CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 19880/S009

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Medical Review(s)	X			
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EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)			X	
Microbiology Review(s)			X	
Clinical Pharmacology Biopharmaceutics Review(s)			X	
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Administrative Document(s)	X			
Correspondence			X	

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 19880/S009

Trade Name: Paraplatin

Generic Name:(carboplatin for injection)

Sponsor:Bristol-Myers Squibb

Approval Date:January 6, 1998

Indication: Provides for Changes Being Effected to include addition of the statement "Safety and effectiveness in pediatric patients have not been established."

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19880/S009

APPROVAL LETTER

DIF

NDA 19-880/S009 JAN - 6 1998

Bristol-Myers Squibb
P.O. Box 4000
Princeton, NJ 08543-4000

Attention: Joseph A. Linkewich, Pharm.D.
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Dear Mr. Linkewich:

Please refer to your supplemental new drug application (S009) dated December 13, 1996, received December 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paraplatin (carboplatin for injection).

The User Fee goal date for this application is June 17, 1997.

The supplemental application provides for Changes Being Effected to include addition of the statement "Safety and effectiveness in pediatric patients have not been established."

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 13, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

We also note that submitted June 8, 1990, has been superseded and will be retained in your files.

If you have any questions, please contact Dianne Spillman, Project Manager, at (301) 594-5746.

Sincerely yours,

/S/ 1/5/98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 19-880
HFD-150/Div. files
HFD-150/CSO/D.Spillman
HFD-150/DGriebel
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)
HFI-20/Press Office (with labeling)

Final typed by: dwpease/December 31, 1997/

APPROVAL (AP) S009 Dwpease 12-31-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19880/S009

FINAL PRINTED LABELING

1-6-98

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

BRISTOL LABORATORIES®

ONCOLOGY PRODUCTS

Paraplatin®

(carboplatin for injection)

WARNING

PARAPLATIN® (carboplatin for injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.

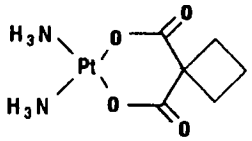
Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to PARAPLATIN have been reported and may occur within minutes of PARAPLATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION

PARAPLATIN® (carboplatin for injection) is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-, (SP-4-2), and has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

CLINICAL PHARMACOLOGY

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m² of PARAPLATIN. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, 16 L and 3.5 hours, respectively. The Cmax values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 - 500 mg/m²).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. PARAPLATIN dosages should therefore be reduced in these patients (see "DOSAGE AND ADMINISTRATION").

CLINICAL STUDIES

Use with cyclophosphamide for initial treatment of ovarian cancer:

In two prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada, Clinical Trials Group (NCIC) and the Southwest Oncology Group (SWOG), 789 chemotherapy naive patients with advanced ovarian cancer were treated with PARAPLATIN or cisplatin, both in combination with cyclophosphamide every 28 days for six courses before surgical reevaluation. The following results were obtained from both studies:

COMPARATIVE EFFICACY

Overview of Pivotal Trials

	NCIC	SWOG
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/M²	100 mg/M²
Dose of carboplatin	300 mg/M²	300 mg/M²
Dose of Cytoxan	600 mg/M²	600 mg/M²
Residual tumor <2 cm (number of patients)	39% (174/447)	14% (49/342)

Clinical Response in Measurable Disease Patients

	NCIC	SWOG
Carboplatin (number of patients)	60% (48/80)	56% (48/83)
Cisplatin (number of patients)	58% (49/85)	43% (33/76)
95% C.I. of difference (Carboplatin – Cisplatin)	(-13.9%, 18.6%)	(-2.3%, 31.1%)

Pathologic Complete Response*

	NCIC	SWOG
Carboplatin (number of patients)	11% (24/224)	10% (17/171)
Cisplatin (number of patients)	15% (33/223)	10% (17/171)
95% C.I. of difference (Carboplatin – Cisplatin)	(-10.7%, 2.5%)	(-6.9%, 6.9%)

*114 Paraplatin and 109 Cisplatin patients did not undergo second look surgery in NCIC study
90 Paraplatin and 106 Cisplatin patients did not undergo second look surgery in SWOG study

Progression-Free Survival (PFS)

	NCIC	SWOG
Median		
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
2-year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C.I. of difference (Carboplatin-Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)

