

**\*Before using carboplatin:**  
 Conditions affecting its use, especially:  
 - Sensitivity to cisplatin or other compounds containing platinum or carboplatin.  
 - **Pregnancy:** its use is not recommended due to its mutagenic, teratogenic and carcinogenic potential; use; advisability of contraception use; informing your doctor/right away if pregnancy is suspected.  
 - **Breast-feeding:** it is not recommended due to the risk of serious side effects.

- **Use in elderly patients:** increased incidence of peripheral neurotoxicity and severity of myelotoxicity.  
 - Other medical problems, especially chickenpox, herpes zoster, infection or renal function impairment.  
 - Other medications, especially myelodepressants.

**Proper use of carboplatin:**  
 - Caution in use in combination with other drug, each medication should be taken properly.  
 - Frequency of nausea and vomiting: importance of continuing treatment despite stomach upset.  
 - Proper dosing.

**Precautions while receiving carboplatin:**  
 - Importance of monitoring by physician.  
 - Avoiding vaccinating, unless approved by physician, other people living with the patient should avoid oral vaccinating against poliovirus, avoiding contact with people receiving said vaccine, or wearing a protective mask to cover nose and mouth.

**Precautions if bone marrow depression occurs:**  
 Avoiding contact with people having bacterial infections, especially during periods of low blood counts; consulting with physician immediately if fever or chills, coughing or wheezing, side pain, painful or difficult urination occur.  
 - Checking with physician immediately if unusual bruising or bleeding, black tarry stools, blood in urine or feces, or tiny spots on the skin occur.

- Caution in regular use of toothbrushes, dental floss or toothpicks; physician or dentist may suggest alternatives; checking with physician before having any dental work.  
 - Not touching eyes or inside of nose without just previously washing hands.  
 - Caution to avoid accidental cuts in the use of sharp objects such us razors or nail scissors.

- Avoiding contact sports or other situations where injury or bleeding may occur.  
**Side effects:**  
 - It may cause adverse effects such as renal, hearing, less problems; it is important to discuss these possible effects with physician.  
 Signs of potential side effects may appear, especially anemia, leukopenia, neutropenia, thrombocytopenia, pain in injection site, allergic reaction, peripheral neurotoxicity, ototoxicity, blurred vision, and mucositis or stomatitis.

Physician may help you to minimize these side effects.  
 Hair loss may occur, regrowth is possible after treatment.

**INFORMATION FOR PATIENTS:**  
 Carboplatin belongs to the group of drugs known as alkylating agents. It is used to treat some kinds of cancer.  
 Carboplatin interferes with the growth of cancer cells, which eventually are destroyed. Since the growth of normal body cells may also be affected by carboplatin, other effects may occur. Some of these may be serious and should be informed to your doctor.  
 Some effects may appear months or years after treatment end.  
 Before undertaking treatment with carboplatin, you should consult your doctor about both the benefits and risks that this medication involves.  
 Carboplatin must be administered only under the immediate supervision of your doctor.

**BEFORE USING CARBOPLATIN:**  
 Before making the decision of starting any treatment, both the risks and the benefits of taking it must be considered.  
 You and your doctor together will make this decision.  
 For carboplatin, the following should be considered:

- **Allergies:** if you ever had any unusual or allergic reaction to compounds containing platinum (cisplatin and/or carboplatin or others).  
 - **Pregnancy:** it is possible that this medicine may cause congenital malformation defects if either man or woman is receiving it at the time of conception or during pregnancy. Carboplatin causes toxicity and harm to the fetus.

Many antineoplastic drugs may cause sterility, which may be permanent. Although this has not been reported in connection with this medication, the possibility still exists. Undoubtedly, you should check with your doctor before starting to receive this medicine.  
 It is advisable to use some kind of contraception while being treated with carboplatin. Tell your doctor immediately if you think you may be pregnant during treatment. Before using carboplatin, make sure that your Doctor knows if you are pregnant or if you may become pregnant.

- **Breast-feeding:** in general breast-feeding is not recommended while receiving this medicine since it may cause serious side effects.  
 - **Children:** studies have only been conducted in adult patients, then there is no specific information comparing use of carboplatin in children with use in other age groups.

- **Elderly patients:** some side effects of carboplatin (especially blood problems, or numbness or tingling in fingers and toes) are more likely to occur in elderly patients.  
 - **Other medications:** although certain medications must not be used together, in some cases two different medications may be used together even if interaction may occur. In these cases, your Doctor may change the dose or take other necessary precautions.

