AUSTRALIAN PRODUCT INFORMATION – Carboplatin Injection (Carboplatin)

1. NAME OF THE MEDICINE

Carboplatin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carboplatin Injection is a sterile, hypotonic, preservative-free solution containing carboplatin 10 mg/mL in Water for Injections.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of advanced ovarian carcinoma of epithelial origin.

4.2 Dose and method of administration

Dosage

The recommended dosage for previously untreated adults (with normal renal function) is 400mg /m^2 as a single intravenous infusion over 15-60 minutes. 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.

Method of administration

Prior to administration, carboplatin solutions should be inspected visually for particulate matter. 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 (see Section 6.6 Special precautions for disposal).

Aluminium reacts with carboplatin causing precipitate formation and loss of potency, therefore aluminium-containing equipment should not be used for preparation or administration of carboplatin.

Dosage adjustment

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/m^2
20-39 mL/min	250 mg/m^2
0-19 mL/min	150 mg/m^2

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.

Handling precautions

As with all antineoplastic agents, trained personnel should prepare Carboplatin Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling carboplatin. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as carboplatin.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare carboplatin, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100ºC (see Section 6.6 Special precautions for disposal).

4.3 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

4.4 Special warnings and precautions for use

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.

Myelosuppression

Myelosuppression associated with carboplatin is closely related to the renal clearance of the drug; therefore patients with impaired renal function are more susceptible.

Myelosuppression, particularly thrombocytopenia (reduction in platelet count), will also be more severe in patients receiving concomitant therapy with other nephrotoxic drugs such as aminoglycoside antibiotics. Toxicity is more likely to be prolonged and more severe in patients who have undergone previous chemotherapy, are more advanced in age, or who are debilitated. Dosage reductions may be necessary in these cases.

The nadir for platelets (peak detrimental effect) is usually between days 14-21 following initial treatment and days 14-28 for white blood cells. Minimum counts should be 50,000/mm^3 for platelets and 2,000/mm^3 for white blood cells. If counts fall below this level, therapy should be suspended until recovery is complete, usually five to six weeks. Supportive transfusional therapy may be necessary in severe cases.

It is important, therefore, that the assessment of renal function and peripheral blood counts (including white blood cells, platelets and haemoglobin) be made prior to, during and following treatment with carboplatin. In order to ensure that the peak detrimental effect on blood cells has occurred, repeat courses of treatment with carboplatin should not be given more frequently than monthly under normal circumstances.

Blood and lymphatic system disorders

Haemolytic anaemia with the presence of serologic drug-induced antibodies has been reported in patients treated with carboplatin. This event can be fatal.

Haemolytic uremic syndrome (HUS) is a potentially life-threatening side effect. Carboplatin should be discontinued at the first sign of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or lactate dehydrogenase (LDH). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Secondary leukaemia

Acute promyelocytic leukaemia (APL) and myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

Hepatobiliary disease

Cases of hepatic veno-occlusive disease (sinusoidal obstructive syndrome) have been reported. Some of them were fatal.

Central Nervous System (CNS)/Hearing Functions

Neurological evaluations and auditory monitoring should be performed regularly during and after carboplatin therapy, particularly in patients previously treated with cisplatin and in patients over 65 years of age.

Ototoxicity is cumulative, and frequency and severity of hearing disorder increases with high dose regimens and repeated doses, or prior treatment with cisplatin (also ototoxic). Auditory function should be monitored during treatment. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides) (see Section 4.5 Interactions with other medicines and other forms of interactions).

Delayed onset hearing loss has been reported in paediatric patients. Long-term audiometric follow-up in this population is recommended.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of RPLS have been reported in patients receiving carboplatin in combination chemotherapy. RPLS is a rare, reversible after treatment discontinuation, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI.

Tumour Lysis Syndrome (TLS)

Patients at high risk of TLS such as patients with high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents should be monitored closely and appropriate precaution taken.

Gastrointestinal

Carboplatin can induce emesis. The incidence and severity of emesis may be reduced by pre-treatment 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. Selective inhibitors of type 3 (5-HT3), serotonergic receptors (e.g., ondansetron) or substituted benzamides (e.g., metoclopramide) may be particularly effective antiemetics and combination therapy may be considered for patients experiencing severe or refractory emetogenic effects.

Hypersensitivity reactions

As in the case of other platinum complexed compounds, allergic reactions to carboplatin have been reported. 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.