3-year PFS*

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY

		Paraplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
Bone Marrow				
Thrombocytopenia,	< 100,000/mm³	70	29	<0.001
	< 50,000 /mm³	41	6	<0.001
Neutropenia,	< 2,000 cells/mm³	97	96	n.s.
	< 1,000 cells/mm³	81	79	n.s.
Leukopenia,	< 4,000 cells/mm³	98	97	n.s.
	< 2,000 cells/mm³	66	52	0.001
Anemia,	< 11 g/dL	91	91	n.s.
	< 8 g/dL	18	12	n.s.
Infections		14	12	n.s.
Bleeding		10	4	n.s.
Transfusions		42	31	0.018
Gastrointestinal				
Nausea and vomiting		93	98	0.010
Vomiting		84	97	<0.001
Other GI side effects		50	62	0.013
Neurologic				
Peripheral neuropathies		16	42	<0.001
Ototoxicity		13	33	<0.001
Other sensory side effects		6	10	n.s.
Central neurotoxicity		28	40	0.009
Renal				
Serum creatinine elevations		5	13	0.006
Blood urea elevations		17	31	<0.001
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		17	13	n.s.
Alkaline phosphatase elevations		-	-	-
Electrolytes loss				
Sodium		10	20	0.005
Potassium		16	22	n.s.
Calcium		16	19	n.s.
Magnesium		63	88	<0.001
Other side effects				
Pain		36	37	n.s.
Asthenia		40	33	n.s.
Cardiovascular		15	19	n.s.
Respiratory		8	9	n.s.
Allergic		12	9	n.s.
Genitourinary		10	10	n.s.
Alopecia +		50	62	0.017
Mucositis		10	9	n.s.

* Values are in percent of evaluable patients
** n.s. = not significant, p>0.05
+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY

		Paraplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
Bone Marrow				
Thrombocytopenia,	< 100,000/mm³	59	35	<0.001
	< 50,000/mm³	22	11	0.006
Neutropenia,	< 2,000 cells/mm³	95	97	n.s.
	< 1,000 cells/mm³	84	78	n.s.
Leukopenia,	< 4,000 cells/mm³	97	97	n.s.
	< 2,000 cells/mm³	76	67	n.s.
Anemia,	< 11 g/dL	88	87	n.s.
	< 8 g/dL	8	24	<0.001
Infections		18	21	n.s.
Bleeding		6	4	n.s.
Transfusions		25	33	n.s.
Gastrointestinal				
Nausea and vomiting		94	96	n.s.
Vomiting		82	91	0.007
Other GI side effects		40	48	n.s.
Neurologic				
Peripheral neuropathies		13	28	0.001
Ototoxicity		12	30	<0.001
Other sensory side effects		4	6	n.s.
Central neurotoxicity		23	29	n.s.
Renal				
Serum creatinine elevations		7	38	<0.001
Blood urea elevations		—	—	-
Hepatic				
Bilirubin elevations		5	3	n.s.
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Alkaline phosphatase elevations		29	20	n.s.
Electrolytes loss				
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	<0.001
Other side effects				
Pain		54	52	n.s.
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Cardiovascular		23	30	n.s.
Respiratory		12	11	n.s.
Allergic		10	11	n.s.
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Alopecia +		43	57	0.009
Mucositis		6	11	n.s.

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Use as a single agent for secondary treatment of advanced ovarian cancer:

In two prospective, randomized controlled studies in patients with advanced ovarian cancer previously treated with chemotherapy, PARAPLATIN achieved six clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71 + weeks.

INDICATIONS

Initial treatment of advanced ovarian carcinoma:

PARAPLATIN is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. One established combination regimen consists of PARAPLATIN and cyclophosphamide (Cytoxan®). Two randomized controlled studies conducted by the NCIC and SWOG with PARAPLATIN vs. cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups (see "CLINICAL STUDIES" section).

There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and longterm survival (≥ 3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

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PARAPLATIN is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

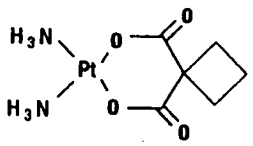
PARAPLATIN is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or mannitol.

PARAPLATIN (carboplatin for injection) should not be employed in patients with severe bone marrow depression or significant bleeding.

