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

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless to pale yellow solution, free from visible particles.

pH- 5.0 to 7.0

Osmolality: 200 - 300 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carboplatin is indicated for the treatment of:
1. advanced ovarian carcinoma of epithelial origin in:

- first line therapy
- 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 minutes 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.

Needles or intravenous sets containing aluminium parts that may come in contact with carboplatin injection should not be used for preparation or administration. Aluminium reacts with carboplatin injection 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.

Renal Impairment:
Patients with creatinine clearance values of less than 60 ml/min are at increased risk of 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 accordingto 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.

Elderly patients:
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
Carboplatin should be used by the intravenous route only.

The medicinal product must be diluted prior to infusion. For instructions on dilution of the medicinal product before administration, see section 6.6.

The safety measures for dangerous substances are to be complied with 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 contra-indicated in patients with:

- hypersensitivity to the active substance or to other platinum containing compounds
- severe myelosuppression
- 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

Warnings:
Carboplatin should be administered 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 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.

Haemolytic-uremic syndrome (HUS)
Haemolytic-uremic 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 thrombocytopenia, 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.

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 injection combination therapy with other myelosuppressive forms of treatment 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.

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

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

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.

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. 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). Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds (see section 4.5).

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

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.

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. Infrequent allergic reactions to carboplatin have been reported, e.g. erythematous rash, fever with no apparent cause or pruritus. Rarely anaphylaxis, angio-oedema and anaphylactoid reactions including bronchospasm, urticaria and facial oedema have occurred. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see section 4.3 and section 4.8).
Patients should be observed carefully for possible allergic reactions and managed with appropriate supportive therapy, including antihistamines, adrenaline and/or glucocorticoids.

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.

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

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 a significant extent within weeks of stopping these high doses.

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).

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.

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. Patient 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.

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).

Vaccinations
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.

Other
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.
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.

Aluminium containing equipment should not be used during preparation and administration of carboplatin (see section 6.2). Aluminium 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 mortality (see section 4.3.).

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 exist (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.

Concomitant use to be taken into consideration

- Chelating agents - decreasing effect of carboplatin
- 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 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 anticoagulativetreatment 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 with concomitant treatment of warfarin with Carboplatin, as increased INR hasbeen 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. No controlled studies in pregnant women have been conducted.

If this drug is used during pregnancy, or if the patient becomes pregnant while treated with 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.

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

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 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 treated with 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 must 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 (≥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*
	Not known	Pneumonia
Neoplasms, benign, malignant and unspecified (inclcysts and polyps)	Uncommon	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Rare	Febrile neutropenia
	Not known	Hemolytic-uraemic syndrome, bone marrow failure,
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
	Rare	Anaphylaxis, anaphylactic shock, angio-oedema
Metabolism and nutrition disorders	Very common	Hyperuricaemia
	Rare	Hyponatraemia, anorexia
	Not known	Dehydration, Tumor lysis syndrome
Nervous system disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Very rare	Cerebrovascular accident*
	Not known	Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Eye disorders	Common	Visual disturbance. Rare cases of loss of vision
	Rare	Optic neuritis
Ear and labyrinth disorders	Very common	Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss
	Common	Tinnitus, ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Very rare	Cardiac failure*
	Not known	Kounis syndrome
Vascular disorders	Very rare	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
Hepatobiliary disorders	Rare	Severe hepatic dysfunction
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder, urticaria, rash, erythematous, pruritus
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal disorder

Renal and urinary disorders	Common	Urogenital disorder
General disorders and administration site conditions	Very common	Asthenia
	Common	flu-like syndrome
	Uncommon	Fever and chills without evidence of infection, 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).

Haematologic
Myelosuppression is the dose-limiting toxicity of carboplatin injection. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm 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.

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 a course without any clinical symptoms.

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 (ie, 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.p>

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

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. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. It is not clear whether an appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41-59 ml/min) or severe renal impairment (creatinine clearance 21-40 ml/min). Carboplatin is contraindicated in patients with a creatinine clearance at or below 20 ml/min.

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.

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 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/microliter after 8-14 days (median: 11) and the thrombocytes values of ≥ 25.000/microliter 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, 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 and auditory function. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological side effects. Use of higher than recommended doses of carboplatin injection has been associated with loss of vision (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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.

Mechanism of action
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
Paediatric patients: safety and efficacy in children has not been established *(see section 4.2, 4.4 and 5.2)*.

5.2 Pharmacokinetic properties

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

Biotransformation
Following the 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 primarily 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.

Elimination
Carboplatin clearance has been reported to vary by 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.

Linearity/non-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.

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 Injections

6.2 Incompatibilities

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

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

6.3 Shelf life

Unopened
2 years

After dilution
Chemical and physical in-use stability has been demonstrated after dilution in Glucose 5 % for 96 hours at 2ºC to 8˚C and 20˚C to 25˚C.

Chemical and physical in-use stability has been demonstrated after dilution in Sodium Chloride 0.9% for 24 hours at 2˚C to 8˚C and 8 hours 20˚C to 25˚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 2ºC to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C. Keep vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section.

6.5 Nature and contents of container

5 ml/15 ml/45 ml/60 ml concentrate for solution in a colorless Ph Eur. Type I glass vial with chlorobutyl or bromobutyl rubber closure with green/blue/red and yellow aluminium flip–off seal for each presentation. Each vial may be shrink wrapped and may/may not be packed in plastic container

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.

Instruction for dilution
The product must be diluted prior to infusion, with 5 % Glucose for Injection or 0.9 % Sodium Chloride for Injection, to concentrations as low as 0.5 mg/ml (500 micrograms/ml).

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.

Guidelines for the safe handling of anti-neoplastic agents:

1. Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents.
2. This should be performed in a designated area.
3. Adequate protective gloves, face mask and protective clothes should be worn.
4. 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.
5. The cytotoxic preparation should not be handled by pregnant staff.
6. 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 polythene bags and incinerating at a temperature of 1,000 °C.
7. The work surface should be covered with disposable plastic-backed absorbent paper.
8. 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.

Disposal
Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
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8 MARKETING AUTHORISATION NUMBER

PA2059/032/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th February 2012

Date of last renewal: 26th January 2017

10 DATE OF REVISION OF THE TEXT

February 2024