PACKAGE INSERT TEMPLATE FOR CARBOPLATIN SOLUTION FOR INJECTION

Brand or Product Name
[Product name] Solution for Injection 10mg/ml

Name and Strength of Active Substance(s)
Carboplatin 10mg/ml

Product Description
[Visual description of the appearance of the product (eg colour etc)
eg Clear colourless liquid

Pharmacodynamics

Carboplatin is a cisplatin analog with similar antineoplastic activity, but with a different adverse effect profile than cisplatin. Carboplatin has a carboxycyclobutane moiety replacing the chloride atoms on cisplatin. It is a cell cycle-nonspecific. The major antineoplastic mechanism of action for carboplatin is the production of crosslinks within and between strands of deoxyribonucleic acid (DNA). Normal DNA synthesis is inhibited by this disruption of cellular DNA conformation.

Pharmacokinetics

Intravenous carboplatin exhibits a biphasic elimination and is excreted mainly in the urine, about 70% of a dose being excreted within 24 hours, the majority in the first 6 hours. About a third of a dose is excreted unchanged.The terminal half-life (as free platinum) is reported to be about 6 hours. Platinum from carboplatin slowly becomes protein bound, and is subsequently excreted with a half-life of 5 days or more.

Indication For the treatment of advanced ovarian carcinoma of epithelial origin

Recommended Dosage

The recommended dosage for previously untreated adults (with normal renal function) is 400mg /m2 as a single intravenous infusion over 15-60 minutes. Dilutions may be made in Glucose 5% Intravenous Infusion to concentrations as low as 0.1 mg/mL. The product and admixture contain no antimicrobial agent. In order to reduce microbiological hazards it is recommended that further dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and any residue discarded.

Therapy should not be repeated again until four weeks have elapsed.

In patients with risk factors, such as previous myelosuppressive therapy or in the aged, the initial dosage may need to be reduced by 20-25%.

Determination of the haematological nadir by weekly blood counts is recommended for adjusting future doses and scheduling of carboplatin therapy.

Renal Impairment

As carboplatin is excreted by the kidney and is nephrotoxic, the optimum dosage should be determined by frequent monitoring of the haematological nadir and renal function.

The suggested dosage schedule for patients with impaired renal function based on creatinine clearance is:

Creatinine Clearance Carboplatin Dose

>40 mL/min 400 mg/m2

20-39 mL/min 250 mg/m2

0-19 mL/min 150 mg/m2

Paediatric

Insufficient information is available to make specific recommendations.

Combination Therapy

Carboplatin has been used in combination with other antineoplastic agents and the dosage varies according to the protocol used.

Dosage adjustments should be made according to the treatment regimen adopted and the results obtained from haematological monitoring.

Mode of Administration
Intravenous Infusion

Contraindications
Carboplatin Injection is contraindicated in the following conditions:

• Pre-existing severe renal impairment

• Severe myelosuppression

• Hypersensitivity to carboplatin or platinum-containing compounds

• Severe bleeding

• During pregnancy or lactation.

Warnings and Precautions

•Anemia, cumulative; may occur, transfusion support may be warranted especially during long-term therapy

•Concomitant use with aluminum-containing needles or IV administration sets should be avoided; formation of precipitate and loss of carboplatin potency

•Elderly patients; increased risk of severe thrombocytopenia and peripheral neuropathy (especially those who have received prior cisplatin-containing regimens)

•Carboplatin should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when potential benefits of carboplatin therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should they arise.

•Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia), dose-dependent and dose-limiting; have occurred; increased risk in patients with renal impairment, those who have received prior chemotherapy (especially with cisplatin-containing regimens), and those receiving concomitant bone marrow suppressing drugs or radiotherapy; monitoring recommended, dosage adjustment may be warranted

•Renal impairment; increased risk for bone marrow suppression; reduce initial dosages; monitoring recommended

•Neurotoxicity: Neurological evaluations and auditory monitoring should be performed regularly during and after carboplatin therapy.

•Ototoxicity: In doses higher than recommended; clinically significant hearing loss (in pediatric patients in combination with other ototoxic drugs). Auditory function should be monitored during treatment. Reversible vision loss, and severe liver function test abnormalities have been reported

•Gastrointestinal: Carboplatin can induce emesis. Severe vomiting; may occur, increased risk in those previously receiving emetogenic therapy. Premedication recommended; alternate dosage regimen may be considered.

The incidence and severity of emesis may be reduced by pretreatment with antiemetics or by carboplatin administration as a continuous IV infusion over 24 hours, or as IV administration of divided doses over 5 consecutive days rather than as a single infusion

- Hypersensitivity Reactions: Anaphylactic-like reactions have occurred within minutes of administration, increased risk with prior platinum therapy

  Patients should be monitored for possible anaphylactoid reactions and appropriate equipment and medication should be readily available to treat such reactions (e.g., antihistamines, corticosteroids, adrenaline, oxygen) whenever carboplatin is administered.

- Immunosuppressant Effects / Increased Susceptibility to Infections: Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Effects on Ability to Drive and Use Machines
The effect of carboplatin on the ability to drive or use machinery has not been systematically evaluated.

