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, colorless to pale yellow solution free from visible particle and with a pH between 5.0 – 7.0.

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/m² 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/m². 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/mm³ and the platelet count is at least 100,000 cells/mm³.

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 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.

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 Patients:

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 or to any of the excipients listed in section 6.1
- 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.)
- a history of severe allergic reaction to carboplatin or other platinum containing compounds.

Dosage adjustment may allow use in the presence of mild renal impairment (see section 4.2).

4.4 Special warnings and precautions for use

Warnings:

Myelosuppression

Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the drug. Therefore, in patients with abnormal renal function, or who are receiving concomitant therapy with nephrotoxic drugs, myelosuppression, especially thrombocytopenia, may be more severe and prolonged.

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

Peripheral blood counts (including platelets, white blood cells and haemoglobin) should be followed during and after therapy. Combination therapy with other myelosuppressive drugs may require modification of dosage/timing of schedules in order to minimise additive effects.

Carboplatin courses should not, in general, be repeated more frequently than every 4 weeks in order to ensure that the nadir in blood counts has occurred and there has been recovery to a satisfactory level.

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 should be discontinued.

Precautions

Carboplatin should be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Peripheral blood counts, renal and hepatic function tests should be monitored closely. Blood counts should be performed prior to commencement of carboplatin therapy and at weekly intervals thereafter. 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 treatment. This will monitor toxicity and help determine the nadir and recovery of haematological parameters and assist in subsequent dosage adjustments. . 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. Lowest levels of platelets are seen between days 14 and 21 of initial therapy. A greater reduction is seen in patients who previously received extensive myelosuppressive chemotherapy.

Lowest levels of white cells occur generally between days 14 and 28 of initial therapy. If neutrophil levels fall below 2000 cells/mm^3 or platelets are less than 100,000 cells/mm^3 then postponement of carboplatin therapy until bone barrow recovery is evident, should be considered. This recovery usually takes 5 to 6 weeks. Transfusions may be necessary and dosage reductions recommended for subsequent treatment..

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.

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.

Hepatic and/or renal insufficiency

Renal and hepatic function impairment may be encountered with carboplatin. Very high doses of carboplatin ($\geq$ 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).

Renal Toxicity

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. 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 severe alteration in renal function test, 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.

Hypersensitivity Reactions As with other platinum-based drugs, allergic reactions appearing most often during administration may occur and necessitate discontinuation of infusionand 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.

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).

Kounis syndrome can develop in patients with and without cardiac risk factors, and may be presented with a combination of cardiac and allergic symptoms, or as standalone. Coronary vasospasm may be eliminated with steroids, antihistamines in addition to spasmolytics treatment

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).

Hearing Functions

Auditory defects have been reported during carboplatin therapy. Ototoxicity may be more pronounced in children and is more likely seen in patients previously treated with Cisplatin. 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. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides) (see Section 4.5).

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.

Carboplatin dosing

Some subgroups of patients (i.e. age 40-59, BMI 20-25) are at particular risk of undertreatment if GFR is estimated using Cockroft Gault Formula. Being an accurate estimation of GFR crucial for treatment with curative intent, in such cases GFR determination using a measured standard method (inulin, 51Cr-EDTA, 99mTc-DTPA, 125I-iothalamate or iohexol) should be preferred when feasible.

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 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 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

Women of childbearing potential
Women of childbearing potential should be advised to avoid becoming pregnant while receiving carboplatin and to use effective contraception during treatment with carboplatin and for at least 7 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with carboplatin and for at least 4 months after the last dose.

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.

Safe use of carboplatin in pregnancy has not been established. Both men and women receiving carboplatin should be informed of the potential risk of adverse effects on reproduction (see section 5.3). 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 of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during carboplatin therapy.. Carboplatin should 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.

Breast feeding
Carboplatin and its active metabolites have been identified in human milk of treated mothers. To avoid possible harmful effects in the infant, breast-feeding must be stopped during carboplatin therapy and for 1 month following last dose or discontinue treatment, taking into account the importance of the drug to the mother.

Fertility
Male and female fertility may be impacted by treatment with carboplatin (see section 5.3). Both men and women should seek advice for fertility preservation before treatment with carboplatin.

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).

MedDRA Organ system classes	Very common	Common	Uncommon	Rare	Very rare	Not Known
Infections and infestations		Infections*				Pneumonia
Neoplasms, benign and malignant (including cysts and polyps)						Treatment related secondary malignancy
Blood and lymphatic	Thrombocytopenia,	Haemorrhage*				Bone marrow

system disorders	neutropenia, leukopenia, anaemia					failure, febrile neutropenia, haemolytic-uraemic syndrome (HUS), haemolytic anaemia (sometimes fatal)
Immune system disorders		Hypersensitivity, anaphylactoid type **reaction,** Anaphylaxis, anaphylactic shock,				
Metabolism and nutrition disorders	Hyperuricaemia			Hyponatraemia, anorexia		Dehydration, anorexia, hyponatraemia, Tumor lysis syndrome
Nervous system disorders		Neuropathy peripheral, paraesthesia, **decrease of osteotendinous reflexes, sensory disturbance, dysgeusia**				Cerebrovascular accident*, encephalopathy, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Eye disorders		Visual disturbance (incl. rare cases of loss of vision).				
Ear and labyrinth disorders	Subclinical decrease in hearing acuity,	Ototoxicity, Tinnitus, hearing loss				
Cardiac disorders		Cardiovascular disorder*			Cardiac failure*	Cardiac failure* Kounis syndrome
Vascular disorders						Embolism*, hypertension, hypotension, venoocclusi

