<sup>[4]</sup>”
- “Delivers **precise, predictable** control”
- A line graph entitled, “Pharmacokinetics Results: Doses 1, 9, and 13 (n=59)<sup>[4]</sup>” that presents maximum concentration ( $C_{max}$ ), AUC, and minimum concentration ( $C_{min}$ ) data across these timepoints.

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<sup>4</sup> Andersson BS, Kashyap A, Gian V, et al. Conditioning therapy with intravenous busulfan and cyclophosphamide (IV BuCy2) for hematologic malignancies prior to allogeneic stem cell transplantation: a phase II study. *Biol Blood Marrow Transplant*. 2002;8:145-154.

Claims and presentations implying that Busulfex has a “predictable pharmacokinetic profile,” “predictable and consistent” area under the curve (AUC) values, and “excellent interdose reproducibility” are misleading. The reference cited to support these claims is a publication (Andersson, et al.) that describes the pivotal study for Busulfex. In this study, blood samples were only collected up to 4 hours after the end of infusion. However, the half-life of busulfan is approximately 3 hours. An acceptable sampling schedule to determine first dose AUC would need to extend up to 15 hours post infusion. Therefore, the first dose AUC was extrapolated by a range of 2% to 68% in order to calculate  $AUC_{0-\infty}$ . This renders a comparison between first dose AUC values to AUC values of subsequent doses invalid and claims implying that Busulfex has a predictable pharmacokinetic profile based on its calculated AUC are misleading. For similar reasons, claims implying that Busulfex has predictable and consistent inter- and inpatient AUC values are unsubstantiated. Additionally, in this study there was a significant difference between dose one and dose nine  $C_{max}$  (ng/ml) values ( $944 \pm 25\%$  vs.  $1222 \pm 18\%$ , respectively) which demonstrates that the  $C_{max}$  of dose one cannot be used to accurately predict  $C_{max}$  of dose nine. Therefore, claims suggesting that Busulfex has “excellent interdose reproducibility” based on dose one  $C_{max}$  predicting dose nine  $C_{max}$  are misleading.

Furthermore, the totality of this presentation misleadingly implies that there is a direct correlation between a “predictable pharmacokinetic profile” and the ability to induce myeloablation in an “accurate,” “controlled” or “optimal” way. OPDP is not aware of substantial evidence or substantial clinical experience that supports any kind of causal or correlative relationship between pharmacokinetic profile and such clinical benefits.

### **Overstatement of Efficacy**

The Clinical Trial Results – 100% Engraftment webpage presents a Kaplan-Meier graph titled, “**Overall Survival and Disease-free Survival.**” The references cited to support this presentation are the Busulfex PI and publication of the single-arm open-label pivotal trial (Andersson, et al.). The graph depicts the probability of overall survival (OS) and disease free survival (DFS) from day 0 to day 583 post-transplant and calls out an 86.9% probability of overall survival at day 100 post transplant. This presentation is misleading because it makes efficacy claims regarding the probability of OS and DFS following Busulfex therapy which have not been demonstrated by substantial evidence or substantial clinical experience. OS and DFS are time-to-event endpoints that represent the likelihood that patients will be alive or free from disease at a given point in time. The accurate method of calculating probability estimates for these endpoints takes into consideration the number of patients who are still alive or free from disease after each pre-specified event has occurred (defined as the population *at risk*) as well as the number of patients censored from analysis at each time point during the period of observation. In contrast, the 86.9% OS probability estimate reported on the website for day 100 was derived by dividing the number of patients alive at day 100 by the *total* number of patients who received Busulfex during the entire clinical trial. This calculation does not accurately reflect the number of patients still at risk for the defined events (i.e., OS, DFS). Failure to incorporate these principles into the derivation of this

statistic overestimates the probability of OS and DFS. Therefore, the 86.9% OS probability reported on the webpage is misleading because it overstates the efficacy of Busulfex.

Moreover, the results of the single-arm, open label pivotal study in 61 patients, as reported in the Busulfex PI, do not support the Kaplan-Meier presentation that approximately 70% of patients were alive at day 583 and approximately 40% of patients were disease-free at this time. The PI states that “twenty-three patients (38%) relapsed at a median of 183 days post-transplant (range 36 to 406 days). Sixty-two percent of patients (38/61) were free from disease with a median follow-up of 269 days post-transplant (range 20 to 583 days). Forty-three patients (70%) were alive with a median follow up of 288 days post-transplant (range 51 to 583 days).” We note that this information is included on this webpage. These data, however, are not OS and DFS probability estimates, nor do they support such implications in a Kaplan Meier presentation. Single-arm trials do not adequately characterize time-to-event endpoints.<sup>5</sup> Therefore, neither the PI nor the referenced publication support the misleading OS and DFS implications made by this presentation.

### **Misleading Claim**

The Busulfex website presents the following claim:

- “Straightforward IV administration”

This claim is misleading because it suggests that the administration of IV Busulfex is straightforward when this is not the case. The Busulfex PI contains several instructions pertaining to the administration of Busulfex. Specifically, the DOSAGE and ADMINISTRATION section of the PI indicates that Busulfex therapy should be administered intravenously via a central venous catheter using an infusion pump to deliver the entire prescribed dose over two hours. An administration set with minimal residual hold-up volume (2-5cc) should be used for administration. Prior to and following each infusion the indwelling catheter should be flushed with five milliliters of 0.9% sodium chloride injection or 5% dextrose injection. Dosing of Busulfex is repeated every six hours for four consecutive days for a total of 16 doses. In light of the several instructions required for the proper administration of Busulfex, it is misleading to suggest that the administration of Busulfex is “straightforward.” We acknowledge that the administration information for Busulfex is presented on the website; however, this is not sufficient to mitigate the misleading impression created by the above claim.

### **Conclusion and Requested Action**

For the reasons discussed above, the US product website for Busulfex misbrands the drug in violation of the FD&C Act, 21 U.S.C. 352(a) & (n); 321(n). See 21 CFR 202.1(e)(5); (e)(6)(i); (e)(7)(i) & (iii).

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<sup>5</sup> Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.(May 2007)

OPDP requests that OPDC immediately cease the dissemination of violative promotional materials for Busulfex such as those described above. Please submit a written response to this letter on or before October 31, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Busulfex that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Busulfex comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Adam George, Pharm.D.  
Regulatory Review Officer  
Division of Professional Promotion  
Office of Prescription Drug Promotion

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ADAM GEORGE  
10/17/2011