- **More common:** injection site pain  
 While you are receiving carboplatin, it is particularly important that your Doctor know if you have ever been treated with radiation therapy or cancer drugs, or if you are receiving any of the following medicines: amphotericin B by injection, anti thyroid agents, azathioprine, chloramphenicol, colchicine or flucytosine, ganciclovir, interferon, plicamycin, zidovudine). Carboplatin may increase the effect of these medicines or radiation on the blood.

- **Other medical problems:** the presence of other medical problems may affect the use of carboplatin. Make sure you tell your Doctor if you have any of the following medical problems: chicken pox (including recent exposure), herpes zoster, hearing problems; infection or kidney disease.

**PROPER USE OF CARBOPLATIN:**  
 This medicine is sometimes administered together with other medicines. If you are receiving a combination of medicines, it is important to have each one at the proper time.  
 This medicine usually causes nausea and vomiting that sometimes may be severe. However, it is very important that you continue taking this medicine even if you feel ill. Consult with your Doctor how to minimize these side effects, especially if they are severe.

- **Dose:** the dose of carboplatin is different for each patient. It depends on a series of factors, including the purpose of treatment, patient's body surface, and whether you are receiving other medicine(s). If you have any doubt regarding carboplatin dose, ask your doctor.

**PRECAUTIONS WHILE USING CARBOPLATINO SERVICAL:**  
 It is very important that your Doctor check your response to treatment by visiting you regularly to make sure that this medication is working properly and to check for unwanted effects.  
 While you are being treated with carboplatin and after treatment ends, do not have any vaccination without your Doctor's approval. Carboplatin may decrease your defenses, and there is a chance you might get the infection that the vaccine is trying to prevent. Also, people living with you should not have oral polio vaccine since they could pass the virus onto you. Do not stay close to them or in the same room for a long time. If you cannot take these precautions, you should consider using a protective mask to cover your nose and mouth.  
 Carboplatin may temporarily lower the number of white blood cells in your blood, increasing the possibility of getting an infection. The number of platelets, which are necessary for proper blood clotting, may also decrease. If this occurs, there are certain precautions you can take to reduce the risk of infection or bleeding, especially when your blood counts are low.

- Avoid contact with people with infections. Check with your Doctor immediately if you believe you have got an infection or if you have fever or chills, coughing or hoarseness, side pain, painful or difficult urination.  
 - Check with your Doctor immediately if any of the following occurs: unusual bruising or bleeding, black tarry stools, blood in urine or feces, or tiny red spots on the skin.

- Be careful with the regular use of toothbrushes, dental floss or toothpicks. Your Doctor or dentist may recommend other ways of cleaning your tooth and gums. Check with your Doctor before having any dental treatment.  
 - Avoid touching your eyes or inside your nose without previously washing your hands, avoid touching any object, person or other parts of your body.

- Be careful not to cut yourself when using sharp objects, like razors or scissors.  
 - Avoid contact sports or other situations where you may get bruising or bleeding.

**SIDE EFFECTS OF CARBOPLATIN:**  
 As well as producing its therapeutic effects, a medication may also cause unwanted effects. Although not all of these side effects may occur, if they do, they may require medical attention.

Because of the action of these medicines on the patient, there is a chance that unwanted effects may also occur, even months or years after treatment ends. These delayed effects may include certain kinds of cancer, like leukemia. Consult your doctor about these possible effects.  
 Check with your Doctor immediately if any of the following side effects occur:

- **Less common:** black tarry stools, blood in urine or feces, coughing or hoarseness, fever or chills, back pain or side pain, tiny red spots on the skin, skin rash or itching, unusual bruising or bleeding, numbness or tingling in toes.  
 - **Rare:** wheezing.  
 - **More common:** injection site pain  
 Check with your Doctor if any of these effects continue or are bothersome, or if you have any question about them.

- **More common:** nausea and vomiting, unusual tiredness or weakness.  
 - **Less common:** constipation or diarrhea, loss of appetite.  
 This medication may cause temporary loss of hair in some patients. After treatment has ended, normal hair regrowth is possible.  
 Other side effects not included in this list may occur in some patients. If you notice any other effect, consult your doctor.

**PRESENTATION:**  
 Carboplatino Servical 150 mg x 1 vial containing lyophilized powder.  
 Carboplatino Servical 450 mg x 1 vial containing lyophilized powder.

