**DESCRIPTION:** Carboxplatin Injection is supplied as a sterile, pyrogen-free solution available in 10 mg/mL multiple-dose vials containing 50 mg, 150 mg, 450 mg or 600 mg of carboxplatin for administration intravenously. Each mL contains: carboxplatin 10 mg, and water for injection to volume.

Carboxplatin is a platinum coordination compound. The chemical name for carboxplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-(SP-4-2), and has the following structural formula:

\[
\begin{align*}
\text{H}_2\text{N}
\end{align*}
\begin{align*}
\text{H}
\end{align*}
\begin{align*}
\text{H}
\end{align*}
\begin{align*}
\text{N}
\end{align*}
\begin{align*}
\text{Pt}
\end{align*}
\begin{align*}
\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{Pt}
\end{align*}
\begin{align*}
\text{M.W 371.25}
\end{align*}

Carboxplatin is a crystalline powder. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in methanol, acetone, and dimethylacetamide.

**CLINICAL PHARMACOLOGY:**

Carboxplatin, like cisplatin, produces predominately 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 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after 60 mL/min, the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should therefore be reduced in these patients (see DOSAGE AND ADMINISTRATION).

The primary determinant of carboplatin clearance is glomerular filtration rate (GFR) and this parameter is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR (see DOSAGE AND ADMINISTRATION) to provide predictable carboplatin plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

**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 carboplatin 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

*Comparative Efficacy*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCIC</th>
<th>SWOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>59 weeks</td>
<td>49 weeks</td>
</tr>
<tr>
<td>2-year PFS*</td>
<td>Carboplatin 31%</td>
<td>21%</td>
</tr>
<tr>
<td>3-year PFS*</td>
<td>Carboplatin 19%</td>
<td>8%</td>
</tr>
<tr>
<td>Hazard Ratio**</td>
<td>(Carboplatin–Cisplatin) 1.10</td>
<td>(0.89, 1.35)</td>
</tr>
<tr>
<td>95% C.I.</td>
<td>1.02</td>
<td>(0.81, 1.29)</td>
</tr>
</tbody>
</table>

**Comparative Toxicity**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCIC</th>
<th>SWOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>110 weeks</td>
<td>86 weeks</td>
</tr>
<tr>
<td>2-year Survival*</td>
<td>Carboplatin 51.9%</td>
<td>40.2%</td>
</tr>
<tr>
<td>3-year Survival*</td>
<td>Carboplatin 34.6%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Hazard Ratio**</td>
<td>(Carboplatin–Cisplatin) 0.99</td>
<td>(0.79, 1.23)</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCIC</th>
<th>SWOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>110 weeks</td>
<td>86 weeks</td>
</tr>
<tr>
<td>2-year Survival*</td>
<td>Carboplatin 51.9%</td>
<td>40.2%</td>
</tr>
<tr>
<td>3-year Survival*</td>
<td>Carboplatin 34.6%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Hazard Ratio**</td>
<td>(Carboplatin–Cisplatin) 0.99</td>
<td>(0.79, 1.23)</td>
</tr>
</tbody>
</table>

**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 carboplatin-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 carboplatin-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The carboplatin-
ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY (Continued)

<table>
<thead>
<tr>
<th>Carbotplatin</th>
<th>Cisplatin</th>
<th>Arm Percent</th>
<th>Arm Percent</th>
<th>P-Values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>Thrombocytopenia</td>
<td>&lt;1,000,000/mm³</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>&lt;50,000/mm³</td>
<td>41</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;2,000 cells/mm³</td>
<td>97</td>
<td>96</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>&lt;1,000 cells/mm³</td>
<td>81</td>
<td>79</td>
<td>n.s.</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>&lt;4,000 cells/mm³</td>
<td>98</td>
<td>97</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>&lt;2,000 cells/mm³</td>
<td>66</td>
<td>52</td>
<td>0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;11 g/dL</td>
<td>91</td>
<td>91</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>&lt;8 g/dL</td>
<td>12</td>
<td>15</td>
<td>n.s.</td>
</tr>
<tr>
<td>Electrolytes loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>29</td>
<td>20</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>7</td>
<td>3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Blood urea elevations</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Bilirubin elevations</td>
<td>5</td>
<td>3</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT elevations</td>
<td>17</td>
<td>13</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Other sensory side</td>
<td>6</td>
<td>10</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>12</td>
<td>30</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Transfusions</td>
<td>42</td>
<td>31</td>
<td>0.018</td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY

<table>
<thead>
<tr>
<th>Carbotplatin</th>
<th>Cisplatin</th>
<th>Arm Percent</th>
<th>Arm Percent</th>
<th>P-Values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>Thrombocytopenia</td>
<td>&lt;1,000,000/mm³</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>&lt;50,000/mm³</td>
<td>41</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Other side effects | | | | |
| Pain | 44 | 52 | n.s. |
| Anemia | 43 | 46 | n.s. |
| Cardiovascular | 23 | 30 | n.s. |
| Nausea and vomiting | 10 | 11 | n.s. |
| Genitourinary | 13 | 11 | <0.001 |
| Alopecia | 43 | 57 | 0.009 |
| Alopecia | 6 | 11 | n.s. |

**Values are in percent of evaluable patients
*May not be affected by cyclophosphamide dosage delivered

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer

In two controlled and randomized controlled studi es in patients with advanced ovarian cancer previously treated with chemotherapy, Carbo platin injection 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

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

Secondary Treatment of Advanced Ovarian Carcinoma

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

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

CONTRAINdications:

Carboplatin Injection is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or manni tol.

