Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin-Teva 10 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml of concentrate for solution for infusion contains 10mg of carboplatin.

Each 5ml vial contains 50mg carboplatin;
Each 15 ml vial contains 150mg carboplatin;
Each 45 ml vial contains 450mg carboplatin;
Each 60ml vial contains 600 mg carboplatin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear, colourless to faintly yellow solution, free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carboplatin is indicated for the treatment of:
1) advanced ovarian carcinoma of epithelial origin in:
a) first line therapy
b)second line therapy, after other treatments have failed.

2)small cell carcinoma of the lung.

4.2 Posology and method of administration

Dosage and Administration:

Carboplatin should be used by the intravenous route only.

The recommended dosage of Carboplatin in previously untreated adult patients with normal kidney function, i.e. creatinine clearance > 60 ml/min is 400 mg/m^2 as a single short term IV dose administered by a 15 to 60 minute infusion. Alternatively, the Calvert formula shown below may be used to determine dosage:

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]		
Target AUC	**Planned chemotherapy**	**Patient treatment status**
5-7 mg/ml.min	Single agent Carboplatin	Previously untreated
4-6 mg/ml.min	Single agent Carboplatin	Previously treated
4-6 mg/ml.min	Carboplatin plus cyclophosphamide	Previously untreated

Note: With the Calvert formula, the total dose of Carboplatin is calculated in mg, not mg/m^2. Calvert's formula should not be used in patients who have received extensive pretreatment**.

** Patients are considered heavily pretreated if they have received any of the following:

- Mitomycin C
- Nitrosourea
- Combination therapy with doxorubicin/cyclophosphamide/cisplatin
- Combination therapy with 5 or more agents
- Radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of not tolerable side effects.

Therapy should not be repeated until four weeks after the previous Carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80).

Determination of the haematological nadir by weekly blood counts during the initial courses of treatment with Carboplatin is recommended for future dosage adjustment.

Impaired Renal Function:
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression.

The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function.

In case of a glomerular filtration rate of ≤ 20 ml/min, carboplatin should not be administered at all.

All of the above dosing recommendations apply to the initial course of treatment.

Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression.

Combination Therapy:
The optimal use of Carboplatin in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

Paediatric patients
There is insufficient information to support a dosage recommendation in the paediatric population.

Elderly:
In patients of more than 65 years of age, dosage adjustment, initially or subsequently, may be necessary, dependent on the physical condition of the patient.

Dilution and reconstitution:
For information on dilution and reconstitution please see section 6.6.

4.3 Contraindications

Carboplatin is contraindicated in patients with:

- hypersensitivity to carboplatin or to any of the excipients
- breast feeding
- severe myelosuppression
- bleeding tumors

- pre-existing severe renal impairment **(creatinine clearance < 30 mL/min)**, unless in the judgement of the physician and patient, the possible benefits of treatment outweigh the risks
- concomitant use with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Carboplatin should be administered by individuals under the supervision of a qualified physician who is experienced in the use of anti-neoplastic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications. Blood counts as well as renal and hepatic function tests must be done regularly and the drug should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Haematologic toxicity
Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood counts should be monitored during carboplatin injection treatment frequently and, in case of toxicity, until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent carboplatin injection and day 15 in patients receiving carboplatin injection in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin injection should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. Therapy should not be repeated until 4 weeks after the previous carboplatin injection course and/or until the neutrophil count is at least 2,000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

Anaemia is frequent and cumulative requiring very rarely a transfusion.

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

Severity of myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial carboplatin injection dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.

Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosages and timing in order to minimise additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patients with severe and persistent myelosuppression are at high risk of infectious complications including fatal outcomes (see section 4.8). If any of these events occurs, carboplatin dosing should be interrupted and dose modification or discontinuation should be considered.

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

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

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.

Renal and hepatic function
Renal and hepatic function impairment may be encountered with Carboplatin. Very high doses of Carboplatin (≥ 5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and/or renal function. It is not clear whether an appropriate hydration programme might overcome effects on renal function. Dose reduction or discontinuation of therapy is required in the presence of moderate to severe alteration in renal or hepatic function test. (See Section 4.8).

In patients with impaired renal function, the effect of carboplatin on the haematopoietic system is more pronounced and longer-acting than in patients with normal renal function. In this risk group, therapy with carboplatin must be performed with special caution (see section 4.2).

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is also more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds

Hypersensitivity reactions
As with other platinum-based drugs, allergic reactions appearing most often during perfusion may occur and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see section 4.3 and section 4.8).

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8 "Undesirable effects").