Use in renal impairment

Renal toxicity is not usually dose-limiting. Unlike cisplatin therapy, pre-treatment and post-treatment hydration is not necessary, although some patients may show a decrease in creatinine clearance. Renal impairment is more likely to be seen in patients who have previously experienced nephrotoxicity as a result of chemotherapy.

Renal function should be assessed prior to and during therapy. (See Section 4.2 Dose and method of administration and Section 4.3 Contraindications). Concomitant administration of other nephrotoxic drugs (e.g., aminoglycoside antibiotics) may increase the risk of nephrotoxicity (see Section 4.5 Interactions with other medicines and other forms of interactions).

Use in the elderly

See Section 4.8 Adverse effects (undesirable effects).

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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 aminoglycoside antibiotics or other nephrotoxic drugs.

Concomitant administration of carboplatin and aminoglycosides results in an increased risk of nephrotoxicity and/or ototoxicity, and the drugs should be used concurrently with caution. The use of other nephrotoxic drugs results in a potentiation of renal effects by carboplatin.

Carboplatin interacts with aluminium to form a black precipitate of platinum and loss of potency. Aluminium-containing IV sets, needles, catheters and syringes should not be used for administration (see Section 6.2 Incompatibilities).

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.

A decrease in phenytoin serum levels has been observed with concurrent administration of carboplatin and phenytoin/fosphenytoin. This may lead to exacerbation of seizures.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Women of childbearing potential should be advised to avoid becoming pregnant while receiving carboplatin and to use effective contraception during treatment with carboplatin and for at least six months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with carboplatin and for at least three months after the last dose.

Male and female fertility may be impacted by treatment with carboplatin. Both men and women should seek advice for fertility preservation before treatment with carboplatin.

Use in pregnancy – Category D

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.

Use in 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.

4.7 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.

4.8 Adverse effects (undesirable effects)

Blood and lymphatic system disorders

Haematological toxicity is the most common dose-limiting toxicity, with leucopenia in 55% of patients, thrombocytopenia in 62% of patients, anaemia in up to 59% of patients and neutropenia. When used as single agent therapy, toxicity is not usually cumulative and is reversible, although transfusional therapy may be necessary in severe cases.

Haemolytic anaemia (sometimes fatal) has also been reported.

Clinical sequelae of bone marrow/haematologic toxicity such as fever, infections, sepsis/septic shock and haemorrhage may be expected.

Haemolytic uraemic syndrome has been reported.

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 leukaemogenic agents.

Renal and urinary disorders

Manifests as reduced creatinine clearance, elevated serum creatinine, blood urea nitrogen and uric acid levels. Acute renal failure has been reported rarely. Risk of carboplatin-induced nephrotoxicity (e.g., impaired creatinine clearance) becomes more prominent at relatively high dosages or in patients previously treated with cisplatin.

Gastrointestinal disorders

Nausea and vomiting: Onset may be delayed for 6-12 hours after administration of carboplatin and usually disappears within 24 hours. Antiemetic medication can be used to adequately control these effects. Stomatitis, mucositis, diarrhoea and constipation have been reported with carboplatin therapy.

Hepatobiliary disorders

Mild and usually transient elevations of serum alkaline phosphatase, aspartate aminotransferase or bilirubin concentrations may occur. Substantial abnormalities in liver function test have been reported in patients treated with carboplatin at high doses and autologous bone marrow transplantation. Abnormalities of liver function tests have been reported in up to 30% of patients. These changes are normally only transient in nature and disappear spontaneously.

Ear and labyrinth disorders

Manifests as tinnitus and hearing loss in the higher frequency range. Hearing impairment may persist or worsen with carboplatin therapy.

Eye disorders

Visual abnormalities, such as transient sight loss (which can be complete for light and colours) or other disturbances may occur in patients treated with carboplatin. Improvement and/or total recovery of vision usually occurs within weeks after the drug is discontinued. Cortical blindness has been reported in patients with impaired renal function receiving high-dose carboplatin.

Cardiac disorders

Cardiac failure, ischaemic coronary artery disorders (e.g., myocardial infarction, cardiac arrest, angina, myocardial ischaemia), Kounis syndrome.

Vascular disorders

Cerebrovascular events.

Immune system disorders

Erythematous rash, fever and pruritus may occur (less than 2% of patients). These include anaphylaxis/anaphylactoid reactions, hypotension, bronchospasm and pyrexia. Hypersensitivity reactions may occur within a few minutes after IV administration of carboplatin.

