



## FOLLOW-UP for INFORMATION LETTER REGARDING AUC-BASED DOSING OF CARBOPLATIN

**DATE:** October 22, 2010

**FROM:** S. Percy Ivy, M.D., Associate Branch Chief, IDB, CTEP, DCTD, NCI  
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI  
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

**SUBJECT:** Area Under the Curve (AUC)-based Dosing of Carboplatin

**TO:** Treating Physicians or Investigators Performing Clinical Trials or Treating Patients with Carboplatin (NSC 241240)

*This follow-up letter is in response to queries regarding a related Action Letter dated October 1, 2010, sent to Investigators conducting CTEP- Sponsored trials with carboplatin who needed to amend their protocols. This follow-up letter includes additional information NCI/CTEP has received since issuing the Action Letter. The new or additional information is bolded and italicized.*

Serum creatinine is used as a surrogate for renal function. Carboplatin dosing using the Calvert formula is based on renal function determined by measured or estimated glomerular filtration rate (GFR). During the last 2 years, the National Institute for Standards and Technology (NIST) has standardized the measurement of serum creatinine using Isotope Dilution Mass Spectrometry (IDMS). By December 31, 2010, all clinical chemistry laboratories in the United States of America (USA) will have switched to the IDMS measurement, and reagents for older methodologies will no longer be available. Older methods were not standardized and led to widely variable creatinine measurements. ***Due to this variability, the use of a single correction factor to convert IDMS creatinine values to "non-IDMS" creatinine values will not work across all labs and institutions.***

***The IDMS method, in general, generates a lower creatinine value than older methods in patients with normal renal function. In addition, the IDMS method is more likely to generate creatinine levels that are below the lower limit of normal. Serum creatinine is used to estimate glomerular filtration rate (GFR). Measurement of serum creatinine by the IDMS method could result in an overestimation of GFR in some patients with normal renal function. If the total carboplatin dose is calculated based on an estimated GFR using an IDMS-measured serum creatinine and the Calvert formula, carboplatin dosing could be higher than desired and could result in increased toxicity.***

In view of the potential increase of known adverse events, NCI/CTEP is recommending that all treating physicians using carboplatin in their protocols do the following:

- 1) Verify that the treatment plan does **NOT** contain a correction factor used to calculate carboplatin doses based on IDMS serum creatinine.

**NOTE: Sites required to submit an amendment were instructed as follows:** Distribute this letter to all participating investigators and IRBs. The principal investigator or lead organization (e.g., coordinating center or group operations office) also needs to forward a copy of the e-mail or other rapid traceable communication (e.g., fax with return requested) to [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) within 7 calendar days of the date of this letter. Failure to comply within the 7-day timeframe may result in the temporary suspension of the principal investigator and enrollment of patients to the study.

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- 2) Verify the treatment plan to assure that your protocol using carboplatin has a maximum dose for carboplatin based on the target AUC **OR** mandate measured GFR for patients with serum creatinine below the lower limit of normal.  
**NOTE: Sites required to submit an amendment were instructed as follows:** Remove any language in protocols indicating that conversion of IDMS creatinine levels to “non-IDMS” values should be performed. No standard correction factor has been adequately validated. Amend the protocol to assure that a correction factor is NOT used to calculate carboplatin doses based on modifications of IDMS serum creatinine measurement.
  
- 3) The initial dose of carboplatin may be calculated using an estimated GFR or a measured GFR. The current label for carboplatin provides safe dosing instructions that are based on measured GFR. Provided that direct GFR measurements are made to assess renal function, carboplatin can be safely dosed according to the instructions described in the label.
  
- 4) *If the initial carboplatin dose is based on an estimated GFR, amend the protocol to assure that your protocol uses a dose not to exceed the maximum dose for carboplatin based on the target AUC. Once the initial dose of carboplatin is calculated it does not need to be recalculated for subsequent cycles unless the patient is experiencing toxicity and requires dose modification to a lower dose of carboplatin.*
  
- 5) Verify that if your study uses the Calvert formula for calculation of carboplatin dose that the patient treatment and drug administration section of the protocol using carboplatin applies the following formula to determine the maximum administered carboplatin dose. GFR may be measured or calculated using a standard formula.

**Calvert Formula**

$$\text{Total Dose (mg)} = (\text{target AUC}) \times (\text{GFR} + 25)$$

**NOTE: the GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.**

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC(mg}\cdot\text{min/mL)} \cdot 150 \text{ mL/min.}$$

\*The maximum carboplatin dose should not exceed target AUC(mg•min/mL)•150 mL/min, but it may be less. Many trials have a target carboplatin AUC of 6 which would result in a maximum dose of 900 mg. Highly specific settings like bone marrow transplant or pediatric studies may target a higher AUC.

<i>Maximum AUC-based Carboplatin Dose</i>	
<i>AUC</i>	<i>Maximum Carboplatin Dose</i>
6	900 mg
5	750 mg
4	600 mg

- 6) For *U.S. sites that have not yet implemented IDMS serum creatinine measurement, or international participants that may or may not be using IDMS serum creatinine measurements*, please use the same dosing instructions outlined above in Point number 5.
  
- 7) *For specific patients, e.g. those with low muscle mass, direct measurement of GFR may be preferable to an estimation of GFR. In patients with an abnormally low serum creatinine, estimate GFR using a*

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*minimum creatinine level of 0.6 mg/dL, or cap the estimated GFR at 125 mL/minute as described in Point number 5.*

- 8) When concerned about safety in a specific patient, **measure GFR.**  
**NOTE: Sites required to submit an amendment were instructed as follows:** Accrual to this trial may continue, but the measures to assure patient safety must be put in place immediately. The safety measures should be implemented while IRB and NCI/CTEP approval is obtained.

Patients currently on study should continue on study and may be informed of the rationale for the possible change in their dosing of carboplatin.

Patients currently on study who are not experiencing toxicity should continue on their current dose of carboplatin.

- 9) Patients currently on treatment should continue on treatment and may be informed of the rationale for the possible change in their dosing of carboplatin. *Patients currently on treatment who are not experiencing toxicity should continue on their current dose of carboplatin.*
- 10) Dose modifications should occur as outlined in the protocol document. Each patient should be thoroughly evaluated, closely monitored and supported as clinically appropriate.
- 11) Adverse event reporting should continue as outlined in the protocol document.

For further information, please contact S. Percy Ivy, MD (301-496-1196; ivyp@ctep.nci.nih.gov).