SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin Venus Pharma 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 15 ml vial contains 150 mg carboplatin

Each 45 ml vial contains 450 mg carboplatin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless to faintly yellow solution.

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

Posology:

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 IV dose administered as 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

5-7mg/ml .min	single agent Carboplatin	Previously untreated
4-6 mg/ml .min	single agent Carboplatin	Previously treated
4-6mg/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.

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.

Initial dosage should be reduced by 20-25% in patients with risk factors such as previous myelosuppressive therapy and or poor performance status (ECOG-Zubrod 2- 4 or Karnofsky below 80).

Determination of haematologic nadir by weekly blood counts during initial courses is recommended for future dosage adjustment and scheduling of carboplatin.

Impaired renal function:

In patients with impaired renal function, dosage of carboplatin should be reduced (refer to Calvert formula) and haematological nadirs and renal function monitored.

Patients with creatinine clearance below 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 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:

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

Paediatric population

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

Method of administration:

Carboplatin should be administrated by the intravenous route only

The medicinal product must be diluted prior to infusion, see section 6.6

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 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:

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- patients with severe myelosuppression
- patients with pre-existing severe renal impairment (with creatinine clearance of ≤ 30 ml per minute) unless in the judgment of the physician and patient, the possible benefits of treatment outweigh the risks. Dosage adjustment may allow uses in the presence of mild renal impairment (see section 4.2)
- patients with bleeding tumors
- concomitant use with yellow fever vaccine (see section 4.5)
- patients with a history of severe allergic reaction to other platinum containing compounds.

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 duration of toxicity is likely to be greater in patients who have received extensive prior treatment carboplatin or 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. Myelosuppressive effects may be additive to those of concomitant chemotherapy.

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 minimize 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.

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 interrupted and dose modification or discontinuation should be considered.

Allergic reactions

As with other platinum-based drugs, allergic reactions appearing most often during administration may occur and necessitate discontinuation of infusion. Patients should be observed carefully and an appropriate symptomatic treatment (including antihistamines, adrenaline and/or glucocorticoids) must be initiated in such cases. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

The vial stopper contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Hypersensitivity Reactions

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).

Renal Toxicity

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

Precautions:

Carboplatin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

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.

Haematologic Toxicity

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 and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. Lowest levels of platelets are generally 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/mm3 or platelets are less than 100,000 cells/mm3 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, however rarely requires a transfusion.

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.

Haemolytic-uraemic syndrome (HUS)
Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant 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.

Venoocclusive liver disease

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

Tumour lysis syndrome (TLS)

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. 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.

Renal toxicity

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

Neurologic Toxicity

Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decreases in 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 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)

Elderly

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.

Ototoxicity

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 pediatric patients. A long-term audiometric follow-up in this population is recommended.

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

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

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Due to the increase of thrombotic risk in cases of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulabilty during diseases, and the possibility of interaction between oral anticoagulants and anticancer chemotherapy, may require an increase in frequency of INR monitoring if a patient is treated with oral anticoagulants.

Concomitant use contraindicated

Yellow fever vaccine: risk of fatal disease (see section 4.3).

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis).

- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

- Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.

- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to Carboplatin induced changes in renal clearance.

- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimize the additive myelosuppressive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Carboplatin can cause foetal harm when administered to a pregnant woman. Carboplatin 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). **Women of childbearing potential should be advised to avoid becoming pregnant by using effective contraception and** 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

It is not known whether Carboplatin is excreted in breast milk.

To avoid possible harmful effects in the infant, breast-feeding must be stopped during carboplatin therapy.

Fertility

Gonadal suppression resulting in amenorrhoea 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 functional impairment is complicated by the frequent 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 advised not to father a child during treatment and up to 6 months afterwards. Male patients should seek advice about sperm preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

4.7 Effects on ability to drive and use machines

No studies of 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 of 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.

Tabulated list of adverse reactions

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, <1/10)
Uncommon (≥1/1,000,
≤1/100) Rare (≥1/10,000,
≤1/1,000)

Very rare (<1/10,000),

Not known (cannot be estimated from the available data)

System Organ Class	**Frequency**	**MedDRA Term**
Neoplasms, benign and malignant and unspecified (incl cysts and polyps)	Not known	Treatment related secondary malignancy
Infections and infestations	Common	Infections*
	Not known	Pneumonia
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Rare	febrile neutropenia,
	Not known	Bone marrow failure, haemolytic-uraemic syndrome, haemolytic anaemia
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
	Rare	Angioedema
Metabolism and nutrition disorders	Rare	hyponatraemia
	Not known	Dehydration, anorexia, Tumor lysis syndrome
Nervous system disorders	Common	Peripheral neuropathy , paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia

