



**Tracking Form for Applicants for New Technology Add-on Payments under
the Acute Inpatient Prospective Payment System (IPPS) for Federal Fiscal
Year (FY) 2013**

1. Technology Name:

Glucarpidase

2. Manufacturer Name:

BTG International Inc.

3. Trade Brand of Technology:

Voraxaze®

4. Brief Description of Service or Device:

Voraxaze® (glucarpidase) is a biologic used as a treatment for patients with toxic methotrexate (MTX) concentrations due to renal impairment. Glucarpidase causes a rapid and sustained reduction of toxic MTX concentrations in these patients.

Newness Criterion

Note: To qualify for a new technology add-on payment, the technology or service must not be reflected in the data used to establish the Medicare severity diagnosis related groups (MS-DRGs).

5. Date of Food and Drug Administration (FDA) approval (or expected approval) for the device or service:

The Biologic License Application for Voraxaze® (glucarpidase) has been accepted by the FDA. The PDUFA date is January 17, 2012.

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage).

Note: The information provided on this tracking form will be made publicly available.

- 6. Was the product available on the market immediately after FDA approval? If not, please provide the date that the medical service or technology came on the market (i.e. first sales or availability) and an explanation for any delay (i.e. manufacturing issues, shelf life concerns or other reasons).**

Voraxaze® (glucarpidase) is not currently approved by the FDA. The PDUFA date is January 17, 2012. In the United States, glucarpidase is currently available under an expanded access IND and cost recovery program, and in selected countries outside of the United States on a named-patient basis. Assuming FDA approval January 17, 2012, BTG will market glucarpidase as commercial product in the United States starting in April 2012.

- 7. Does the technology have an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and/or ICD-10-PCS procedure code(s) or is an application pending?**

As of the date of submission of this New Technology Tracking Form, November 21, 2011, Voraxaze® (glucarpidase) does not have an ICD-9-CM or an ICD-10-PCS procedure code. However, BTG will apply for a new ICD-9-CM Procedure Code in 2012.

- a. **If yes, please provide the ICD-9-CM and/or ICD-10-PCS procedure code(s) used to identify the clinical procedure(s) with which the medical service and technology is used.**
- b. **If there is no existing ICD-9-CM and/or ICD-10-PCS code that captures this new technology, please indicate whether you will be applying for a new code. (Refer to http://www.cms.hhs.gov/ICD9ProviderDiagnosticCodes/01_overview.asp#TopOfPage for more information.) We note that, if the product were to receive add-on payment status approval, it would need to be distinctly identifiable by ICD-9-CM and effective October 1, 2013 by ICD-10-PCS code(s) in the MedPAR claims data in order to receive add-on payment.**

BTG will apply for a new ICD-9-CM Procedure Code in 2012.

- 8. Have you submitted an application for outpatient pass-through payments under the Medicare outpatient prospective payment system? If so, please provide the tracking number or, if it was approved, please provide the date of approval. (Please refer to http://www.cms.hhs.gov/HospitalOutpatientPPS/04_passthrough_payment.asp#TopOfPage for more information.)**

We anticipate that there will be very little glucarpidase used outside of the hospital inpatient setting. However, we intend to apply for pass-through status to cover those rare cases.

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage).

Note: The information provided on this tracking form will be made publicly available.

Cost Criterion

Note: To qualify for a new technology add-on payment, the technology or service must result in average charges for cases using the technology in excess of the lesser of 75 percent of the standardized amount increased to reflect the difference between costs and charges or 75 percent of 1 standard deviation beyond the geometric mean standardized charge for all cases in the MS-DRGs to which the new technology is assigned. Table 10 from the annual final rule lists the thresholds by MS-DRG. The most recent version of Table 10 can be downloaded at:

<https://www.cms.gov/AcuteInpatientPPS/FR2012/itemdetail.asp?filterType=none&filterByDID=->

[99&sortByDID=1&sortOrder=ascending&itemID=CMS1250507&intNumPerPage=10](https://www.cms.gov/AcuteInpatientPPS/FR2012/itemdetail.asp?filterType=none&filterByDID=-99&sortByDID=1&sortOrder=ascending&itemID=CMS1250507&intNumPerPage=10).

Provide the following information to demonstrate the technology or service meets the criterion.

8. **What is the anticipated average standardized charge per case involving this new technology? For details how to standardize charges please refer to the technical appendix of the application form.**

We are in the process of determining the anticipated average standardized charge per case and intend to forward it to CMS prior to December 31, 2011.

9. **A. What is the total estimated cost per case for the service or technology (this will include all costs involved in the case, including the cost of the service or device)?**

We intend to send to CMS the answer to this question prior to December 31, 2011.

B. What is the cost of the technology per patient? Please provide a breakdown how the cost of the technology is calculated (i.e. Drugs- Average dosage or number of units per patient (ml/kg/hr); Devices- breakdown of the cost of all components used in the new technology, clearly showing which components are the “new” ones).

We intend to send to CMS the answer to this question prior to December 31, 2011.

10. **List the Medicare severity diagnosis-related groups (MS-DRGs) to which cases involving this new technology will most likely be assigned.**

The current MS-DRGs do not adequately capture the treatment of patients suffering from poisoning from antineoplastic drugs. Current MS-DRGs contain codes identifying treatment with chemotherapy agents.