						ve disease (fatal)
Respiratory, thoracic and mediastinal disorders		Respiratory disorder, interstitial lung disease, bronchospasm				
Gastrointestinal disorders	Vomiting, nausea, abdominal pain	Diarrhoea, constipation, mucous **membrane disorder**				Stomatitis, pancreatitis
Hepatobiliary disorders				Severe hepatic dysfunction		
Skin and subcutaneous tissue disorders		Alopecia, skin disorder,				**urticaria, rash, erythematous,pruritus**
Musculoskeletal and connective tissue disorders		Musculoskeletal disorder				
Renal and urinary disorders		Urogenital disorder				
General disorders and administration site conditions		Asthenia				Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise
Investigations	Creatinine renal clearance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased,	Blood bilirubin increased, blood creatinine increased, blood uric acid increased				

	liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased.					

* Fatal in <1%, fatal cardiovascular events in <1% included cardiac failure, embolism, and cerebrovascular accident combined.

***Blood and lymphatic system disorders*:**
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.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Secondary acute 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).

***Respiratory, thoracic and mediastinal disorders*:**
Pulmonary fibrosis has been reported very rarely, manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see General disorders below).

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, are readily controlled or prevented with antiemetics and disappear within 24 hours. Vomiting is more likely when carboplatin injection is given in combination with other emetogenic compounds.
The other gastrointestinal complaints corresponded to pain in 8% of patients, diarrhoea, and constipation in 6 % of patients. Cramps have also been reported.

Nervous system disorders:
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. Parasthesias present prior to treatment, especially if caused by cisplatin, may persist or worsen during carboplatin therapy (see section 4.4).

Eye disorders:
Visual disturbances, including sight loss, are usually associated with high dose therapy in renally impaired patients.

Ear and labyrinth disorders:
A subclinical decrease in hearing acuity in the high frequency range (4000-8000 Hz), determined by audiogram, occurred in 15% of patients. Very rare cases of hypoacusia have been reported.

Tinnitus was also commonly reported. Hearing loss as a result of cisplatin therapy may give rise to persistent or worsening symptoms. At higher than recommended doses, in common with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin is administered.

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)

Fever with no apparent cause has also been reported.
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.

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

Skin and subcutaneous tissue disorders:
Erythematous rash, fever and pruritis have been observed. These were reactions similar to those seen after cisplatin therapy but in a few cases no cross-reactivity was present.

Investigations:
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.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 hematological 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 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. No overdosage occurred during clinical trials. If necessary, however, the patient may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment.

Reports of doses up to 1600mg/m^2 indicate patients feeling extremely ill with diarrhoea and alopecia developing. 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

Safety and efficacy in children has not been established (see section 4.2, 4.4 and 5.2).

5.2 Pharmacokinetic properties

Absorption

After a 1-hour infusion (20-520mg/m^2), plasma levels of total platinum and free (ultra filterable) 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. Total platinum has the same initial half-life, while the terminal half-life is longer (approx. 5 days). All free platinum is in the form of carboplatin in the first 4 hours after administration.

Distribution

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. Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin. 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 is excreted primarily by glomerular filtration in urine, with recovery of 65% of a dose within 24 hours. Most of the drug is excreted within the first 6 hours. Approximately 32% of a given dose of carboplatin is excreted unchanged. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

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

3 years.

<u>After dilution</u>

Carboplatin 10 mg/ml concentrate for solution for infusion may be further diluted in Glucose 5% and administered as an intravenous infusion. Chemical and physical in-use stability has been demonstrated for 56 days to final concentrations of 0.2 mg/ml

and 3.5mg/ml when stored at 2-8 °C in non-PVC (polyolefin) infusion bags when protected from light.

Carboplatin 10 mg/ml concentrate for solution for infusion may also be further diluted in Sodium Chloride 0.9% and administered as an intravenous infusion. Chemical and physical in-use stability has been demonstrated in final concentrations of 0.2 mg/ml and 3.5mg/ml when stored 24 hours at 2-8°C and up to 8 hours at 22°C in non-PVC (polyolefin) infusion bags when protected from light.

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 30°C.

Keep the vials in outer carton in order to protect from light.

'For storage conditions of the diluted medicinal product, see section 6.3'

6.5 Nature and contents of container

Carboplatin is supplied in 5 ml, 15 ml, 45 ml and 60 ml concentrate solution in type-I modulated clear glass vial of 5, 20 or 100 ml with grey bromobutyl rubber stopper and sealed with aluminum seal having polypropylene disc.

1 vial with 5 ml concentrate for solution for infusion contains 50 mg of carboplatin.

1 vial with 15 ml concentrate for solution for infusion contains 150 mg of carboplatin.

1 vial with 45 ml concentrate for solution for infusion contains 450 mg of carboplatin.

1 vial with 60 ml concentrate for solution for infusion contains 600 mg of carboplatin.

Pack size: 1 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product is for single dose 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.

The compatibility of Carboplatin solution for infusion has been tested with representative, Non-PVC (Polyolefin) based administration sets.

Disposal

“Remnants of the medicinal product as well as all materials that have been used for reconstitution, for dilution and administration must be destroyed according to hospital standard procedures applicable to antineoplastic agents, which due regard to current laws related to the disposal of hazardous waste”.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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