

December 21, 2010

**RE: ACTION ALERT—Platinol Discontinuation**

Dear Colleague:

Bristol-Myers Squibb Co. (BMS) has announced that on December 31, 2010, they will no longer provide powdered cisplatin for use in patients undergoing chemoembolization. This decision has been made based on:

1. The lack of FDA approval for this use
2. BMS believes that equivalent agents exist for this use, such as carboplatin
3. Powdered cisplatin is not used in a number of chemoembolization regimens
4. BMS does not think that this decision will impact patient care
5. BMS is pursuing development of new therapeutic agents

This decision clearly does not reflect the thoughts of the majority of interventional radiologists actively involved in interventional oncology. **SIR members are strongly encouraged to contact BMS at (800) 321-1335 between 8 a.m.–5 p.m. EST from Monday–Friday to share their concerns about this decision.** SIR has put together some talking points and a partial reference list, which is provided below.

**Talking Points**

1. SIR supports Bristol-Myers Squibb's development of novel therapies for cancer treatment.
2. The only cure for primary or metastatic liver cancer remains transplantation or resection, depending on the type of malignancy. Even with development of new effective systemic or targeted therapies, it is likely that patients will progress on treatment with subsequent referral for chemoembolization.
3. Combining chemoembolization with systemic or targeted therapies is currently an area of clinical interest with multiple trials evaluating chemoembolization plus either bevacizumab, sunitinib or sorafenib.
4. Powdered cisplatin is one of the common agents used in chemoembolization regimens in the United States. One key advantage of using the powdered form is that a substantially smaller volume of solution (~10cc) can be used to reconstitute 100 mgs of Cisplatinum (10mg/ml) compared to Cisplatinum solution, which has a final concentration of 1mg/ml. This smaller reconstituted volume is a critical feature of chemoembolization regimens as the chemotherapeutic agent(s) is typically mixed 1:1 with Lipiodol/Ethiodol to create an emulsion just prior to intra-arterial administration. Use of the Cisplatinum solution would automatically increase the final volume of the chemoembolization regimen 10 fold and this would not be a feasible alternative. Carboplatinum may potentially be an alternative, but it is not clear at this point if the equivalent dose can be reconstituted in similar small (10–15 cc) volumes of solution.
5. It is estimated that greater than 33,000 chemoembolizations will be performed in the United States in 2010, up from 26,000 in 2008. Based on current trends, estimates for the number of chemoembolization procedures performed in the United States in 2014 are as high as 50,000.

6. The most widely utilized and best defined chemoembolization regimen in the United States includes powdered cisplatin. The U.S.-based chemobolization publications with the largest sample sizes have used powdered cisplatin (references below). Additionally, powdered cisplatin was also used as the solitary agent in one of the prospective randomized controlled trials that demonstrated benefit of chemoembolization for hepatocellular carcinoma.
7. SIR recognizes that powdered cisplatin is not FDA approved for chemoembolization. However, no drugs are currently approved for this use. Based on the scientific evidence presented below, along with procedural reimbursement by third-party payers, including Medicare, use of powdered cisplatin for chemoembolization represents reasonable and necessary medical care and is justified for off-label use.
8. Chemoembolization with powdered cisplatin as part of the treatment regimen is cost-effective when compared to other options, including drug-eluting microspheres and yttrium-90 radioembolization.
9. Discontinuing the manufacture of powdered cisplatin without a reasonable alternative will present a hazard to patient care. Patients will fail systemic therapies with liver dominant disease and lose the primary alternative that has been used in the United States for more than 30 years. If alternatives to powdered cisplatin, such as carboplatin, are identified with guidelines regarding maximal concentration, substitution may then be considered reasonable. Delaying removal of powdered cisplatin from the market is the appropriate choice until a suitable alternative is defined.

### **Partial Reference List**

#### **HCC**

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3. Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008;248:617-625.
4. Lewandowski RJ, Mulcahy MF, Kulik LM, et al. Chemoembolization for hepatocellular carcinoma: comprehensive imaging and survival analysis in a 172-patient cohort. *Radiology* 2010;255:955-965.
5. Wible BC, Rilling WS, Drescher P, et al. Longitudinal quality of life assessment of patients with hepatocellular carcinoma after primary transarterial chemoembolization. *JVIR* 2010;21:1024-1030.
6. Solomon B, Soulen MC, Baum RA, Haskal ZJ, Shlansky-Goldberg RD, Cope C. Chemoembolization of hepatocellular carcinoma with cisplatin, doxorubicin, mitomycin-c, ethiodol, and polyvinyl alcohol: prospective evaluation of response and survival in a US population. *JVIR* 1999;10:793-798.
7. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-1171.

### Neuroendocrine

1. Ruutainen AT, Soulen MC, Tuite CM, et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. *JVIR* 2007;18:847-855.
2. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. *AJR* 2007;188:1201-1207
3. Gupta S, Johnson MM, Murthy R, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. *Cancer* 2005;104:1590-1602.

### Cholangiocarcinoma

1. Kiefer MV, Albert M, McNally M, et al. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatin, doxorubicin, mitomycin c, ethiodol and polyvinyl alcohol. *Cancer*; epub ahead of print

### Uveal Melanoma

1. Gupta S, Bedikian AY, Ahrar J, et al. Hepatic Artery Chemoembolization in Patients With Ocular Melanoma Metastatic to the Liver: Response, Survival, and Prognostic Factors *Am J Clin Oncol* 2010;33:474-480.
2. Sharma KV, Gould JE, Harbour JW, et al. Hepatic arterial chemoembolization for management of metastatic melanoma. *AJR Am J Roentgenol.* 2008;190:99–104

### Colorectal

1. Albert M, Kiefer MV, Sun W, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. *Cancer* 2010; Epub ahead of print
2. Tellez C, Benson AB, Lyster MT, et al. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. *Cancer* 1998;82:1250-1259.

We will keep you informed as we receive any additional information.

Sincerely,



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President, SIR



Michael Wallace, MD, FSIR  
Chair, SIR Interventional  
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Daniel B. Brown, MD  
Chair, Post-Graduate

cc: Tricia McClenny, SIR Interim Executive Director  
Bristol-Myers Squibb Customer Relations