Carboplatin Injection should not be employed in patients with known 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 carboplatin treatment and, when appropriate, until recovery is achieved. Media racid occurs at day 21 in patients receiving single-agent carboplatin. In general, single intermittent cycles of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.

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

Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression may also occur in patients with impaired kidney function. Initial carboplatin dosages in these patients should be appropriately reduced (see DOSAGE AND ADMINISTRATION). (DOSAGE AND ADMINISTRATION)

and blood counts should be carefully monitored between courses. The use of carbo platin in combination with other forms of marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audio logic toxicity, and toxicity must be monitored when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients with carboplatin-induced audiologic toxicity Administered at a higher than recommended doses with other chemotherapeutic agents. There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and longterm survival ( ³ 3 years) because of the small number of patients with these outcomes. A small number of patients with residual tumor < 2 cm after initial surgery also because of the small number of patients with severe bone marrow depression ³ 3 years.

Carboplatin has limited nephrotoxic potential, but when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients with carboplatin-induced audiologic toxicity. These patients were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor, and is also the dose-limiting toxicity.

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenic profiles 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 have mutagenic activity in vitro in the mouse and rat. These effects may have been reported. These may occur within 24 hours of treatment.

PREGNANCY

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

Carboplatin has limited nephrotoxic potential, but when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients with carboplatin-induced audiologic toxicity. These patients were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor, and is also the dose-limiting toxicity.

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenic profiles 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 have mutagenic activity in vitro in the mouse and rat. These effects may have been reported. These may occur within 24 hours of treatment.

PREGNANCY

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

Carboplatin has limited nephrotoxic potential, but when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients with carboplatin-induced audiologic toxicity. These patients were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor, and is also the dose-limiting toxicity.

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenic profiles 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 have mutagenic activity in vitro in the mouse and rat. These effects may have been reported. These may occur within 24 hours of treatment.

PREGNANCY

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

Carboplatin has limited nephrotoxic potential, but when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients with carboplatin-induced audiologic toxicity. These patients were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor, and is also the dose-limiting toxicity.

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenic profiles 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 have mutagenic activity in vitro in the mouse and rat. These effects may have been reported. These may occur within 24 hours of treatment.
Bone Marrow
Thrombocytopenia
<10,000/mm³
66 62
<5,000/mm³
33 67
Neutropenia
<0.5,000 cells/mm³
98 87
<1,000 cells/mm³
82 100
Leukopenia
<2,000 cells/mm³
50 58
<4,000 cells/mm³
71 76
Anemia
< 8 g/dL
90 90
< 5 g/dL
14 21
Hemoglobin
10

Hematologic Toxicity

Neutropenia has been reported in 66% 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 likely to vomit on the first day of treatment in addition 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 carboplatin, 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 carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

Neurologic Toxicity
Peripheral neurotoxicity has been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild parasthesias being the most frequent. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 60 years of age and those treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with preexisting creatinine value of 60 mL/min or more demonstrated a less severe toxicity and actual abnormalities were rarely associated with symptoms.

Nephrotoxicity
Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been tolerated without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function test results were 2% and 6% in 71% of the patients, respectively. Malaise, anorexia and hypertension have been reported in over 2% of the patients. Cardiovascular events (cardiac failure, pulmonary edema) were reported rarely in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemorrhagic cystic syndrome has been reported rarely. Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

Overdosage:
There is no known antidote for carboplatin overdosage. The anticipated complications of overdose 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 Carboplatin injection.

Single Agent Therapy
Carboplatin 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 over 30 minutes (see Table 1 and “Calcium Chloride—100,000”). In general, however, single intermittent courses of Carboplatin Injection should not be repeated until the neutrophil count is at least 2000 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:

Carboplatin Injection—500 mg/m² IV on day 1 every four weeks for six cycles. For directions regarding the use and administration of carboplatin, please refer to its package insert. See “Cyclophosphamide—600 mg/m² IV on day 1 every four weeks for six cycles” (see Table 1, “Calcium Chloride—100,000”). In general, however, single intermittent courses of Carboplatin Injection in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Dose Adjustment Recommendations
Pretherapy levels for creatinine and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.

The suggested dose adjustments for single agent or combination therapy shown in the table 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.
In these studies, GFR was measured by the creatinine clearance (in mg/mL•min), has been proposed by Calvert. Under the concentration versus time curve (AUC in mL/min) and Carboplatin Injection target area upon a patient’s glomerular filtration rate (GFR with impaired renal function) or overdosing (in patients with above average renal function) or underdosing (in patients with below average renal function) or post-treatment hydration or forced diuresis is recommended.

**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 Carboplatin Injection therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Recommended Dose on Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 to 59 mL/min</td>
<td>250 mg/m²</td>
</tr>
<tr>
<td>16 to 40 mL/min</td>
<td>200 mg/m²</td>
</tr>
</tbody>
</table>

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. 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 Carboplatin Injection is the use of mathematical formulae, which are based on a patient’s pre-existing renal function or renal function and desired platelet nadir. 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 Carboplatin Injection target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert. In these studies, GFR was measured by 51Cr-EDTA clearance.

**CALVERT FORMULA FOR CARBOPlatin DOSING**

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

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

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

**Geriatric Dosing**

Because renal function is often decreased in elderly patients, formula dosing of carboplatin based on estimates of GFR should be used in elderly patients to provide predictable plasma carboplatin AUCs and thereby minimize the risk of toxicity.

**PREPARATION OF INTRAVENOUS SOLUTIONS:**

Carboplatin Injection is a premixed aqueous solution of 10 mg/mL carboplatin. When prepared as directed, Carboplatin Injection solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin Injection solu-