WARNINGS

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and

(CI-973), and has the following structural formula:



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Progression-Free Survival (PFS)

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2-year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C.I. of difference (Carboplatin-Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)
3-year PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
95% C.I. of difference (Carboplatin-Cisplatin)	(-11.5, 4.5)	(-14.1, 0.3)
Hazard Ratio**	1.10	1.02
95% C.I. (Carboplatin – Cisplatin)	(0.89, 1.35)	(0.81, 1.29)

* Kaplan-Meier Estimates
Unrelated deaths occurring in the absence of progression were counted as events (progression) in this analysis.
**Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.

	Survival	
	NCIC	SWOG
Median		
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	79 weeks
2-year Survival*		
Carboplatin	51.9%	40.2%
Cisplatin	48.4%	39.0%
95% C.I. of difference (Carboplatin-Cisplatin)	(-6.2, 13.2)	(-9.8, 12.2)
3-year Survival*		
Carboplatin	34.6%	18.3%
Cisplatin	33.1%	24.9%
95% C.I. of difference (Carboplatin-Cisplatin)	(-7.7, 10.7)	(-15.9, 2.7)
Hazard Ratio**	0.98	1.01
95% C.I. (Carboplatin-Cisplatin)	(0.78, 1.23)	(0.78, 1.30)

* Kaplan-Meier Estimates
** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.

COMPARATIVE TOXICITY

The pattern of toxicity exerted by the PARAPLATIN-containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the two studies may be explained by different cisplatin dosages and by different supportive care.

The PARAPLATIN-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The cisplatin-containing regimen produced significantly more anemia in one study. However, no significant differences occurred in incidences of infections and hemorrhagic episodes.

Non-hematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia, and alopecia) were significantly more frequent in the cisplatin-containing arms.

Alopecia +	50	62	0.017
Mucositis	10	9	n.s.

* Values are in percent of evaluable patients
** n.s. = not significant, p>0.05
+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY

		Paraplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
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Thrombocytopenia,	< 100,000/mm³	59	35	<0.001
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Anemia,	< 11 g/dL	88	87	n.s.
	< 8 g/dL	8	24	<0.001
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Transfusions		25	33	n.s.
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Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		23	16	n.s.
Alkaline phosphatase elevations		29	20	n.s.
Electrolytes loss				
Sodium		–	–	–
Potassium		–	–	–
Calcium		–	–	–
Magnesium		58	77	<0.001
Other side effects				
Pain		54	52	n.s.
Asthenia		43	48	n.s.
Cardiovascular		23	30	n.s.
Respiratory		12	11	n.s.
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Use as a single agent for secondary treatment of advanced ovarian cancer:

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INDICATIONS

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There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and longterm survival (≥ 3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

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Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

PARAPLATIN is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or mannitol.

PARAPLATIN (carboplatin for injection) should not be employed in patients with severe bone marrow depression or significant bleeding.

WARNINGS

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during PARAPLATIN treatment and, when appropriate, until recovery is achieved. Median nadir occurs at day 21 in patients receiving single-agent PARAPLATIN. In general, single intermittent courses of PARAPLATIN should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.

Since anemia is cumulative, transfusions may be needed during treatment with PARAPLATIN, particularly in patients receiving prolonged therapy.

Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial PARAPLATIN dosages in these patients should be appropriately reduced (see **"DOSAGE AND ADMINISTRATION"**) and blood counts should be carefully monitored between courses. The use of PARAPLATIN in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

PARAPLATIN has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs.

PARAPLATIN can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of PARAPLATIN, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five consecutive daily bolus doses has resulted in reduced emesis.

Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving PARAPLATIN as secondary treatment.

Loss of vision, which can be complete for light and colors, has been reported after the use of PARAPLATIN with doses higher than those recommended in the package insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

As in the case of other platinum coordination compounds, allergic reactions to PARAPLATIN (carboplatin for injection) have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy.

High dosages of PARAPLATIN (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.

PARAPLATIN may cause fetal harm when administered to a pregnant woman. PARAPLATIN has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General: Needles or intravenous administration sets containing aluminum parts that may come in contact with PARAPLATIN should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Drug Interactions: The renal effects of nephrotoxic compounds may be potentiated by PARAPLATIN.

Carcinogenesis, mutagenesis, impairment of fertility: The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles

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have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both in vitro and in vivo. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis.

Pregnancy: Pregnancy "category D": (see "WARNINGS").

