SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin 10 mg/ml Concentrate for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials containing 50 mg, 150 mg, 450 mg and 600 mg of carboplatin (cis-diammine (1,1-cyclobutanedicarboxylato)platinum) as a 10 mg/ml solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Carboplatin 10 mg/ml concentrate for solution for infusion is a clear, colourless to faintly yellow solution, free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carboplatin is indicated for the treatment of
1. Advanced ovarian carcinoma of epithelial origin in:
- first line therapy
- second line therapy, after other treatments have failed.
2. Small cell carcinoma of the lung, in association with other chemotherapeutic agents.

4.2 Posology and method of administration

Posology
The recommended dosage of carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m^2 as a single i.v. dose administered by a short term (15 to 60 minutes) infusion. 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.

For patients who experience no hematologic toxicity (i.e., platelet and neutrophil counts remain above 100,000 and 2,000/mm^3 respectively) with the previous dose, dosage of carboplatin in single or combination (e.g., cyclophosphamide) therapy may be increased by 25%.

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 haematologic nadir by weekly blood count during the initial courses of treatment with carboplatin is recommended for dosage adjustment for subsequent courses of therapy.

Dose recommendations according to AUC

Alternatively, the initial dose can be calculated using the Calvert formula. This is based on renal function (glomerular filtration rate [GFR]). Thereby, the risk of underdosing or overdosing due to individual differences in renal function is reduced.
Calvert formula: total dose (mg) = (target AUC*) × (GFR + 25)
Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m2.

***target AUC**	**planned chemotherapy**	**pre-treatment status**
5-7 mg/ml min	single agent carboplatin	no prior therapy
4-6 mg/ml min	single agent carboplatin	prior therapy
4-6 mg/ml min	carboplatin plus cyclophosphamide	no prior therapy

The Calvert formula should not be used in heavily pre-treated patients who have already received one of the following regimens:
- mitomycin C
- nitrosourea
- doxorubicin/cyclophosphamide/cisplatin combination chemotherapy
- combination therapy including 5 or more cytostatic agents
- radiation therapy ≥ 5000 rad focused on a field of 20 × 20 cm or more than one field.

Renal Impairment

Patients with creatinine clearance values 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 in patients with creatinine clearance of 15 mL/min or less to permit a recommendation for treatment.

All of the above dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression.

The optimal use of carboplatin in patients presenting with renal impairment requires frequent monitoring of haematological nadirs, electrolytes and renal function.

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

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

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.

Method of administration
Carboplatin should be used by the intravenous route only. The solution for infusion is administered by a short term (15 to 60 minutes) infusion.

Dilution
The product may be diluted with 5% Glucose for Injection or 0.9% Sodium Chloride for Injection to concentrations as low as 0.5 mg/ml (500 micrograms/ml).

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

The safety measures for dangerous substances are to be complied with 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 (see section 6.6).

4.3 Contraindications

- Hypersensitivity to the active substance, other platinum containing compounds or to any of the excipients listed in section 6.1.
- 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.
- Severe myelosuppression.
- Bleeding tumours.
- Concomitant use with yellow fever vaccine (see section 4.5).
- During breast-feeding.

4.4 Special warnings and precautions for use

Carboplatin should be used only by physicians experienced with cancer chemotherapeutic drugs. 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.

Hematologic toxicity
Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood counts should be monitored during carboplatin treatment frequently and, in case of toxicity, until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent carboplatin and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin 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 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.

Anemia is frequent and cumulative requiring very rarely a transfusion.

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

Severity of myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial carboplatin dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.
Carboplatin combination therapy with other myelosuppressive forms of treatment must be planned very carefully with respect to dosages and timing in order to minimise additive effects.

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

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

Nausea and vomiting
Carboplatin can cause nausea and vomiting. Pre-medication with anti-emetics and slower drug administration have been reported to be useful in reducing the incidence and intensity of these effects.

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

Hypersensitivity reactions
As with other platinum-based drugs, allergic reactions appearing most often during perfusion may occur and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).
There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

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).