Neurologic toxicity
Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decrease of osteotendinous reflexes, its frequency is increased in patients older than 65 years and/or in patients previously treated with cisplatin. Monitoring and neurological examinations should be carried out at regular intervals..

Visual disturbances, including loss of vision, have been reported after the use of carboplatin injection in doses higher than those recommended in patients with renal impairment. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

Use in elderly patients
In studies involving combination therapy with carboplatin and cyclophosphamide, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. Because renal function is often decreased in the elderly, renal function should be considered when determining dosage (see section 4.2).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (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 (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Venoocclusive liver disease
Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases.

Tumour lysis syndrome (TLS)
In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Other
Auditory defects have been reported during carboplatin therapy. Ototoxicity may be more pronounced in children. Cases of hearing loss with a delayed onset have been reported in paediatric patients. A long-term audiometric follow-up in this population is recommended.

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.

The carcinogenic potential of Carboplatin has not been studied but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic (See section 5.3)

Safety and effectiveness of carboplatin administration in children are not proven.

Aluminium containing equipment should not be used during preparation and administration of Carboplatin (See section 4.2, 4.5 and 6.2).

4.5 Interaction with other medicinal products and other forms of interaction

Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent.

The high intra-individual variability of the coagulabilty during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy, require, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the control of the INR monitoring.

Concomitant use contraindicated

- Yellow fever vaccine: risk of generalised vaccinal disease mortal (see section Contraindications).

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis).
- Phenytoin, fosphenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.
- Concurrent administration of carboplatin and chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin. However, the antineoplastic effect of carboplatin was not influenced by diethyl-dithiocarbamate in animal experiments or in clinical use.

Concomitant use to take into consideration

- Cyclosporin (and by extrapolation tacrolimus and sirolimus): excessive immunosuppression with risk of lymphoproliferation.
- Aminoglycosides: the concomitant use of carboplatin with aminoglycosides antibiotics should be taken into account due to the cumulative nephrotoxicity and ear toxicity, particularly in renal failure patient.
- Loop diuretics: the concomitant use of carboplatin with loop diuretic should be taken into account due to the cumulative nephrotoxicity and ear toxicity.
- When combining carboplatin with other myelosuppressive compounds, the myelosuppressive effect of carboplatin and/or the other compounds may be more pronounced. Patients receiving concomitant therapy with other nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity due to decreased renal clearance of carboplatin.

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come into contact with carboplatin, should not be used for the preparation or administration of the drug.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Due to the genotoxic potential of carboplatin (see section 5.3 in the SPC), women of childbearing potential should use effective contraceptive measures while being treated with carboplatin for 6 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving carboplatin and for 3 months following completion of treatment.

Pregnancy
Carboplatin injection can cause foetal harm when administered to a pregnant woman. Carboplatin injection has been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. No controlled studies in pregnant women have been conducted. 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 foetus. Women with child-bearing potential should be advised to avoid becoming pregnant.

Fertility
Gonadal suppression resulting in amenorrhea or azospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.

Men of sexually mature age treated with carboplatin are recommended to ask advice about spermatic preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

Lactation:
It is not known whether Carboplatin is excreted in human milk. If treatment becomes necessary during the lactation period, breastfeeding must be stopped.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, carboplatin may cause nausea, vomiting, vision abnormalities and ototoxicity; therefore, patients should be warned on the potential effect of these events on the ability to drive or to use machines.

4.8 Undesirable effects

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single agent carboplatin injection and post-marketing experience.

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (³ 1/10), common (³ 1/100 to < 1/10), uncommon (³ 1/1,000 to < 1/100), rare (³ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Neoplasms, benign and malignant (including cysts and polyps)	Not known	Treatment related secondary Malignancy
Infections and infestations	Common	Infections*
	Not known	Pneumonia
Blood and lymphatic system	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, hemolytic-uraemic syndrome
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia, tumor lysis syndrome

Nervous system disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Not known	Cerebrovascular accident*, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)[#]
Eye disorders	Common	Visual disturbance, rare cases of loss of vision
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Not known	Cardiac failure* Kounis syndrome
Vascular disorders	Not known	Embolism*, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory disorder, interstitial lung disease, bronchospasm
Gastrointestinal disorders	Very common	Vomiting, nausea, abdominal pain
	Common	Diarrhoea, constipation, mucous membrane disorder
	Not known	Stomatitis, pancreatitis[#]
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal disorder
Renal and urinary disorders	Common	Urogenital disorder
General disorders and administration site conditions	Common	Asthenia
	Not known	Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise
Investigation	Very common	Creatinine renal celarance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased.
	Common	Blood bilirubin increased, blood creatinine increased, blood uric acid increased

* Fatal in < 1%, fatal cardiovascular events in <1% included cardiac failure, embolism, and cerebrovascular accident combined.
[#] based on post-marketing experience.

