# Megaplatin®

**CARBOPLATIN**

## 150mg/15ml sol.iv.inf

**Indications**

Carboplatin is indicated for the treatment of the following carcinoma:
Advanced ovarian carcinoma
Initial treatment of advanced ovarian carcinoma: Carboplatin 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. Two randomized controlled studies conducted by the NCIC and SWOG with caarboplatin vs. cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups. There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and long term 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.
Secondary treatment of advanced ovarian carcinoma: Carboplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have 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.
Small cell lung carcinoma. Non-small lung carcinoma. Head and neck carcinoma. Bladder cancer from transitional epithelium (in combination with other cytostatics)

**Contraindications**

Carboplatin is contraindicated in patients with severe long existing renal impairment (see Dosage and administration). Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding. Carboplatin is contraindicated in patients with a history of severe allergic reactions to carboplatin or the other platinum-containing compounds or mannitol.

**Special warnings and precautions for use**

**General**

Carboplatin is a cytotoxic drug and it must be used only by doctor with experience in chemotherapy. A regular blood control as well as a control of renal and hepatic function must be conducted. The administration of the drug should be stopped if pathological bone marrow suppression or pathological change in renal or hepatic function occurs.
Bone marrow suppression (leucopenia, 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. Median nadir occurs at day 21 in patients receiving single-agent carboplatin and day 15 in patients receiving combined therapy with carboplatin and other chemotherapeutic agents. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.
Since anemia 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 is also increased in patients with impaired kidney function. Initial Carboplatin dosages in these patients should be appropriately reduced (See dosage and administration) and blood counts should be carefully monitored between courses. The use of carboplatin in combination with other bone 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 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 doses in combination with other ototoxic agents.
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 schedules of Carboplatin, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five 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 previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving Carboplatin as secondary treatment. In patients with renal damage and after the use of Carboplatin with doses higher than the recommended ones, vision disturbances, including loss of vision, have been reported. 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 risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy.High dosages of Carboplatin (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests. Safety and effectiveness in pediatric patients have not been established.
Of the 789 in initial treatment combination therapy studies, 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 severe thrombocytopenia than younger patients. In a combined database of 1942 patients (414 were 65 years of age) that received single agent carboplatin for different tumor types, a similar incidence of adverse events was seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage.

**Pregnancy and lactation**

Carboplatin 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 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. It is known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breast-feeding be discontinued if the mother is treated with carboplatin.

**Effect on the ability to drive and use machines**

There is no effect reported. It must be taken into consideration the possibility of optical and audiologic toxicity and also the physical condition of the patients.

**Incompatibilities**

General: Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin 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 interaction with other medicinal products and other forms of interaction**

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

**Dosage and administration**

Megaplatin is only given by intravenous infusion. For adults patients with normal renal function that had not been previously submitted to therapy, the usual recommended dosage is 400 mg/m2 body area once that is given by intravenous infusion (duration 15-60 min). Treatment should not be repeated before a period of 4 weeks has passed from the previous treatment or/and since leukocyte and platelet levels are below 2000 and 100000 per mm3, respectively. Reduction of the initial dosage at 20-25% is recommended in patients with predisposing factors such as previous bone marrow depression therapy and not good function (Performance status scale ECOG-Zubrod 2-4 or Karnofsky less than 80). Weekly determination of haematological nadir is necessary at the first stages of therapy in order to determine the following dosage. Single agent therapy for ovarian cancer: Carboplatin, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m2 i.v. on a day 1 every 4 weeks (alternatively see formula dosing). In general, however, single intermittent courses of carboplatin should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100000.
Combined therapy: When Carboplatin is used in combination with other myelosuppressive agents, adjustments of dosage should be made according to regimen followed. Combination therapy with cyclophosphamide: In the chemotherapy for advanced ovarian cancer, an effective combination for previously untreated patients consists of: Carboplatin 300 mg/m2 i.v. on day 1 every four weeks for six cycles (alternatively see formula dosing).
Cyclophosphamide 600 mg/m2 i.v. on day 1 every four weeks for six cycles. For directions regarding the use and administration of cyclophosphamide, please refer to package insert. Intermittent courses of carboplatin in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100000. Dose adjustments recommendations: Pretreatment platelet count 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.

| Platelets | Neutrophils | Adjusted dose* (from prior course) |
|---|---|---|
| >100000 | >2000 | 125% |
| 50-100000 | 500-2000 | No adjustment |
| <50000 | <500 | 75% |