	Not known	Cerebrovascular accident* encephalopathy, Reversible Posterior Leukoencephalopathy Syndrome (RPLS).
Eye disorders	Common	Visual disturbance (incl. rare cases of loss of vision)
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Not known	Cardiac failure* Kounis syndrome
Vascular disorders	Not known	Embolism*, hypertension, hypotension venoocclusive disease (fatal)
Respiratory, thoracic and mediastinal disorders	Common	Respiratory disorder, interstitial lung disease, bronchospasm
Gastrointestinal disorders	Very common	Vomiting, nausea, abdominal pain
	Common	Diarrhoea, constipation, mucous membrane disorder
	Not known	Stomatitis, pancreatitis.
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal disorder
Renal and urinary disorders	Common	Urogenital disorder
General disorders and administration site conditions	Common	Asthenia
	Not known	Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise

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.

Description of selected adverse reactions

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

Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65.

At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than 50 x 10^9/l, occurs in about a third of the patients. The nadir usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy.

Leukopenia has also occurred in approximately 20% of patients but its recovery from the day of nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy. Neutropenia with granulocyte counts below 1 x 10^9/l occurs in approximately one fifth of patients. Haemoglobin values below

9.5 mg/100ml have been observed in 48% of patients with normal base-line values.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.

Respiratory, thoracic and mediastinal disorders

Pulmonary fibrosis manifested by tightness of the chest and dyspnoeahas been reported very rarely. This 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, are readily controlled or prevented with antiemetics and disappear within 24hours. 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. In patients who have developed hearing loss related to cisplatin, the hearing impairment may worsen during carboplatin treatment. . 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.

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 half of the patients.

In a limited series of patients receiving very high dosages of carboplatin injection and autologous bone marrow transplantation, severe elevation of liver function tests has occurred.

Cases of an acute, fulminant liver cell necrosis occured after high-dose 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.

Immune system disorders

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

Fever with no apparent cause has also been reported.

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.

Cardiac disorders

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

General disorders and administration site conditions

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

Fever, chills and mucositis have occasionally been observed.

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 at www.mhra.gov.uk/yellowcard.

4.9 Overdose

No overdosage occurred during clinical trials.

Symptoms:

Symptoms may include myelosuppression, renal, hepatic and auditory function impairment. Reports of doses up to 1600mg/m2 indicate patients feeling extremely ill with diarrhoea and alopecia developing. Use of higher than recommended doses of carboplatin has been associated with loss of vision (see section 4.4).

Management:

There is no known antidote for carboplatin overdosage. If necessary, however, the patient may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Platinum compounds ATC code: L01XA02

Carboplatin, like Cisplatin, interferes with DNA intrastrand and interstrand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.

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

5.2 Pharmacokinetic properties

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

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. After a 1-hour infusion (20-520 mg/m2), plasma levels of total platinum and free (ultrafilterable) platinum decay biphasically following first order kinetics. For free platinum, the initial phase (t alpha) half life is approximately 90 minutes and the later phase (t beta) half life approximately 6 hours. All free platinum is in the form of carboplatin in the first 4 hours after administration.

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.

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.

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

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

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or intravenous sets containing aluminium parts that may come into contact with carboplatin should not be used for preparation or administration of carboplatin. Precipitation can lead to a reduction of the antineoplastic activity.

6.3 Shelf life

Unopened:

2 years

After dilution

In use: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 30 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not refrigerate or freeze.

Keep vial in the 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 20 ml or 50 ml Type I moulded glass vials closed with omniflex rubber stoppers and sealed with aluminium flip-off seals

Each 20 ml vial contains 150 mg/15 ml of carboplatin (10 mg/ml)

Each 50 ml vial contains 450 mg/45 ml of carboplatin (10 mg/ml)

Pack size of 1 vial.

Not all presentations listed above may be marketed.

6.6 Special precautions for disposal

This product is for single use only.

Contamination

In the event of contact of carboplatin with eyes or skin, wash affected area with copious amounts of water or normal saline. A bland cream may be used to treat transient stinging of skin. Medical advice should be sought if the eyes are affected.

Disposal

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

Dilution

The product must be diluted prior to infusion, with 5% glucose solution or 0.9% sodium chloride solution, to concentrations as low as 0.5 mg/ml.

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 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. Liquid waste may be flushed with copious amounts of water.

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.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 34985/0014

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