Nursing mothers: It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to PARAPLATIN treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with PARAPLATIN.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

For a comparison of toxicities when carboplatin or cisplatin was given in combination with cyclophosphamide, see the COMPARATIVE TOXICITY subsection of the CLINICAL STUDIES section.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER

		First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
Bone Marrow			
Thrombocytopenia,	< 100,000/mm³	66	62
	< 50,000/mm³	33	35
Neutropenia,	< 2,000 cells/mm³	96	67
	< 1,000 cells/mm³	82	21
Leukopenia,	< 4,000 cells/mm³	97	85
	< 2,000 cells/mm³	71	26
Anemia,	< 11 g/dl.	90	90
	< 8 g/dl.	14	21
Infections		16	5
Bleeding		8	5
Transfusions		35	44
Gastrointestinal			
Nausea and vomiting		93	92
Vomiting		83	81
Other GI side effects		46	21
Neurologic			
Peripheral neuropathies		15	6
Ototoxicity		12	1
Other sensory side effects		5	1
Central neurotoxicity		26	5
Renal			
Serum creatinine elevations		6	10
Blood urea elevations		17	22
Hepatic			
Billirubin elevations		5	5
SGOT elevations		20	19
Alkaline phosphatase elevations		29	37
Electrolytes loss			
Sodium		10	47
Potassium		16	28
Calcium		16	31
Magnesium		61	43
Other side effects			
Pain		44	23
Asthenia		41	11
Cardiovascular		19	6
Respiratory		10	6
Allergic		11	2
Genitourinary		10	2
Alopecia		49	2
Mucositis		8	1

***Use with cyclophosphamide for initial treatment of ovarian cancer:** Data are based on the experience of 393 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with PARAPLATIN and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC (see "CLINICAL STUDIES" section).

Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.

****Single agent use for the secondary treatment of ovarian cancer:** Data are based on the experience of 553 patients with previously treated ovarian carcinoma (regardless of baseline status) who received single-agent PARAPLATIN.

In the narrative section that follows, the incidences of adverse events are based on data from 1,893 patients with various types of tumors who received PARAPLATIN as single-agent therapy.

Hematologic toxicity: Bone marrow suppression is the dose-limiting toxicity of PARAPLATIN. Thrombocytopenia with platelet counts below 50,000/mm³ occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1,000/mm³ occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2,000/mm³ occurs in 15% of the patients (26% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm³; 74% have neutrophil counts above 2,000/mm³; 67% have leukocyte counts above 4,000/mm³.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with PARAPLATIN, with drug related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dl. has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to PARAPLATIN. Transfusions have been administered to 26% of the patients treated with PARAPLATIN (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when PARAPLATIN is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal toxicity: Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of PARAPLATIN, either by continuous 24-hour infusion or by daily pulse doses given for five consecutive days, was associated with less severe vomiting than the single dose intermittent schedule. Emesis was increased when PARAPLATIN was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 8%; and constipation, also in 6%.

Neurologic toxicity: Peripheral neuropathies have been observed in 4% of the patients receiving PARAPLATIN (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neuretadicity, there was no worsening of symptoms during therapy with PARAPLATIN. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

Although the overall incidence of peripheral neurologic side effects induced by PARAPLATIN is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

Nephrotoxicity: Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving PARAPLATIN, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of the patients who had a baseline value of 60 mL/min or more demonstrated a reduction below this value during PARAPLATIN therapy.

Hepatic toxicity: The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a

below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Platelets	Neutrophils	Adjusted Dose * (From Prior Course)
>100,000	>2,000	125%
50 - 100,000	500 - 2,000	No Adjustment
<50,000	<500	75%

*Percentages apply to PARAPLATIN (carboplatin for injection) as a single agent or to both PARAPLATIN and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50 to 60%) for severe myelosuppression. Escalations above 125% were not recommended for these studies.

PARAPLATIN is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

Patients with impaired kidney function: Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single agent PARAPLATIN therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

Baseline Creatinine Clearance	Recommended Dose on Day 1
41 - 59 mL/min	250 mg/m²
16 - 40 mL/min	200 mg/m²

The data available for patients with severely impaired kidney function (creatinine clearance below 15 mL/min) are too limited to permit a recommendation for treatment.[1,2]

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

Formula Dosing: Another approach for determining the initial dose of PARAPLATIN is the use of mathematical formulae, which are based on a patient's pre-existing renal function[3-5] or renal function and desired platelet nadir.[6] Renal excretion is the major route of elimination for carboplatin. (see CLINICAL PHARMACOLOGY). The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).