Interactions with Other Medicaments

When used with docetaxel, clearance of carboplatin has been reported to be about 50% higher than values reported for carboplatin monotherapy.

The combination of carboplatin therapy and other myelosuppressive agents may warrant dosage adjustments in order to avoid cumulative toxic effects. Due to the possibility of impairment in renal function, it is recommended that carboplatin therapy be avoided in patients receiving amino-glycoside antibiotics or other nephrotoxic drugs. An increased incidence of emesis has been reported when carboplatin and other emetogenic drugs are given concurrently or carboplatin is administered to patients who previously received emetogenic therapy.

Vaccination with a live vaccine should be avoided in patients receiving carboplatin as concurrent use may result in an increased risk of infection by the live vaccine

Concurrent use of rotavirus vaccine and chemotherapeutic agents is contraindicated; may result in an increased risk of infection by the live vaccine

Concurrent use of carboplatin and warfarin may result in increased risk for elevated INR and subsequent bleeding.

Concurrent use of topotecan and carboplatin may result in severe myelosuppression.

Concurrent use of carboplatin and phenytoin may result in decreased phenytoin effectiveness.

Concurrent use of carboplatin and the following drugs may result in ototoxicity

- kanamycin
- gentamicin
- netilmicin
- streptomycin
- amikacin
- tobramycin

Statement on Usage During Pregnancy and Lactation

Pregnancy

Carboplatin has been shown to be embryo-toxic and mutagenic, and its use in pregnant women is not recommended. Women of child-bearing potential should use adequate contraception and carboplatin should only be used in women of child-bearing potential if the expected benefits outweigh the risks of such therapy. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazard to the foetus.

Lactation

It is not known whether or not carboplatin is excreted in breast milk so breast feeding should be discontinued during carboplatin therapy in lactating women.

Adverse Effects / Undesirable Effects

- *Dermatologic:* Alopecia, Injection site extravasation, Injection site reaction, Necrosis / ulceration of skin due to extravasation of drug, Pseudoscleroderma due to cytotoxic therapy, rash, pruritus, urticaria
- *Endocrine metabolic:* Hypocalcemia, Hypokalemia, Hypomagnesemia, Hyponatremia
- *Hematologic:* Myelosuppression; Anemia , Leukopenia, Neutropenia , Thrombocytopenia
- *Hepatic:* Alkaline phosphatase raised , AST/SGOT level raised
- *Renal:* Blood urea abnormal , Serum creatinine raised , reduced creatinine clearance
- *Hematologic:* Myelosuppression
- *Immunologic:* Immune hypersensitivity reaction
- *Ophthalmic:* Unexplained visual loss, Visual disturbance
- Neurologic Effects: Asthenia, Neurotoxicity, Paresthesia
- *Other:* Pain , flu-like symptoms (Innovator)
- Musculoskeletal and connective tissue disorders: myalgia/arthralgia(Innovator)
- *Cardiac disorders:* Cardiac failure, ischaemic coronary artery disorders (e.g. myocardial infarction, cardiac arrest, angina, myocardial ischaemia). (Innovator)
- *Vascular disorders:* Cerebrovascular events. (Innovator)

- Neoplasms - benign, malignant and unspecified: There have been rare reports of acute myelogenous leukaemias and myelodysplastic syndromes arising in patients who have been treated with carboplatin, mostly when given in combination with other potentially leukemogenic agents (Innovator)
- *Gastrointestinal:* Nausea , Vomiting, Abdominal pain , Diarrhea,

*Nausea and Vomiting: Onset may be delayed for 6-12 hours after administration of carboplatin and usually disappears within 24 hours.

Overdose and Treatment

Symptoms

Mild to moderate toxicity: Nausea and vomiting, and less often diarrhea, may develop within hours. Transient renal insufficiency, mucositis, hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia may develop within days. Myelosuppression develops within the first two weeks. Nadir occurs in about 21 to 28 days, but may be earlier after an overdose.

Severe toxicity: Severe mucositis, diarrhea, and myelosuppression have been reported after large overdoses. Ototoxicity (ie, tinnitus, high-frequency deafness), and peripheral neuropathy (mostly sensorineuronal) may develop. Cortical blindness has been reported rarely following high doses

Treatment

There are no known antidotes for carboplatin overdosage

Aggressive IV fluid resuscitation with normal saline 3 to 6 L per day. Target urine output to 1 to 3 mL/kg/hr. Avoid nephrotoxic drugs. Treat persistent nausea and vomiting with several antiemetics of different classes .Administer colony stimulating factors (filgrastim or sargramostim) as these patients are at risk for severe neutropenia.

Transfusion of platelets and/or packed red cells may be needed in patients with severe thrombocytopenia, anemia, or hemorrhage.

Haemodialysis is only effective, even then partially, up to 3 hours after administration because of the rapid and extensive binding of platinum to plasma proteins. Signs and symptoms of overdosage should be managed with supportive measures.

The patient may need to be sustained through complications relating to myelosuppression, renal and hepatic impairment.

Incompatibilities

[To add appropriate information based on formulation]

Instructions for use and handling, and disposal

[To add appropriate information and graphic]

Storage Conditions

[eg Store below…. °C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]