Description of selected adverse reactions

Haematologic:
Myelosuppression is the dose-limiting toxicity of carboplatin injection. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of patients, neutropenia with granulocyte counts below 1,000/mm^3 in 18% of patients, and leukopenia with WBC counts below 2,000/mm^3 in 14% of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin injection with other myelosuppressive compounds or forms of treatment.

Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired kidney function. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia. These effects, although usually reversible, have resulted in infectious and hemorrhagic complications in 4% and 5% of patients given carboplatin injection, respectively. These complications have led to death in less than 1% of patients.

Anaemia with haemoglobin values below 8 g/dl has been observed in 15% of patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to carboplatin injection.

Gastrointestinal:
Vomiting occurs in 65% of patients, in one-third of whom it is severe. Nausea occurs in an additional 15%. Previously treated patients (in particular patients previously treated with cisplatin) appear to be more prone to vomiting. These effects usually disappear within 24 hours after treatment and are generally responsive to or prevented by antiemetic medication. Vomiting is more likely when carboplatin injection is given in combination with other emetogenic compounds.

The other gastro-intestinal complaints corresponded to pain in 8% of patients, diarrhoea, and constipation in 6% of patients.

Neurologic:
Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4% of patients administered carboplatin injection. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin injection, appear to be at increased risk.

Clinically significant sensory disturbances (i.e. visual disturbances and taste modifications) have occurred in 1% of patients.

The overall frequency of neurologic side effects seems to be increased in patients receiving carboplatin injection in combination. This may also be related to longer cumulative exposure.

Ototoxicity:
Auditory defects out of the speech range with impairments in the high-frequency range (4,000-8,000 Hz) were found in serial audiometric investigations with a frequency of 15%. Very rare cases of hypoacusia have been reported.

In patients with a hearing organ predamaged due to cisplatin, a further exacerbation in the hearing function sometimes occurs during treatment with carboplatin.

Renal:
When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin injection has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6% of patients, elevation of blood urea nitrogen in 14%, and of uric acid in 5% of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven to be the most sensitive renal function measure in patients receiving carboplatin injection. Twenty-seven percent (27%) of patients who have a baseline value of 60 ml/min or greater, experience a reduction in creatinine clearance during carboplatin injection therapy.

Electrolytes:
Decreases in serum sodium, potassium, calcium, and magnesium occur in 29%, 20%, 22%, and 29% of patients, respectively. In particular, cases of early hyponatraemia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.

Hepatic:
Modification of liver function in patients with normal baseline values was observed, including elevation of total bilirubin in 5%, SGOT in 15%, and alkaline phosphatase in 24% of patients. These modifications were generally mild and reversible in about one-half the patients. In a limited series of patients receiving very high dosages of carboplatin injection and autologous bone marrow transplantation, severe elevation of liver function tests has occurred.

Cases of an acute, fulminant liver cell necrosis occurred after high-dosed administration of carboplatin.

Allergic Reactions:
Anaphylactic-type reactions, sometimes fatal, may occur in the minutes following injection of the product: facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm.

Other undesirable effects:
Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.

Alopecia, fever and chills, mucositis, asthenia, malaise as well as dysgeusia have occasionally been observed.

In isolated cases, a haemolytic-uraemic syndrome occurred.

Isolated cases of cardiovascular incidents (cardiac insufficiency, embolism) as well as isolated cases of cerebrovascular accidents have been reported.

Cases of hypertension have been reported.

Local reactions:
Reactions at the site of injection (burning, pain, reddening, swelling, urticaria, necrosis in connection with extravasation) have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms of overdose
Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m^2 i.v. per course. At this dosage, life-threatening haematological side effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9-25 (median: days 12-17). The granulocytes had reached values of ≥ 500/µl after 8-14 days (median: 11) and the thrombocytes values of ≥ 25.000/microlitre after 3-8 days (median: 7).

The following non-haematological side effects also occurred: renal function disturbances with a 50% drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, alopecia, erythema, and severe infection. In the majority of cases, hearing disturbances were transient and reversible.

Treatment of Overdose
There is no known antidote for carboplatin over dosage. The anticipated complications of over dosage would be related to myelosuppression as well as impairment of hepatic and renal function. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological side effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Platinum compounds
ATC code: L01X A02

Carboplatin is an antineoplastic agent. Its activity has been demonstrated against several murine and human cell lines. Carboplatin exhibited comparable activity to cisplatin against a wide range of tumours regardless of implant site. Alkaline elution techniques and DNA binding studies have demonstrated the qualitatively similar modes of action of Carboplatin and cisplatin.