A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and PARAPLATIN target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert[7,8]. In these studies, GFR was measured by ^{51}Cr-EDTA clearance[9].

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg)=(target AUC) x (GFR + 25)

Note: With the Calvert formula, the total dose of PARAPLATIN is calculated in mg, not mg/m².

The target AUC of 4-6 mg/mL•min using single agent PARAPLATIN appears to provide the most appropriate dose range in previously treated patients[8]. This study also showed a trend between the AUC of single agent PARAPLATIN administered to previously treated patients and the likelihood of developing toxicity[8].

	% Actual Toxicity in Previously Treated Patients	
AUC (mg/mL•min)	Gr 3 or Gr 4 Thrombocytopenia	Gr 3 or Gr 4 Leukopenia
4 to 5	16%	13%
6 to 7	33%	34%

PREPARATION OF INTRAVENOUS SOLUTIONS

Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D$_5$W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL.

PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D$_5$W) or 0.9% Sodium Chloride Injection, USP.

STABILITY

Unopened vials of PARAPLATIN for injection are stable for the life indicated on the package when stored at controlled room temperature 15°-30° C (59°-86° F), and protected from light.

When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25° C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN solutions be discarded 8 hours after dilution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

NDC 0015-3213-30	50 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Yellow flip-off seals)
NDC 0015-3214-30	150 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Violet flip-off seals)
NDC 0015-3215-30	450 mg vials, individually cartoned, shelf packs of 6 cartons, 10 shelf packs per case. (Blue flip-off seals)

STORAGE

Store the unopened vials at controlled room temperature 15°-30° C (59°-86° F). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published[10-14]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES:

1. Egorin, MJ, et al: Pharmacokinetics and dosage reduction of cis-diammine (1,1-cyclobutanedicarboxylate) platinum in patients with impaired renal function. Cancer Res 1984; 44:5432-5438.
2. Carboplatin, Etoposide, and Bleomycin for Treatment of Stage IIC Seminoma Complicated by Acute Renal Failure. Cancer Treatment Reports, Vol. 71, No. 11, pp. 1123-1124, November 1987.
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7. Daugaard G, et al: Effects of cisplatin on different measures of glomerular function in the human kidney with special emphasis on high-dose. Cancer Chemother Pharmacol. 1988; 21:163-167.
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10. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
11. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.
12. Jones RB, et al: Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; (Sept/Oct) 258-263.
13. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.

Renal		
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Bilirubin elevations	5	5
SGOT elevations	20	19
Alkaline phosphatase elevations	29	37
Electrolytes loss		
Sodium	10	47
Potassium	16	28
Calcium	16	31
Magnesium	61	43
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Although the overall incidence of peripheral neurologic side effects induced by PARAPLATIN is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

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Electrolyte changes: The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with PARAPLATIN, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic reactions: Hypersensitivity to PARAPLATIN has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Other events: Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

OVERDOSAGE

There is no known antidote for PARAPLATIN overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

DOSAGE AND ADMINISTRATION

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of PARAPLATIN.

Single agent therapy:

PARAPLATIN (carboplatin for injection), as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m² IV on day 1 every 4 weeks (Alternatively see Formula Dosing). In general, however, single intermittent courses of PARAPLATIN should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

Combination therapy with cyclophosphamide:

In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of:

PARAPLATIN—300 mg/m² IV on day 1 every four weeks for six cycles (Alternatively see Formula Dosing).

Cyclophosphamide (Cytoxan®)—600 mg/m² IV on day 1 every four weeks for six cycles. For directions regarding the use and administration of cyclophosphamide (Cytoxan®) please refer to its package insert. (See "CLINICAL STUDIES" section).

Intermittent courses of PARAPLATIN in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

Dose Adjustment Recommendations:

Pretreatment platelet count and performance status are important prognostic factors for severi-

A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and PARAPLATIN target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert[2,3]. In these studies, GFR was measured by ^{51}Cr-EDTA clearance[4].

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg) = (target AUC) x (GFR + 25)

Note: With the Calvert formula, the total dose of PARAPLATIN is calculated in mg, not mg/m².

The target AUC of 4-6 mg/mL•min using single agent PARAPLATIN appears to provide the most appropriate dose range in previously treated patients[4]. This study also showed a trend between the AUC of single agent PARAPLATIN administered to previously treated patients and the likelihood of developing toxicity[4].

