Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin 10 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 10 mg of carboplatin.
One vial of 5 ml contains 50 mg carboplatin.
One vial of 15 ml contains 150 mg carboplatin.
One vial of 45 ml contains 450 mg carboplatin.
One vial of 60 ml contains 600 mg carboplatin.
One vial of 100 ml contains 1000 mg carboplatin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Carboplatin is a clear, colourless to pale yellow solution free from particles.

pH: 5.0 – 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Carboplatin is indicated for the treatment of:
- Advanced ovarian carcinoma of epithelial origin in:
  - First line therapy
  - Second line therapy, after other treatments have failed.
- Small cell carcinoma of the lung.

4.2 Posology and method of administration

Posology

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. with creatinine clearance > 60 ml/min is 400 mg/m^2 as a single intravenous 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]

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 formula should not be used in patients who have received extensive pre-treatment**.

** Patients are considered heavily pre-treated 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 4 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 count during the initial courses of treatment with carboplatin is recommended for dosage adjustment for subsequent courses of therapy.

Patients with renal impairment:
Patients with creatinine clearance values below 60 ml/min are at increased risk of developing severe myelosuppression.

The frequency of severe leukopenia, neutropenia, or thrombocytopenia has been maintained at about 25% with the following dosage recommendations

Baseline Creatinine Clearance	**Initial Dose (Day 1)**
41 – 59 ml/min	250 mg/m^2 I.V.
16 – 40 ml/min	200 mg/m^2 I.V.

Insufficient data exist on the use of carboplatin injection in patients with creatinine clearance of 15 ml/min or less to permit a recommendation for treatment.

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.

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.

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.

Older people:
In patients of more than 65 years of age, adjustment of the carboplatin dose to the general condition and renal function is necessary during the first and the subsequent therapeutic courses.

Paediatric population:
There is insufficient information available to recommend a dosage in the paediatric population.

Method of administration
Precautions to be taken before handling or administering the medicinal product.

For instructions on dilution of the medicinal product before administration, see section 6.6.

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 for 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.

4.3 Contraindications

Carboplatin is contraindicated in patients with:
- hypersensitivity to the active substance or to other platinum containing compounds
- breast feeding
- severe myelopsuppression
- bleeding tumours
- 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

Warning
Carboplatin should be administered only by individuals under the supervision of a qualified physician who is experienced in the use of anti-neoplastic therapy.

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.

Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Haematological toxicity

Carboplatin infusion courses should not be repeated more frequently than monthly under normal circumstances.

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 and day 15 in patients receiving carboplatin 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.

Severity of myelosuppression is increased in patients with prior treatment (in particular cisplatin) and/or impaired kidney function. Initial carboplatin 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 injection 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.

Hepatic and/or renal insufficiency
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. 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 Posology and method of administration and 4.4 haematological toxicity).

Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

Allergic 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 platinum compounds (see Section 4.3 and Section 4.8).

Patients should be observed for possible allergic reactions.

The occurrence, and severity of toxicity is likely to be greater in patients who have received extensive prior treatment for their disease, have poor performance status and are advanced in years. Renal function parameters should be assessed prior to, during and after carboplatin therapy.

Neurotoxicity
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 significant extent within weeks of stopping these high doses.

Ototoxicity
Auditory defects have been reported during carboplatin therapy.

Ototoxicity in children
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.

Geriatric use
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).

Live vaccinations
Administration of live or live-attenuated vaccines in patients immune-compromised 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 of such vaccines may be diminished.

Aluminium containing equipment should not be used during preparation and administration of carboplatin (see section 6.2). Aluminum reacts with carboplatin injection causing precipitate formation and/or loss of potency.

4.5 Interaction with other medicinal products and other forms of interaction

When combining carboplatin with other myelosuppressive compounds or radiation therapy, 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.

Concomitant use contraindicated
- Yellow fever vaccine: risk of generalised vaccinal disease mortal (see section 4.3).

Concomitant use not recommended (see section 4.4)
- 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 therapy with nephrotoxic drugs or ototoxic drugs such as amino glycoside, vancomycin, capreomycin and diuretics is not recommended, since this may lead to increased or exacerbated toxicity due to carboplatin induced changes in renal clearance of these substances.

Concomitant use to be taken into consideration
- Chelating agents - decreasing effect of carboplation
- Cyclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Aminoglycosides: The concomitant use of carboplatin with aminoglycoside antibiotics should be taken into account due to the cumulative nephrotoxicity and ear toxicity, particularly in patients with severe renal impairment.

- Loop diuretics: The concomitant use of carboplatin with loop diuretics should be taken into account due to the cumulative nephrotoxicity and ear toxicity.

- 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 coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with VKA, to increase frequency of the control of the INR monitoring. Caution and more frequent INR monitoring is recommended at concomitant treatment of warfarin with carboplatin, as increased INR has been reported.

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

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 (see section 5.3). No controlled studies in pregnant women have been conducted.

The safe use of carboplatin during pregnancy has not been established: Studies in animals have shown reproductive

toxicity. Carboplatin has been shown to be an embryo toxin and teratogen in rats and mutagenic *in vivo* and *in vitro*.

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

Fertility
Gonadal suppression resulting in amenorrhea and 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 not to father a child during treatment and up to 6 months afterwards and to ask advice about spermatic preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

Women with child-bearing potential
Women with child-bearing potential should be advised to avoid becoming pregnant. Carboplatin must not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus. 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.