Carboplatin, like cisplatin, induces changes in the superhelical conformation of DNA, which is consistent with a DNA shortening effect.

Paediatric patients: safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties

Following administration of carboplatin in man, linear relationships exist between dose and plasma concentrations of total and free ultrafilterable platinum. The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose when creatinine clearance ≥ 60 ml/min.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. After a 1-hour infusion (20-520 mg/m^2), plasma levels of total platinum and free (ultrafilterable) platinum decay biphasically following first order kinetics. For free platinum, the initial phase (t alpha) half life is approximately 90 minutes and the later phase (t beta) half life approximately 6 hours. All free platinum is in the form of carboplatin in the first 4 hours after administration. Protein binding of carboplatin reaches 85-89% within 24 hours of administration, although during the first 4 hours, only up to 29% of the dose is protein bound. Carboplatin is excreted primarily in the urine, with recovery of approximately 65% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours.

Approximately 32% of a given dose of carboplatin is excreted unchanged. Total body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion. Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin.

Carboplatin clearance has been reported to vary by 3- to 4- fold in paediatric patients. As for adult patients, literature data suggest that renal function may contribute to the variation in carboplatin clearance.

5.3 Preclinical safety data

Carboplatin has been shown to be embryotoxic and teratogenic in rats. It is mutagenic *in vivo* and *in vitro* and although the carcinogenic potential of Carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Water for injections

6.2 Incompatibilities

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or intravenous administration sets that contain aluminium parts which may come into contact with carboplatin, should not be used for the preparation or administration of the drug. Stainless steel types SS304 and SS316 have been found to be compatible with carboplatin.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

Unopened:
2 years.

After dilution:
Carboplatin-Teva may be diluted under aseptic conditions with water for injection, 0.9% sodium chloride Injection or 5% dextrose injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2°C to 8°C.
Since the formulations of carboplatin do not contain preservatives, it is recommended that any solution remaining after this time should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.
Keep vial in the outer carton.

6.5 Nature and contents of container

Carboplatin-Teva is available in-
Amber glass vials, USP type I of 5ml, 15ml, 45ml or 60ml capacity. Rubber closures 20mm. Nature of Elastomer: chlorobutyl, siliconized grey.

Each vial is packed in an individual carton.

Pack sizes are 5ml, 15ml, 45ml or 60 ml containers.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Dilution:
Carboplatin-Teva may be diluted under aseptic conditions to the required strength with Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, to concentrations as low as 0.5 mg/ml.

Carboplatin-Teva does not contain any antimicrobial preservation; it is intended for single-dose administration only. Following dilution, carboplatin solution must be refrigerated at 2-8°C. Any solution remaining after 24 hours must be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Needles or intravenous sets containing aluminium parts that may come in contact with carboplatin should not be used for preparation or administration. Aluminium reacts with carboplatin causing precipitate formation and/or loss of potency.

The safety measures for dangerous substances are to be complied with during preparation and administration. Preparation must be carried out by personnel who have been trained in the safe use while wearing protective gloves, face mask and protective clothes.

As with all cytotoxic preparations, the following special precautions should be taken for safe handling and disposal:
1. Trained personnel only should dilute the drug. Pregnant staff should not be involved in its handling.
2. Preparation of the drug should be performed in a designated area, ideally in a vertical laminar flow hood (Biological Safety Cabinet - Class II). The work surface should be covered with disposable plastic-backed absorbent paper.
3. Adequate protective clothing should be worn, i.e. PVC gloves, safety glasses, disposable gowns and masks. In the event of contact with the eyes, wash with copious amounts of water or saline.
4. Luer-Lock fittings should be used on all syringes and sets. The possible formation of aerosols may be reduced by using large-bore needles and venting needles.
5. All unused material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be segregated, placed in double-sealed polyethylene bags and incinerated at 1000^{o}C or more. Excreta should be similarly treated. Liquid waste should be flushed away with copious amounts of water.
6. In the event of spillage, trained personnel wearing appropriate personal protective equipment as outlined above, should mop the spilled material with a spill kit or sponge kept in the area for that purpose. Rinse the area with copious amounts of water. Put all solutions and sponges into a designated suitable high risk waste disposal bag and then seal it.

For single use only. Discard any remaining solution appropriately.

The solution should be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if it is clear and free from particles.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/004/001

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