	% Actual Toxicity in Previously Treated Patients	
AUC (mg/mL•min)	Gr 3 or Gr 4 Thrombocytopenia	Gr 3 or Gr 4 Leukopenia
4 to 5	16%	13%
6 to 7	33%	34%

PREPARATION OF INTRAVENOUS SOLUTIONS

Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D_5W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL.

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

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NDC 0015-3213-30	50 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Yellow flip-off seals)
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14. Controlling occupational exposure to hazardous drugs. (OSHA WORK-PRACTICE GUIDELINES). Am J Health-Syst Pharm 1996; 53:1669-1685.

U.S. Patent Nos. 4,140,707
4,657,927

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543
U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19880/S009

MEDICAL REVIEW(S)

MAR 1 1996

MEDICAL OFFICER CONSULTATION ON DRUG MEDICATION ERRORS

NDA # 18-057 PLATINOL (Cisplatin for Injection)
NDA # 19-880 PARAPLATIN (Carboplatin for Injection)
NDA # 12-142 CYTOXAN for Injection

Sponsor: Bristol-Myers Squibb
Consultation Date: December 29, 1995
Date Received (CDER): January 22, 1996

Background:

The Division of Oncology Products received a consultation request from the Medication Errors Subcommittee on 1/22/96 regarding serious adverse events, including fatalities, occurring as a result of accidental overdose or erroneous administration of cisplatin, carboplatin, or cytoxan. The committee recommended revising the overseals for vials of carboplatin and cytoxan with a maximum dose warning, similar to the overseal proposed for cisplatin.

The annual safety report of NDA # 18-057 (received 2/3/95) cited 9 cases of cisplatin overdose. In a letter dated 8/9/95, DODP requested Bristol-Myers Squibb to warn pharmacists of the potential for overdosage by imprinting "Call Dr. if dose > 100 mg/m²/cycle" on the aluminum and flip-off seals of cisplatin vials. In addition, labeling changes that included statements regarding maximum dosage were also recommended. In the DOSAGE and ADMINISTRATION Section, for each of the indications for cisplatin, the recommended dosage would be clarified by adding "per cycle". A new statement in the BOXED WARNINGS Section would indicate that "doses > 100 mg/m²/cycle are being used only in rare cases and care should be taken to avoid inadvertent overdoses due to confusion with PARAPLATIN (Carboplatin for Injection) doses or daily x 5 schedules. It was also suggested that the name of either cisplatin or carboplatin be changed to the reduce the number of cisplatin overdoses.

On 12/21/96, the sponsor submitted a meeting request package to DODP. This document states that new aluminum caps and flip-off seals with the dose warning imprinted have been ordered, and that the proposed labeling changes are acceptable. The sponsor is also considering changing the proprietary name PLATINOL. A meeting with members of DODP will take place in the near future.

In related correspondence, it was learned that effective November 13, 1995, Bristol-Myers Squibb will market only its PLATINOL-AQ formulation in the US. Since this is a liquid formulation and PARAPLATIN is available only in lyophilized form, this action is expected to further distinguish the two drugs. This is a voluntary measure on the part of BMS. BMS will notify DODP prior to any resumption in the marketing of the lyophilized cisplatin formulation in the US.

Five adverse event case reports were reviewed by the Medication Errors Subcommittee prompting this consultation request. Briefly, these were:

Report E080322 (6/19/95): Cisplatin given in error, resulting in overdose

USP Practitioner's Reporting Network report of death resulting from the inadvertent administration of cisplatin. The patient should have received carboplatin. No demographic or clinical data were provided on the patient. Pharmacist was "very busy and did not have time to properly supervise technician - similarity in names".

Report E41439 (5/9/95): Cisplatin overdose

USP Practitioner's Reporting Network report of deaths in two male patients with melanoma who received "three times the recommended dose" of cisplatin in February 1991, while hospitalized at the New England Medical Center in Boston. "The nurses and pharmacist misunderstood the doctor's order" according to a Washington Post article dated 4/18/95. The patients, aged 52 and 44, initially experienced deafness, then kidney and liver failure. The former died within 2 weeks, the latter died more than 3 months later. The hospital has since banned handwritten orders for chemotherapy, adopting a printed form, and requires two senior physicians to verify every order for high-dose chemotherapy.

