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TRANSMITTED VIA E-MAIL

On behalf of BTG International Inc., I respectfully request the NCCN Panel on Acute Lymphoblastic Leukemia (ALL) to review the enclosed data for inclusion of VORAXAZE® (glucarpidase) for the treatment of toxic plasma methotrexate (MTX) concentrations in ALL patients receiving high-dose methotrexate therapy and who have delayed methotrexate clearance due to impaired renal function. Of the patients in whom glucarpidase was administered under the Voraxaze® US Open-Label Treatment Protocol IND (as of Oct. 2010), approximately 23% had received high-dose methotrexate in treatment of ALL.

Specific Changes: Recommend the use of glucarpidase in patients who have received high-dose methotrexate and are experiencing delayed elimination of methotrexate (concentration >1 micromole per liter) due to impaired renal function.

FDA Clearance Status: Glucarpidase was approved on January 17, 2012 for the treatment of toxic plasma methotrexate concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function and is commercially available in the United States as of April 30, 2012.

Rationale: Methotrexate-associated renal impairment is an oncologic emergency that continues to occur despite the best medical management. Frequencies of Common Terminology Criteria for Adverse Events Grade ≥2 nephrotoxicity depend on tumor type and patient age, and occur at a frequency of 2 to 10% of patients being treated with high-dose methotrexate (Widemann 2004, 2010). These data include patients treated after 1980, when management began to routinely include IV hydration, urinary alkalinization and leucovorin rescue.

Glucarpidase hydrolyzes the terminal glutamate residue from naturally-occurring folates and folate analogs such as MTX. The hydrolysis of MTX and its active metabolite, 7 hydroxymethotrexate (7-OH MTX), by glucarpidase forms inactive metabolites, including glutamate, 2,4-diamino-N10-methylpteroic acid (DAMPA), and 7 hydroxy DAMPA (7-OH

DAMPA), which are eliminated from the body through non-renal mechanisms; therefore, in patients with impaired renal function who are unable to clear MTX efficiently, treatment with glucarpidase therefore provides an alternate route of MTX clearance (Christensen, 2012). In data published by the National Cancer Institute on 100 patients, plasma MTX concentrations decreased within 15 minutes of glucarpidase administration by 98.7% (Widemann, 2010). BTG International's Biologics Licensing Application (approved in 2012) presented an efficacy analysis of 156 patients where, at the first measurement (median 15 minutes post-glucarpidase), plasma MTX was reduced by a median of 99% relative to their pre-glucarpidase baseline. At the last measurement (median 40 hours post-glucarpidase) median plasma MTX reduction remained at 99% compared with baseline measurement. The data that supported the BLA were presented at the American Society for Clinical Oncology (ASCO) 2012 Annual Congress in June and are included in this submission package.

The following citations are submitted in support of this proposed change.

1. Widemann BC, Balis FM, Kempf-Bielack B et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. Cancer 2004;100:2222¬32.

2. Widemann BC, Balis FM, Kim AR et al. Glucarpidase, Leucovorin, and Thymidine for High-Dose Methotrexate-Induced Renal Dysfunction: Clinical and Pharmacologic Factors Affecting Outcome. Journal of Clinical Oncology 2010;28:3979¬86.

3. Christensen AM, Pauley JL, Molinelli AR et al. Resumption of high-dose methotrexate after acute kidney injury and glucarpidase use in pediatric oncology patients. Cancer;2012 epub 17 January 2012.

4. Widemann BC, Jayaprakash N, Howard SC, et al. Compassionate Use Clinical Trial Experience with Glucarpidase for Methotrexate Toxicity. Presented at: American Society of Clinical Oncology Annual Meeting (poster discussion session, Abstract 6530), Friday 1 June 2012, Chicago, IL.

Sincerely,

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