**Keep between 15°C and 30°C, protected from light.**

**This medicine must be used under medical prescription and supervision, and it must not be repeated without a new prescription.**

Medicinal Specialty authorized by the Argentine Ministry of Health (A.N.M.A.T.).  
 Certificate No. 49.961

**In case of overdosage, go to the nearest Hospital.**

**KEEP OUT FROM THE REACH OF CHILDREN.**

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Revision date: 03/2002

## Carboplatino Servical

### Carboplatin 150 and 450 mg

LYOPHILIZED POWDER FOR INJECTION

Sale under filed prescription  
 Made in Argentina

**All patients having carboplatin as active ingredient may produce the effects mentioned below. Carboplatin must only be administered by an oncologist.**

**QUAL-QUANTITATIVE COMPOSITION:**  
 Each vial of Carboplatino Servical contains:

<b>Carboplatin</b>	<b>150 mg</b>	<b>450 mg</b>
Mannitol	150 mg	450 mg

**DRUG CATEGORY:** antineoplastic.

**INDICATIONS:**  
**Initial treatment of advanced ovarian carcinoma.**  
 Carboplatino Servical is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other chemotherapeutic agents. One established combination regime consists of Carboplatino Servical and cyclophosphamide. Two randomized controlled studies carried out by the NCI and the SWOG using carboplatin vs. cisplatin, both in combination with cyclophosphamide, have shown similar survival rates between the two groups.

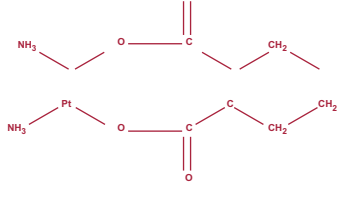
There is limited statistical power to demonstrate overall equivalence in pathologic response and long-term survival ( > 3 years) due to the small number of patients with these characteristics: the small number of patients with residual tumors < 2 cm after initial surgery also limits the statistical power 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 previously treated with cisplatin.

Within the group of patients treated with cisplatin, those who developed progressive health decline during cisplatin therapy may show lower response rates.

**Mechanism of action-effect.**  
 Carboplatin resembles an alkylating agent. Although its mechanism of action is unknown, it is thought that its action is similar to that of bifunctional alkylating agents, that is, possible cross-linking and interference with the DNA function. It is cell-cycle nonspecific.

**PHARMACOLOGY – PHARMACOKINETICS:**  
 Physicochemical characteristics:  
 Molecular weight: 371.25  
 Structural formula:



**Protein Binding.**  
 It is very low; however, carboplatin is irreversibly bound to plasma proteins.

and is slowly eliminated, with a minimum half-life of 5 days.

**Metabolism:**  
 By hydrolysis in aqueous solution, it is converted into active species that react with DNA, at a lower rate than cisplatin.

**Half-life:**  
 Alpha phase: 1.1 to 2.0 hours.  
 Beta phase: 2.6 to 5.9 hours.

**Elimination:**  
 In urine (71% within 24 hours at creatinine clearances of 60 ml/min and greater).

**GENERAL DOSING INFORMATION:**  
 It is recommended that during the administration of Carboplatino Servical patients should be under the supervision of a physician experienced in cancer chemotherapy. It is also advised that during carboplatin administration the necessary equipment and emergency medication (epinephrine, oxygen, antihistamines, and intravenous adrenocorticosteroids) be readily available in case an anaphylactic reaction occurs.

The dose should be adjusted to meet the particular needs of each patient, on the basis of clinical response and toxicity severity. Carboplatin may be used in combination with other agents in several schemes. As a result, the incidence and/or severity of side effects may be altered, and different doses may be used (generally reduced). Carboplatin is recommended to be administered by intravenous infusion, generally over 15 to 60 minutes. No pre- or post- treatment hydration or forced diuresis is required.

Carboplatin has also been administered by a continuous intravenous infusion of 24 hours, or dividing the total dose into 5 daily consecutive doses. This method of administration seems to reduce nausea and vomiting, but nephrotoxicity and ototoxicity remain.

It is advisable that intervals between courses should last more than 4 weeks in order to allow bone marrow recovery. Subsequent doses of carboplatin should not be administered until platelet count is at least 100,000/mm<sup>3</sup> and leukocyte count is at least 4,000/mm<sup>3</sup>.

Special precautions should be taken in patients developing thrombocytopenia due to carboplatin administration. These may include precautions in performing invasive procedures, regular inspection of IV injection sites, skin (including the perineal area), and surfaces of the mucous membranes for signs of bleeding or bruises; limiting the frequency of venipunctures and avoiding intramuscular injections; testing urine, emesis, feces, and secretions for occult blood, care in use of toothbrushes, dental floss, toothpicks, razors and nail scissors; avoiding constipation; being careful to avoid falls and other injuries. Such patients should avoid drinking alcohol and taking aspirins because of the risk of gastrointestinal bleedings. Platelet transfusions may be required.