Report 118738 (6/13/95): Carboplatin overdose

MedWatch report of a patient given carboplatin 600 mg daily for 3 days. The patient should have received carboplatin for one dose and etoposide daily for 3 days. No demographic or clinical data were provided on the patient. The outcome of the event is unknown.

Report 118729 (4/11/95): Cytoxan overdose

MedWatch report of serious adverse events related to cytoxan overdose in a 52 year old woman with metastatic breast cancer. The patient was enrolled on DFCI Protocol 94-060. During her third cycle of therapy she received cytoxan 4 gm/m²/day for 4 days instead of 1 gm/m²/day (11/16 to 11/20/94). She experienced severe diarrhea, visual hallucinations, skin rash and fluid overload with weight gain, pleural effusions, and ascites. She required intubation, diuretic therapy, and bilateral chest tube drainage and pleurodesis with talc. On 1/6/95 she was discharged to a rehabilitation hospital. She was later readmitted with fever, hematemesis, diarrhea and polyserositis, and was found to have a large pericardial effusion with cardiac tamponade. She required a pericardial window, and subsequently repeat intubation and corticosteroids for treatment of pneumonia. MRI revealed pericardial metastases and increased liver metastases. A 15-day follow-up report (#118803, 4/25/95) indicated that the patient was expected to be discharged to her home with supportive care. In February 1995, it was discovered that the patient had received a very high dose of cytoxan prompting further investigation.

Report 118804 (4/25/95): Cytoxan overdose

A 15-day follow-up report of death related to cytoxan overdose in a 39 year old woman with

metastatic breast cancer. The patient was enrolled on DFCI Protocol 94-060. During her third cycle of therapy she received cytoxan 4 gm/m²/day for 4 days instead of 1 gm/m²/day (11/14 to 11/18/94). She experienced several expected adverse events including 1) mild fluid overload during the time of stem cell reinfusion, 2) pharyngitis, esophagitis, anal irritation requiring analgesics, 3) febrile neutropenia requiring treatment with broad spectrum antibiotics and amphotericin B, and 4) phosphate and potassium wasting as a result of antibiotic therapy. Engraftment was prompt, antibiotics were withdrawn, and she was expected to be discharged on 12/4/94. On that day she was discovered by her physicians on rounds to be cyanotic, without a pulse or BP. She could not be successfully resuscitated. An autopsy was performed but a cause of death was not determined. In particular, there was no evidence for a cardiomyopathy or cardiac failure. In February 1995, it was discovered that the patient had received a very high dose of cytoxan prompting further investigation.

Comments:

Please convey the following suggestions to Anna Marie Hommonay-Weikel, Chair, Medication Errors Subcommittee (HFD-617).

1. Cisplatin

At a DODP Staff Meeting held February 5, 1996, the 5 case reports of overdosage of cisplatin, carboplatin, and cytoxan cited in the consultation request dated 12/29/95 were presented. Actions taken or proposed by Bristol-Myers Squibb in the past few months with regard to cisplatin were reviewed, including:

a. new aluminum caps/seals imprinted with "Call Dr. if dose > 100 mg/m²/cycle" - soon to be implemented, if not already implemented

b. accompanying changes in labeling, including a new BOXED WARNING - accepted by sponsor and soon to be implemented

c. voluntary "restriction" in the marketing of cisplatin in the US to the liquid formulation only - effective 11/95

d. sponsor is considering changing the proprietary name PLATINOL.

Further details regarding these action items will be discussed at an upcoming meeting of Bristol-Myers Squibb with members of DODP.

The consensus of those attending the Staff Meeting was that sufficient time has not elapsed to determine whether the new imprinted caps/seals and accompanying labeling changes will alter clinical practice. It is anticipated that these efforts, in combination with use of different formulations for cisplatin and carboplatin, and a possible name change for PLATINOL could help

distinguish the two agents.

Close monitoring of serious adverse events due to cisplatin overdoses has been initiated through the efforts of David Banks, Division of Pharmacovigilance and Epidemiology, Reports Evaluation Branch (HFD-735). He has identified 44 reports to the Spontaneous Reporting System since 1983 implicating cisplatin as the suspect drug in serious adverse events related to overdose or medication error. These reports include 21 fatalities. Copies of the original reports will be retrieved for review by DODP. An ongoing review of such cases is planned on an annual basis.