Skin and subcutaneous tissue disorders

Exfoliative dermatitis may rarely occur. Erythematous rash, pruritus, urticaria and alopecia have also been reported in association with carboplatin.

Musculoskeletal and connective tissue disorders

Myalgia/arthralgia.

Nervous system disorders

In the majority of patients, neurotoxicity manifests mainly as paraesthesias and decreased deep tendon reflexes. The effect, more common in patients over 65 years of age, appears to be cumulative, occurring mainly in patients receiving prolonged therapy and/or in those who have received prior cisplatin therapy. Central nervous system effects may also occur. Pre-existing paraesthesias (especially those related to previous cisplatin treatment) may worsen during carboplatin therapy. Dysgeusia has been reported in patients taking carboplatin.

Metabolism and nutrition disorders

Electrolyte abnormalities (hypokalaemia, hypocalcaemia, hyponatraemia and/or hypomagnesaemia).

Others

Asthenia, flu-like symptoms (1%) and reactions at injection site (<1%).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There are no known antidotes for carboplatin overdosage, thus every possible measure should be taken to avoid an overdose; this includes full awareness of the potential danger of an overdose, careful calculation of the dose to be administered and availability of adequate diagnostic and treatment facilities. Acute overdosage with carboplatin may result in an enhancement of its expected toxic effects (e.g. severe myelosuppression, intractable nausea and vomiting, severe neurosensorial toxicities, liver failure, kidney failure, etc.). Death may follow. 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. Diarrhoea and alopecia may develop.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Class: Antineoplastic agent.

Carboplatin has an inorganic heavy metal complex containing a central atom of platinum. It is an analogue of cisplatin. Carboplatin has biochemical properties similar to those of cisplatin. It is believed to bind to DNA to produce intra- and inter-strand (predominantly) crosslinks which modify structure and inhibit DNA synthesis.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Distribution

Protein binding is less than with cisplatin. Initially protein binding is low, with up to 29% of carboplatin bound during the first 4 hours. After 24 hours 85-89% is protein bound.

Elimination

After intravenous infusion of a single dose over one hour, plasma concentrations of total platinum and free platinum decline biphasically following first order kinetics. For free platinum, reported value for the initial phase of the half-life (t alpha½) is about 90 minutes and in the later phase the half-life (t beta½) is about 6 hours. Total platinum elimination has a similar initial half-life, while in the later phase the half life of total platinum may be greater than 24 hours.

Excretion

Carboplatin is mainly excreted by the kidneys. Most excretion occurs within the first 6 hours of administration with 50-70% excreted within 24 hours. 32% of the dose is excreted as unchanged drug. A reduction in dosage is recommended for patients with poor renal function.

5.3 Preclinical safety data

Genotoxicity

Animal studies demonstrate that carboplatin is mutagenic and teratogenic.

Carcinogenicity

The carcinogenic potential of carboplatin has not been studied; however, compounds with a similar mechanism of action have been reported to be carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Carboplatin interacts with the aluminium containing components of needles, syringes, catheters and intravenous administration sets to form a black precipitate so these items should not be used for the administration of carboplatin injections.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Single use only. Discard unused portion.

6.5 Nature and contents of container

AUST R 42853 Carboplatin Injection 50 mg in 5 mL (sterile) Plastic Vial.

AUST R 49348 Carboplatin Injection 150 mg in 15 mL (sterile) Plastic Vial.

AUST R 49349 Carboplatin Injection 450 mg in 45 mL (sterile) Plastic Vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

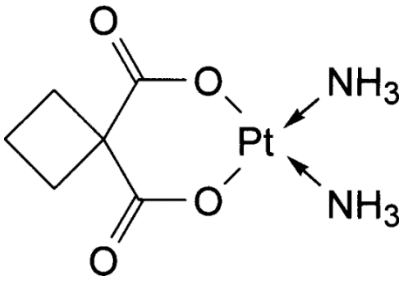
Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 3M sulphuric acid with 0.3M potassium permanganate (2:1) or 5% sodium hypochlorite. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100ºC'. Waste material should be incinerated at 1100ºC for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Molecular Formula: $C_6H_{12}N_2O_4Pt$

Molecular Weight: 371.3

CAS number

41575-94-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

09 November 1992

10. DATE OF REVISION

31 March 2020

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes.
4.4	Addition of information concerning reversible posterior leukoencephalopathy syndrome (RPLS).