Patients who develop leukopenia should be carefully observed for signs of infection. Supportive therapy with antibiotics may be required. Neutropenic patients who develop fever should be started empirically on broad-spectrum antibiotics, depending on the bacteria cultures and appropriate diagnostic tests.

**Safety considerations for handling this medication:**  
 There is limited but increasing evidence concerning personnel involved in the preparation and administration of parenteral antineoplastic, who may be exposed to certain risks due to the mutagenic, teratogenic or carcinogenic potential of these agents, although the actual risk is unknown. Suggested precautions include:

\* Use of a biological containment cabinet during reconstitution and dilution of parenteral medications, and wearing of masks and surgical gloves.  
 \* Use of proper techniques to prevent contamination of the medication, working area and operator during transfer between containers (including proper personnel training in this technique).  
 \* Caution and proper disposal of needles, syringes, vials, ampoules and unused medications.

**PARENTAL DOSAGE FORM:**  
**Usual dose for adults:**  
 -Advanced ovarian carcinoma:  
 Initial treatment: IV, 300 mg/m<sup>2</sup> of body surface area, once every 4 weeks (day 1) for six cycles; in combination with cyclophosphamide: IV,

600 mg/m<sup>2</sup> of body surface area, once every 4 weeks (day 1) for 6 cycles. Refractory to other chemotherapy regimens: IV, 360 mg/m<sup>2</sup> of body surface area, once every 4 weeks (day 1).  
 One initial dose of 250 mg/m<sup>2</sup> of body surface area is recommended in patients with creatinine clearance of 41-59 ml/min, and one initial dose of 200 mg/m<sup>2</sup> of body surface area is recommended in patients with creatinine clearance of 16-40 ml/min.  
 suggested dose adjustment plan for subsequent doses is:

Nadir after main dose (cell/mm <sup>3</sup> )		% of the dose to be administered
Neutrophils	Platelets	
> 2,000	> 100,000	125
500 - 2,000	50,000 - 100,000	100
< 500	< 50,000	75

The dose may be increased only once.  
 Elderly patients may require lower doses.  
**Usual dose for pediatric patients:**  
 It has not been established.

**Preparation of dosage form:**  
 Carboplatino Servical, sterile lyophilized powder, is reconstituted for intravenous use by adding 15 or 45 ml of sterile water for injection, 5% dextrose injection, or 0.9% sodium chloride injection to the 150 mg or 450 mg vial respectively, obtaining a 10 mg/ml carboplatin solution. This solution should be further diluted to a concentration of 500 µg (0.5 mg/ml) with 5% dextrose or 0.9% sodium chloride, if a further dilution is required for intravenous administration.

**Stability:**  
 Reconstituted solutions of carboplatin are stable for 8 hours at 25°C.  
**Precaution:**  
 If carboplatin comes in contact with aluminum, a black-silver precipitate is formed.

**Incompatibilities:**  
 Needles, intravenous sets or equipment containing aluminum should not used for administration since carboplatin is incompatible with aluminum.

**PRECAUTIONS TO BE CONSIDERED:**  
**\*Cross-sensitivity and/or related problems.**  
 Patients who are sensitive to cisplatin or other compounds containing platinum may be sensitive to carboplatin as well.

**\*Carcinogenicity.**  
 Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether this effect is related to its mutagenic or immunosuppressive action. The dose effect and therapy duration are also unknown, but risks seems to increase with long-term use.

Although there is limited information about carboplatin carcinogenic risk, the available data seems to indicate that this risk is higher with alkylating agents.

**\*Mutagenicity.**  
 In vivo and in vitro studies have demonstrated that carboplatin is mutagenic.

**\*Pregnancy-Reproduction.**  
**Fertility:**  
 Gonadal suppression resulting in amenorrhea and azoospermia may occur in patients under antineoplastic therapy, especially alkylating agents. In general, these effects seem to be related to dose and length of therapy, and appear to be irreversible. Prediction of the degree of testicular and ovarian function impairment is complicated due to the common use of combinations of several antineoplastic, which make it difficult to determine the effects of individual agents.

**Pregnancy:**  
 Carboplatin is embryotoxic and teratogenic in rats. During the first quarter of pregnancy, it is recommended that the use of antineoplastic be avoided, especially combination chemotherapy. Although information is limited because of the relatively few instances of antineoplastic administration during pregnancy, the risk-benefit relation should be considered due to the mutagenic, teratogenic and carcinogenic potential of these medications.

Other hazards to the fetus include adverse reactions observed in adults. Generally, the use of contraceptive is recommended during therapy with cytotoxic drugs.

