

# KARBOTEEN®

(Carboplatin aqueous solution) INJECTION

## WARNING

**Karboteen (carboplatin aqueous solution) 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. The major marrow suppressive effect of carboplatin is myelosuppression, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect. Antiemetic-like reactions to carboplatin have been reported and may occur within minutes of Karboteen administration. Etoposide, corticosteroids, and antiemetics have been employed to alleviate symptoms.

## ACTION

### Mechanism of Action / Pharmacodynamics

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This is apparently due to the different aquation of carboplatin, which is thought to produce the active species. Crosslinks occur 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 potency between carboplatin and cisplatin appear to be directly related to the differences in aquation rates.

### PHARMACOKINETICS

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of infant carboplatin decay in a biphasic manner after a 30-minute intravenous infusion (900 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> of carboplatin). The initial plasma half-life ( $t_{1/2}$ ) was found to be 1.1 to 2 hours (n=6), and the postdistribution plasma half-life ( $t_{1/2}$ ) 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, 24 to 35 hours, respectively. The major route of elimination of carboplatin is renal excretion. The plasma concentration versus time curves from 0 to infinity (AUC) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup>).

Karboteen is not bound to plasma proteins. No significant quantities of protein-bound, ultrafiltrable 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 platinum 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. Karboteen dosages should therefore be reduced in these patients. Primary tumor determinants of plasma clearance are plasma protein concentration (GFR) and the parameter of renal function is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR to provide predictable Karboteen plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

### INDICATIONS

#### Primary Treatment of Advanced Ovarian Carcinoma:

Karboteen (carboplatin aqueous solution) 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 Karboteen and cyclophosphamide.

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#### Secondary Treatment of Advanced Ovarian Carcinoma:

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### DOSE 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 Karboteen.

#### Single-Agent Therapy

Karboteen (carboplatin aqueous solution) INJECTION, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m<sup>2</sup> IV on day 1 every 4 weeks. In general, however, single intermittent courses of Karboteen 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 Karboteen—600 mg/m<sup>2</sup> IV on day 1 every 4 weeks for 2 cycles, followed by cyclophosphamide 500 mg/m<sup>2</sup> IV on day 1 every 4 weeks for 2 cycles. In patients with creatinine clearances below 60 mL/min, the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Karboteen dosages should therefore be reduced in these patients. Primary tumor determinants of plasma clearance are plasma protein concentration (GFR) and the parameter of renal function is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR to provide predictable Karboteen plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

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Since anemia is cumulative, transfusions may be needed during treatment with Karboteen, 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 Karboteen dosages in these patients should be appropriately reduced. In patients with impaired kidney function, the use of a single intravenous infusion in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

Karboplatin has limited cross-reactivity, but concomitant treatment with antimetabolites has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients when carboplatin was administered at higher than recommended dosages along with other ototoxic agents. In patients receiving carboplatin and cisplatin, carboplatin 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 combination regimens, carboplatin, lengthened to 30 minutes, and cisplatin administration to 24 hours or dividing the total dose over 5 consecutive daily pulse doses has resulted in reduced emesis.

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

Doses of vision, which can be complete for light and colors, has been reported after the use of carboplatin with doses higher than those recommended on 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 carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased incidence of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy. High dosages of carboplatin (more than 4 times the recommended dose) have resulted in severe abnormalities of liver function tests. Karboteen (carboplatin aqueous solution) INJECTION may cause fetal harm when administered to a pregnant woman. Carboplatin 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 taking 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

Needs or intravenous administration sets containing aluminum parts that may come in contact with Karboteen (carboplatin aqueous solution) INJECTION 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 Karboteen.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity 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 be embryotoxic and teratogenic in rats. Carboplatin has been shown to be embryotoxic and teratogenic in rats. Secondary malignancies have been reported in association with multi-drug therapy.

#### 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 to nursing infants it is recommended that Karboteen (carboplatin aqueous solution) INJECTION be discontinued if the mother is breastfeeding.

#### Paternal Use

Safety and effectiveness in pediatric patients have not been established.

#### Geriatric Use

Of 176 patients in initial treatment combination therapy studies (NCIC and SWOG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop neutropenia and leukopenia than younger patients. In patients older than 100,000/m<sup>3</sup>, 74% had neutrophil counts above 2,000/mm<sup>3</sup>; 67% had leukocyte counts above 4,000/mm<sup>3</sup>.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance are more likely to experience 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 carboplatin, with drug-related death occurring in less than 1% of the patients. Fever has also been reported in patients with carboplatin. 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 Karboteen. Transfusions have been administered to 26% of the patients treated with carboplatin. 44% of previously treated ovarian cancer patients. Bone marrow depression may be more severe when Karboteen is combined with other bone marrow suppressing drugs or with radiotherapy.

#### Gastrointestinal Toxicity

Vomiting occurs in 65% of the patients (61% of previously treated ovarian cancer patients) and in about one-third of these patients if severe. In combination with cisplatin or other emetogenic agents, 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 occur within 24 hours of treatment and are often responsive to antiemetic therapy. In patients receiving carboplatin on a continuous 24-hour infusion or 24-hour schedule, prolonged administration of carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for 5 consecutive days, was associated with less severe vomiting than the single-dose intermittent schedule. Emesis was increased when carboplatin was administered in combination with other emetogenic agents. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

#### Neurologic Toxicity

Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (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 (15% for peripheral neuropathies). In 70% of the patients with existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients with peripheral neurotoxicity. Sensory 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 carboplatin 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 carboplatin 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 carboplatin therapy.

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 33%, respectively, in pretreated ovarian cancer patients). In patients with abnormal baseline values, the incidences of abnormal liver function tests were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%, (5%, 19%, and 33%, respectively, in pretreated ovarian cancer patients). In patients with abnormal baseline values, the incidences of abnormal liver function tests were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%, (5%, 19%, and 33%, respectively, in pretreated ovarian cancer patients). In patients with abnormal baseline values, the incidences of abnormal liver function tests were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%, (5%, 19%, and 33%, respectively, in pretreated ovarian cancer patients).

#### 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 carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

#### Allergic Reactions

Hypersensitivity to carboplatin 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, i.e., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance (see WARNINGS). These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

#### Injection Site Reactions

Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

#### 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 musculoskeletal 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.

Widespread morbilliform, hypersensitivity, dehydration, and stomatitis have been reported as part of postmarketing surveillance. There is no known antidote for Karboteen (carboplatin aqueous solution) INJECTION overdose. The anticipated complication of overdose would be secondary bone marrow suppression and/or hepatic toxicity.

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#### STORAGE

Store at 25°C. Protect from light.

#### PRESENTATIONS

#### Vials

KARBOTEEN 50 mg Carboplatin 50 mg/5 mL

KARBOTEEN 150 mg Carboplatin 150 mg/15 mL

KARBOTEEN 450 mg Carboplatin 450 mg/45 mL

KARBOTEEN 600 mg Carboplatin 600 mg/60 mL

Excipients: hydrochloric acid and/or sodium hydroxide, water for injection.

## THIS IS A MEDICATION

- A medication is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medication.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the periodic treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

## THYMOORGAN®

Manufactured by:  
Thymogon GmbH, Germany  
For H&K Pharmaceuticals GmbH - Jordan

Keep medication out of the reach of children  
2NKBT05-E-12/2010