2. Carboplatin

With regard to the Medication Errors Subcommittee's suggestion to place a dose warning on the caps/seals of carboplatin vials, the following concerns were raised by the medical officers and chemists in attendance at the February 5th Staff Meeting:

a. Unlike cisplatin, carboplatin is used off-label at high doses in the transplant setting; the current label recommends conventional doses of carboplatin. In addition, many oncologists prefer to use AUC for calculating doses of carboplatin rather than mg/m^2. Thus, it is problematic to recommend a maximum dose of carboplatin that should appear on a warning seal or in product labeling.

b. New imprinted caps/seals on carboplatin vials could make them **more** similar in appearance to cisplatin vials, not less similar.

c. If cisplatin is ordered and carboplatin administered instead, the patient would be underdosed with carboplatin, not overdosed.

There was consensus that carboplatin overdoses due to medication errors should be monitored closely. Since 1991, there have been 8 serious adverse events, including 3 fatalities, reported to SRS implicating carboplatin as the suspect drug in instances of overdose or medication error. The frequency of carboplatin overdoses will be monitored annually in light of the new cisplatin vials and other measures to be implemented by BMS as noted above. At this time, DODP does not plan to suggest the adoption of new carboplatin caps/seals.

3. Cytoxan

With regard to the Medication Errors Subcommittee's suggestion to place a dose warning on the caps/seals of cytoxan vials, the following concerns were raised by the medical officers and chemists in attendance at the February 5th Staff Meeting:

a. Unlike cisplatin, cytoxan is used off-label at high doses in the transplant setting; the current label recommends conventional doses of cytoxan. Again, it is problematic to recommend a maximum dose of cytoxan that should appear on a warning seal or in

product labeling.

b. Labeling changes prompted by the overdoses described in case reports 118729 and 118804 were recommended at a special in-house meeting DODP held with Mr. Jerry Phillips (HFD-613) on April 20, 1995. A labeling supplement to the cytoxan NDA is expected in the near future.

Again, there was consensus that cytoxan overdoses due to medication errors should be monitored closely. Since 1984, there have been 20 serious adverse events, including 15 fatalities, reported to SRS implicating cytoxan as the suspect drug in instances of overdose or medication error. Apparently, many of the fatalities occurred in South Africa; when only domestic reports are included, there were only 10 serious events and 5 fatalities. Copies of the original reports will be reviewed by DODP and the frequency of cytoxan overdoses will be monitored annually in light of the new labeling changes to be implemented by BMS. At this time, DODP does not plan to suggest the adoption of new cytoxan caps/seals.

/S/ 2/26/96

Julie Beitz, MD Date

/S/ 3/1/96

Robert Justice, MD Date

cc:
NDA # 18-057 PLATINOL (Cisplatin for Injection)
HFD-150/ Division File
HFD-150/ A. Martin
HFD-150/ P. Dietze

NDA # 19-880 PARAPLATIN (Carboplatin for Injection)
HFD-150/ Division File
HFD-150/ G. Williams
HFD-150/ D. Klein

NDA # 12-142 CYTOXAN for Injection
HFD-150/ Division File
HFD-150/ G. Schechter
HFD-150/ D. Klein

HFD-150/ J. Beitz
HFD-150/ D. Spillman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19880/S009

ADMINISTRATIVE DOCUMENTS

DIV

DEC 31 1997

CSO REVIEW OF LABELING

NDA: 19-880/009

TRADE NAME: PARAPLATIN (carboplatin for injection)

SPONSOR: Bristol-Myers Squibb
P.O.Box 4000
Princeton, NJ 08543-4000

SUBMISSION DATE: December 17, 1996

REVIEW DATE: December 16, 1997

I have reviewed special supplement to the package insert dated on December 13, 1996 and have found some differences between it and the latest approved labeling submitted may 30, 1995 and accepted September 12 1995 (S008).

The changes in the labeling are:

I find the revisions are appropriate and recommend that the changes to the package insert be accepted and the supplement approved. It should further be noted that S005 submitted June 8, 1990 has been superseded by approved supplement S008.

Guli Achamyeleh
Pharmacy Intern

cc: ORIG. NDA 19-880/009
HFD-150/Div. Files
HFD-150/CSO/Dspillman
HFD-150/PDietze
HFD-150/WSchmidt
HFD-150/DGriebel

12-31-97