**\*Breast-feeding.**  
 Although there is little information available regarding the risk of excretion of antineoplastic agents into breast milk, breast-feeding is not recommended during carboplatin administration due to the risk to the baby (adverse effects, mutagenicity, carcinogenicity).  
 It is unknown whether carboplatin is excreted in breast milk.

**\*Pediatrics.**  
 There is no available information relating age to the effects of carboplatin in pediatric patients.

**\*Patient monitoring.**  
 The following determinations may be especially important in patient monitoring (other tests may be required in some patients, depending on their condition):

- **Audimetric test:** it should be performed before the initiation of therapy and, during therapy, if ototoxicity is believed to exist.  
 - **Blood urea nitrogen (BUN), creatinine clearance and serum creatinine concentrations** (determinations recommended before starting therapy and prior to each course of carboplatin to establish renal toxicity).  
 - **Concentrations of serum calcium, magnesium and potassium** (determinations recommended at periodic intervals during therapy).  
 - **Hematocrit or hemoglobin, platelet count, differential and total leukocyte count** (determinations are recommended before commencing therapy, at periodic intervals during therapy; frequency varies according to the clinical state, chemotherapeutic agent and other medications being used concurrently).

- **Neurologic function studies** (recommended prior to the initiation of therapy and at periodic intervals during therapy).

**\*Drug interactions and/or related problems.**  
 They have been selected on the basis of their potential clinical significance. Combinations containing any of the following medications, depending on the amount present, may also interact with carboplatin:

- **Medications causing blood dyscrasias.**  
 Leukopenic and/or thrombocytopenic effects of carboplatin may be increased with concurrent or recent therapy if these medications cause the same effects; dosage adjustment, if necessary, should be based on blood counts.

- **Myelodepressants or radiation therapy.**  
 Concurrent use may increase the side effects of these medications and radiation therapy; dosage reduction is recommended.

- **Cisplatin.**  
 Incidence of neurotoxicity or ototoxicity induced by carboplatin may be increased in patients previously treated with cisplatin; use of carboplatin worsens the pre-existing neurotoxicity induced by cisplatin (in about 30% of these patients) or ototoxicity; additive nephrotoxicity has not been reported.

- **Other nephrotoxic or ototoxic medications.**  
 Concurrent and/or sequential administration may increase potential ototoxicity or nephrotoxicity.

- **Virus vaccines.**  
 Because normal defense mechanisms may be suppressed by carboplatin therapy, the patient's antibody response to the vaccine may be decreased. The interval between interruption of medication causing immunosuppression and restoration of the patient's capacity to respond to the vaccine depends on the intensity and the type of administered medication causing immunosuppression, the underlying disease, and other factors; it is estimated to vary from three months to one year.

**Laboratory values alterations.**  
 The following have been selected on the basis of their potential clinical significance.

- **Laboratory tests:** serum bilirubin concentrations, serum alkaline phosphatase, and serum aspartate aminotransferase (AST-GOT) may be increased; said increases are generally moderate and reversible in 50% of the cases; severe abnormalities occur at carboplatin doses over 3 times higher than the recommended dose.

- **Rare effects, blurred vision, mucositis or stomatitis** (sores in mouth and on lips).  
**\*Effects requiring medical attention only if they continue or are bothersome:**

- **More frequent effects:** asthenia (usual tiredness or weakness, may be related to anemia); nausea and vomiting (they occur in about 65% of patients, and only in one third of them these effects are severe). Nausea only occurs in about 10 to 15% of patients, and it generally starts 6 to 12 hours after a dose; vomiting persist for 24 hours. They may be treated or prevented with antiemetic medication.

- **Less frequent effects:** constipation or diarrhea; loss of appetite.  
**\*Effects not requiring medical attention:**  
 - Less frequent effects: hair loss.

generalized disease); hearing impairment; infection; renal function impairment; increased bone marrow depression; incidence and severity of nephrotoxicity may be increased. A lower dose of carboplatin is recommended in patients with renal function impairment, and careful monitoring of blood counts is also advised. Caution should be taken in patients who have previously received cytotoxic drug therapy or radiation therapy.

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 Concurrent use may increase the side effects of these medications and radiation therapy; dosage reduction is recommended.

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- **Less frequent effects:** constipation or diarrhea; loss of appetite.  
**\*Effects not requiring medical attention:**  
 - Less frequent effects: hair loss.

**PATIENT CONSULTATION:**  
 As an aid to patient consultation, refer to INFORMATION FOR PATIENTS. The doctor should warn the patient about the following:

**6.** **7.** **8.** **1.** **2.** **3.** **4.** **5.**