Neurologic toxicity
Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decrease of osteotendinous reflexes, its frequency is increased in patients older than 65 years and/or in patients previously treated with cisplatin. Monitoring and neurological examinations should be carried out at regular intervals.
Visual disturbances, including loss of vision, have been reported after the use of carboplatin 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.

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).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) have been reported in patients receiving carboplatin in combination chemotherapy. RPLS is a rare, reversible after treatment discontinuation, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

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

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

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

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Men and women should use effective methods of contraception (see section 4.6).

Paediatric population
Safety and efficacy of carboplatin in paediatric patients have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy, require, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the control of the INR monitoring.

Concomitant use contraindicated
- Yellow fever vaccine: risk of generalised vaccinal disease mortal (see section 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 lose of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.
- Complex forming compounds: Concomitant administration of carboplatin and complex forming compounds should be avoided as theoretically, the antineoplastic effects of carboplatin might be decreased. However, in animals and clinically, the antineoplastic effects of carboplatin were not influenced by diethylthiocarbamate.

Concomitant use to take into consideration
- Cyclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Nephrotoxic and/or ototoxic drugs: The concomitant use of carboplatin with nephrotoxic and/or ototoxic drugs (e.g. aminoglycoside antibiotics, loop diuretics) should be taken into account due to the cumulative nephrotoxicity and ear toxicity, particularly in renal failure patient.
- Myelosuppressive compounds: Myelosuppression is worsened by therapy combining carboplatin with other compounds that are myelosuppressive.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Due to the genotoxic potential of carboplatin (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with carboplatin and for 6 months following completion of treatment.
Men are recommended to use effective contraceptive measures and not to father a child while receiving carboplatin and for 3 months following completion of treatment.

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. If this medicinal product is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to the foetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

For women who are pregnant or become pregnant during therapy, genetic counselling should be provided.

Breastfeeding
Carboplatin and/or its metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. Breastfeeding should be discontinued during treatment with carboplatin.

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 medicinal products.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single agent carboplatin and post-marketing experience.
The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100 to

< 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), and 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 (incl. cysts and polyps)	Not known	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, hemolytic-uraemic syndrome
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia, tumor lysis syndrome
Nervous system disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Not known	Cerebrovascular accident*, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)[#]
Eye disorders	Common	Visual disturbance, rare cases of loss of vision
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Not known	Cardiac failure*, Kounis syndrome
Vascular disorders	Not known	Embolism*, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory disorder, interstitial lung disease, bronchospasm
Gastrointestinal disorders	Very common	Vomiting, nausea, abdominal pain
	Common	Diarrhoea, constipation, mucous membrane disorder
	Not known	Stomatitis, pancreatitis[#]
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal disorder
Renal and urinary disorders	Common	Urogenital disorder
General disorders and	Common	Asthenia

System Organ Class	Frequency	MedDRA Term
administration site conditions	Not known	Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise
Investigation	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.
# based on the post-marketing experience

Description of selected adverse reactions

Blood and lymphatic system disorders

Myelosuppression is the dose-limiting toxicity of carboplatin. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of patients, neutropenia with granulocyte counts below 1,000/mm^3 in 18% of patients, and leukopenia with WBC counts below 2,000/mm^3 in 14% of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin with other myelosuppressive compounds or forms of treatment. Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired kidney function. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia. These effects, although usually reversible, have resulted in infectious and hemorrhagic complications in 4% and 5% of patients given carboplatin, respectively. These complications have led to death in less than 1% of patients. Anaemia with haemoglobin values below 8 g/dL has been observed in 15% of patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to carboplatin.

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. 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 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.

Nervous system disorders
Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4% of patients administered carboplatin. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin, appear to be at increased risk.
Clinically significant sensory disturbances (i.e., visual disturbances and taste modifications) have occurred in 1% of patients.
The overall frequency of neurologic side effects seems to be increased in patients receiving carboplatin in combination. This may also be related to longer cumulative exposure.

Ear and labyrinth disorders
Auditory defects out of the speech range with impairments in the high-frequency range (4,000-8,000 Hz) were found in serial audiometric investigations with a frequency of 15%. Very rare cases of hypoacusia have been reported.
In patients with a hearing organ predamaged due to cisplatin, a further exacerbation in the hearing function sometimes occurs during treatment with carboplatin.