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage).

Note: The information provided on this tracking form will be made publicly available.

Glucarpidase offers a treatment option for patients suffering from poisoning due to toxic level of methotrexate administered as part of the chemotherapy.

11. What is the anticipated volume of Medicare cases involving this technology in FY 2013 (by MS-DRG)?

We intend to calculate the anticipated volume for glucarpidase for FY 2013, and send our answer to CMS prior to December 31, 2011.

Clinical Improvement Criterion

Note: To qualify for a new technology add-on payment, the technology or service must represent a substantial clinical improvement over existing technologies or services.

12. Please provide a short synopsis of the following clinical issues added to the new technology. Use the regular application to submit full details.

a. Briefly describe how the new service or technology represents a substantial clinical improvement over existing services or technologies:

Proposed Indication and Product Description

Glucarpidase is indicated for the rapid and sustained reduction of toxic methotrexate concentrations due to impaired renal function. Glucarpidase is supplied as a sterile, white, preservative-free, lyophilized powder. Each vial contains 1,000 Units of glucarpidase, which should be reconstituted with 1 mL of normal saline.

Treatment of Methotrexate Toxicity

Measures that are routinely employed to reduce MTX toxicity, such as administration of leucovorin, hydration and urinary alkalinization, are not effective in all patients. Leucovorin does not reduce the amount of circulating MTX and when MTX concentrations remain high, toxicity may still occur because leucovorin cannot compete effectively with MTX for transport into cells (*Pinedo et al., 1976*).

Methotrexate-induced renal impairment is a medical emergency that continues to occur even with the best medical management. In a recent literature review of patients with osteogenic sarcoma who received high dose MTX, the reported incidence of renal toxicity in the reported studies ranged from 0-12.4%. When combined with additional data from the authors' patient series, 68 of 3887 patients (1.8%) developed Grade ≥ 2 nephrotoxicity and three deaths were attributable to MTX toxicity (*Widemann et al., 2004*). This series included only patients treated after 1980, when management routinely included IV hydration, urinary alkalinization and leucovorin rescue. Renal impairment occurs much more frequently in older patients; in a series of 23 patients 19 to 94 years of age receiving high dose MTX for Primary

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage).

Note: The information provided on this tracking form will be made publicly available.

Central Nervous System Lymphoma, 48% experienced a doubling of serum creatinine (sCr) during treatment, and nine patients met criteria for administration of glucarpidase under the National Cancer Institute (NCI) protocol with respect to presence of toxic MTX concentrations and renal impairment (*Green et al., 2006; Green and Chamberlain, 2009*).

There are currently no approved pharmaceutical treatment options for patients with toxic MTX concentrations due to renal impairment. Instead, extracorporeal methods such as hemodialysis, hemodiafiltration, high-flux hemodialysis, charcoal hemoperfusion or hemofiltration, peritoneal dialysis, exchange transfusion or plasma exchange are employed. The results of these methods are mixed (reviewed by *Widemann et al., 2004; Vilay et al., 2010*). High-flux hemodialysis is the most effective method of extracorporeal MTX removal, but requires five to six days of daily treatments (4-6 hours per session) (*Wall et al., 1996*). The risks associated with repeated hemodialysis, especially in a neutropenic or thrombocytopenic patients, are significant.

There is a clear, unmet medical need for a rapid, safe means of reducing toxic MTX concentrations in patients with renal impairment that is met by glucarpidase. When administered IV to patients with toxic MTX concentrations, glucarpidase rapidly hydrolyzes extracellular MTX and its active metabolite 7-OH MTX into the inactive metabolites glutamate, DAMPA and 7-OH DAMPA, which are metabolized hepatically. In clinical studies, administration of glucarpidase resulted in a 99% median reduction in plasma or serum MTX concentration within 15 minutes of administration, thereby profoundly decreasing both the magnitude and duration of exposure to circulating MTX.

b. List all published peer-reviewed articles relevant to the new service or technology.

1. Levy CC, Goldman P. The enzymatic hydrolysis of methotrexate and folic acid. *J Biol Chem.* 1967; 242:2993-2998.
2. Minton NP, Atkinson T, Sherwood RF. Molecular cloning of the *Pseudomonas* carboxypeptidase G2 gene and its expression in *Escherichia coli* and *Pseudomonas putida*. *J Bacteriol.* 1983; 156: 1222-1227.
3. Widemann BC, Balis FM, Kim A, et al. Glucarpidase, leucovorin and thymidine for high-dose methotrexate induced renal dysfunction. Clinical and pharmacologic factors affecting outcome. *J Clin Oncology* 2010; 28:1-8.
4. Patterson DM, Lee SM. Glucarpidase following high-dose methotrexate: update on development. *Expert Opin Biol Ther.* 2010;10(1):105-111.
5. Phillips M, Smith W, Balan G, et al. Pharmacokinetics of glucarpidase in subjects with normal and impaired renal function. *J Clin Pharmacol* 2008; 48:279-284.

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage).

Note: The information provided on this tracking form will be made publicly available.

6. Bleyer WA. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat Rev.* 1977;4:87–101.

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage).

Note: The information provided on this tracking form will be made publicly available.