*Percentages apply to Carboplatin as a single agent or to both Carboplatin 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.
Carboplatin is usually administered by an infusion lasting 15 min or longer. No pre- or post-treatment hydration or forced diuresis is required.
Patients with impaired kidney function: Patients with creatinine clearance values below 60ml/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single agent carboplatin therapy, the incidence of severe leukopenia, neutropenia or thrombocytopenia has been about 25% with the following dosage modifications:
-250 mg/m2 carboplatin i.v. on the first day in patients with baseline creatinine clearance levels between 41-59 ml/min.
-200 mg/m2 carboplatin i.v. on the first day in those patients baseline creatinine clearance between 16-40 ml/min.
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 patient's tolerance on the degree of bone marrow suppression.
Formula dosing: Another approach for determining the initial dose of carboplatin is the use of mathematical formula, which is based on a patient's pre-exisitng renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. The use of dosing formula, 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 calculatin dosage has been proposed by Calvert:
Dose (mg) = (target AUC) * x (GFR + 25)
GFR: Glomerular filtration rate (ml/min)
AUC: Target area under the concentration versus time curve

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

| *TARGET AUC | Treatment | Patient's condition |
|---|---|---|
| 5-7 mg/ml.min | Monotherapy with carboplatin | No therapy used in the past |
| 4-6 mg/ml.min | Monotherapy with carboplatin | Therapy used in the past |
| 4-6 mg/ml.min | Combined therapy of carboplatin with Cyclophosphamide | No therapy used in the past |

For patients heavily treated** in the past and administered single agent carboplatin, when the aim is to obtain a specific platelet nadir, the Egorin formula can be used:
Dose (mg/m2) = 86 +

$$0{,}091 \left[\frac{\text{Creatinine clearance (ml/min)}}{\text{Body area (m2)}}\right] \left[\left[\frac{\text{Platelet No before treatment Desirable platelet nadir}}{\text{Platelet count before therapy}}\right] \times 100 - 17\right]$$

**Patients heavily treated are those who received: mitomycin C, nitrosuria, combined chemotherapy with 5 different substances or radiotherapy 4500 rads in a radiation field 20 x 20 cm or more than one field.
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.

**Instructions for use and handling**

Product can be diluted with 5% Dextrose solution or 0.9% Sodium chloride to concentrations as low as 0.5 mg/ml. Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.
Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Overdosage**

There is no known antidote for carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.Use of doses higher than the recommended ones in case of renal malfunction has been connected to vision loss (See special warnings and precautions).

**Undesirable effects**

In the narrative section that follows, the incidences of adverse events are based on data from 1893 patients with various types of tumors who received carboplatin as single-agent therapy.
Hematological Toxicity: Bone marrow suppression is the dose-limiting of carboplatin. Thrombocytopenia with platelet counts below 50000/mm3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1000/mm3 occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2000/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 100000/mm3; 74% have neutrophil counts above 2000/mm3; 67% have leukocyte counts above 4000/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 infections 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 neutropenia. Anemia with hemoglobin less than 1 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 carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin.
Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.
Gastrointestinal Toxicity: Vomiting occurs in 65% of the 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 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 neuropathies have been observed in 4% of the patients receiving Carboplatin 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 neurotoxicity, there was no worsening of symptoms during therapy with Carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and changes 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 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.
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.
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). 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 limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.
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. 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.
Malaise, anorexia and hypertension as well as injection site reactions, including redness, swelling, and pain, have been reported been reported as part of postmarketing surveillance.

**Missed dose**

Not applicable

**Self life**

24 months

**Storage**

At temperature ≤ 25°C, protected from light.

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**INFORMATION ON THE RATIONAL USE OF MEDICINES**

This drug was prescribed to you by your doctor only for your specific medical problem. You should not give it to other people or use it for any other disease without first consulting your doctor.
If any problem with the medicine is experienced during the treatment, tell your doctor or your pharmacist immediately.
If you have any questions regarding the information concerning the medicine you are taking or if you need to be better informed about your medical problem, do not hesitate to request this information from your doctor or your pharmacist.
In order for the drug that has been prescribed to you to be effective and safe, it must be taken according to the instructions given to you.
For your safety and good health, it is necessary to read carefully any information concerning the medicine that was administered to you.
Do not keep medicines in bathroom cabinets, because heat and humidity may spoil the medicine and render it harmful for your health.
Do not keep medicines that you do not need any more or that have already expired.
For increased safety, keep all medicines in a safe place away from children.
**This medicine is given only under physician's prescription.**


## Bibliography

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