Renal and urinary disorders
When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin 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. 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 therapy.

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

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 and autologous bone marrow transplantation, severe elevation of liver function tests has occurred.
Cases of an acute, fulminant liver cell necrosis occurred after high-dosed administration of carboplatin.

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.

Other undesirable effects
Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.
Alopecia, fever and chills, mucositis, asthenia, malaise as well as dysgeusia have occasionally been observed.
In isolated cases, a haemolytic-uraemic syndrome occurred.
Isolated cases of cardiovascular incidents (cardiac insufficiency, embolism) as well as isolated cases of cerebrovascular accidents have been reported.
Cases of hypertension have been reported.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known antidote for carboplatin overdosage

No overdosage occurred during clinical trials. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal and auditory function. Use of higher than recommended doses of carboplatin has been associated with loss of vision (see section 4.4).

Symptomatic measures should be taken to sustain the patient through any period of toxicity that might occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic and immunomodulating agents, Platinum compounds, ATC code: L01XA 02.

Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks.

Paediatric population:
Safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties

Following administration of carboplatin in man, linear relationship exists 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.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of carboplatin reported values for the terminal elimination half-lives of free ultrafilterable 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 clearance of free ultra-filterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

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

In animals, symptoms of acute toxicity consisted of emesis, anorexia, adipsia, postural changes, troubled respiration and diarrhoea. Symptoms of long term toxicity included myelosuppression, depression of the immune system, necrosis of the mucosae of the gastrointestinal system, reduction in body weight, increases in the levels of enzymes of the liver and blood urea nitrogen, bleeding, bacterial infection, bronchitis, damage to the retinae, mild ototoxicity and damage to the kidneys. Carboplatin induces cytogenetic effects suggesting that it is likely to be mutagenic/carcinogenic.

Reproduction and teratology: increases in toxicity to the mother and foetus were observed in a dose dependent fashion. Changes to the foetuses included alterations to the weight and length of the body, increases in the incidences and severity of abnormalities to the skeleton and internal organs. At doses higher than 4 mg/kg/day, spontaneous abortion of most of the foetuses and severe deformities to the skeletons of surviving foetuses were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Water for Injection.

6.2 Incompatibilities

This medicinal product should not be mixed with other medical products except those mentioned in sections 4.2 and 6.4.
This product should not be used with aluminium-containing infusion assemblies, syringes and injection needles. The antineoplastic activity can be reduced.

6.3 Shelf life

2 years

After first opening

Immediate and single use.

After reconstitution, dilution

When reconstitution/dilution is carried out under validated aseptic conditions, and if justified, the product may be stored for a maximum period of 24 hours (at 2 – 8°).

6.4 Special precautions for storage

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

Dilution: The product may be diluted with 5% Glucose for Injection, or 0.9% Sodium Chloride for Injection, to concentrations as low as 0.5 mg/ml (500 micrograms/ml).

When diluted as directed, carboplatin solutions should be used within three hours when stored at room temperature (15 - 25°C) protected from light or within 24 hours when stored at 2 - 8°C if dilution is carried out under validated aseptic conditions. Since no antibacterial preservatives are contained in the formulation, it is recommended that any carboplatin solution be discarded three hours after dilution if stored at room temperature protected from light or after 24 hours, if stored under refrigeration. This product is for single dose use only.

6.5 Nature and contents of container

Amber coloured glass vials, USP type I with chlorobutyl, black teflon-coated, grey stoppers and aluminium caps.

5 ml, 15 ml, 45 ml and 60 ml vials containing 10 mg/ml of carboplatin.

Pack sizes:
5 ml vials: 1 vial; 10 vials
15 ml vials: 1 vial; 10 vials
45 ml vials: 1 vial
60 ml vials 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution for infusion must be visually inspected for particulate matter before use.

Guidelines for the safe handling of anti-neoplastic agents:

1. Trained personnel should handle the drug

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 1000°C. Liquid waste may be flushed with copious amounts of water.

Dilution:

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 00289/0847

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/02/1999 / 28/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2026