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 and post-marketing experience.

The list is presented by system organ class, MedDRA preferred term and frequency using the following frequency categories:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 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**
Infections and infestations	Common	Infections*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
Metabolism and nutrition	Not known	Dehydration, anorexia, hyponatraemia

disorders		
Nervous system disorders	Common	Neuropathy peripheral, paresthesia, decrease of osteotendinous reflexes, sensory disturbances, dysgeusia
	Not known	Cerebrovascular accident*
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*
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
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
Investigations	Very common	Creatinine renal clearance 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.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Secondary malignancies (including promyelocytic leukaemia which occurred 6 years after monotherapy with carboplatin and preceding irradiation) have been reported following administration of carboplatin as a single agent or in combination therapy (causal relationship not established).

Blood and lymphatic system disorders:
Myelosuppression is the dose-limiting toxicity of carboplatin. 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 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

haemorrhagic complications in 4% and 5% of patients given carboplatin, 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.

Immune system disorders

Allergic Reactions:
Anaphylactic-type reactions, sometimes fatal, may occur most often in the minutes following injection of the product: facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm (see section 4.4).

These reactions are similar to those observed after administration of other platinum containing compounds and should be managed with appropriate supportive therapy.

Metabolism and nutrition disorders

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 course without any clinical symptoms.

Neurologic:
Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4% of patients administered carboplatin. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin, 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 in combination. This may also be related to longer cumulative exposure.

Eye disorders
Visual disturbances, and rare loss of vision, sometimes including transient sight loss, have been reported with platinum therapy. This is usually associated with high dose therapy in renally impaired patients. Optic neuritis has been reported in post marketing surveillance.

Ear and labyrinth disorders
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 pre-damaged due to cisplatin, a further exacerbation in the hearing function sometimes occurs during treatment with carboplatin.

At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

Respiratory, thoracic and mediastinal disorders
In addition to Interstitial lung disease, pulmonary fibrosis should be considered if a pulmonary hypersensitivity state is excluded.

Gastrointestinal disorders
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.

Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin.

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.

Hepatobiliary disorders
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.

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

Renal and urinary disorders

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.

Other undesirable effects:
Alopecia, fever and chills, mucositis, asthenia, malaise as well as dysgeusia have occasionally been observed.
Isolated cases of haemolytic-uraemic syndrome have been reported.
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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option. FREEPOST, Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: +353 1 6764971 Fax: +353 1 6762517. Website: www.imb.ie e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Symptoms of overdose
Carboplatin was adminstered in phase I studies at a dosage of up to 1600 mg/m^2 i.v. per course. At this dosage, life-threatening haemological 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/µl after 3-8 days (median: 7).

The following non-haematological side effects also occured: renal function disturbances with a 50% drop is the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, 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 overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and auditory function.

Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological sife effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {other antineoplastic agents, platinum compounds}, ATC code: L01XA02.

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 population: safety and efficacy in children have not been established (see section 4.2, 4.4 and 5.2).

5.2 Pharmacokinetic properties

Linearity

Following administration of carboplatin in man, linear relationships exist between dose and plasma concentrations of total and free ultra-filterable 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.

Absorption

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma.

Elimination

Following administration of carboplatin reported values for the terminal elimination of half-lives of free ultra-filterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultra-filterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours.Approximately 87% of plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primiarly in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultra-filterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

Carboplatin clearance has been reported to vary 3 to 4 fold in paediatric patients (see section 4.2 and 4.4). 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.

Toxicity studies have shown that extravasal administration of carboplatin causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection.

6.2 Incompatibilities

Carboplatin may react 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 preparing or administering the drug.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 2 years.

Diluted product: Chemical and physical in-use stability has been demonstrated after dilution for 24 hours at 2 to 8^{o}C. From a microbiological point of view however, 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 normally not be longer than 24 hours at 2 to 8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Carboplatin is supplied in type I transparent, flint moulded glass vial containing either 5 ml, 15 ml, 45 ml, 60 ml or 100 ml concentrate for solution for infusion. Vials are closed with grey rubber stoppers and white/blue (60 ml vial only) flip-off aluminium seals.

Pack size:
1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product is for single use only. Any unused infusion solution should be discarded.

Handling and use
The preparation and administration of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this

purpose. It is forbidden to smoke, eat or drink in this area.

Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

Spills and leakages must be wiped up, wearing protective gloves.

Precautions should be taken to avoid exposing staff during pregnancy.

On completion, any exposed surface should be thoroughly cleaned and hands and face washed.

Guidelines for the safe handling of anti-neoplastic agents:

- Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents
- This should be performed in a designated area.
- Adequate protective gloves, face mask and protective clothes should be worn.
- Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. In the event of contact with the eyes, wash with water and/or saline.
- The cytotoxic preparation should not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc...) used to reconstitute cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polyethylene bags and incinerating at a temperature of 1,000^{oC}.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

Preparation of the solution for infusion

The product must be diluted before use, with glucose solution 50 mg/ml or sodium chloride solution 9 mg/ml, to concentrations as low as 0.5 mg/ml. The carboplatin in the vial prior to dilution is at strength 10 mg/ml. The dilutions should be used within 24 hours once diluted with glucose solution 50 mg/ml or sodium chloride solution 9 mg/ml and stored at 2°C to 8°C.

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

Disposal

Any unused medicinal product, infusion solution or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1897/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 4th October 2013

10 DATE OF REVISION OF THE TEXT