SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin Hikma 10 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for infusion contains 10mg 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

Solution for infusion.

It is a clear and colorless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of advanced ovarian carcinoma of epithelial origin in:

- first line therapy
- second line therapy, after other treatments have failed

High risk seminoma (stage I) testicular germ cells tumors as adjuvant treatment

Treatment of small cell carcinoma of the lung.

4.2 Posology and method of administration

Posology

Adults

The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m^2, as a single dose during 15 to 60 minutes. Alternatively, the Calvert formula 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 + 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 4 weeks after the previous administration 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 prior myelosuppressive treatment and/or low 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 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 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 an 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.

Paediatric population

Use in children and infants is not recommended due to lack of sufficient data in this area.

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 injection should be used by the intravenous route only.

Injection or intravenous infusion.

Carboplatin may interact with aluminum, forming a black precipitate. Needles, syringes, catheters or IV administration sets containing aluminum should not be used for preparation and administration of Carboplatin in order to avoid interactions.

The safety measures used for preparation and administration of dangerous substances should be applied. Preparation must be carried out byprofessionals who have been trained in the safe use while wearing protective gloves, face mask and protective clothing.

Duration of treatment

The duration of treatment depends on the condition and the clinical protocol used.

4.3 Contraindications

Carboplatin is contraindicated in:

- hypersensitivity to the active substance, other platinum containing compounds 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 less than 30 ml/min) unless in the judgment of the physician and patient, the possible benefits of treatment outweigh the risks. Dosage adjustment may allow use in the presence of mild renal impairment (see section 4.2).
- patients with bleeding tumours
- concomitant use with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Myelosuppression

The severity of myelosuppression is superior in previously treated patients (particularly with cisplatin) and/or impaired renal function. Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the drug. Therefore, in patients with abnormal renal function, with prolonged prior treatment, general malaise or more than 65 years of age, or who are receiving concomitant therapy with nephrotoxic drugs, myelosuppression, especially thrombocytopenia, may be more severe and prolonged.

Parameters of renal function should be assessed before, during and after treatment with carboplatin. The initial dose of carboplatin in these groups of patients, should be appropriately reduced and the effects closely monitored through frequent blood counts between courses (see section 4.2). 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 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.

Patients with severe and persistent myelosuppression present a high risk of infectious complications, including fatal outcomes (see section 4.8). If any of these events occur, administration of carboplatin should be discontinued and treatment modification or discontinuation should be considered.

Haematologic Toxicity

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

Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting.

Peripheral blood counts should be monitored before start of treatment with carboplatin and then at weekly intervals and, in case of toxicity, until recovery is achieved.

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. 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. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. If 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.

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.

Renal toxicity

In patients with impaired renal function, the effect of carboplatin in the hematopoietic system is more pronounced and more prolonged action than in patients with normal renal function. In this risk group, treatment 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. Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

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.

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.

Allergic Reactions

As with other platinum-based drugs, allergic reactions appearing most often during administration may occur and necessitate discontinuation of infusion. In such cases, an appropriate symptomatic treatment must be initiated. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

Neurologic Toxicity

Although peripheral neurologic toxicity is generally common and mild, as well as limited to paresthesia and responsible for 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.

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).

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 pediatric 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. Inactivated virus vaccines may be administered; however, the response to such vaccines may be diminished.

Precautions:

Carboplatin should only be prepared and administered by professionals trained in the safe use of chemotropic agents. Due to the possibility of serious toxic reactions, the patient should be fully informed by the physician of the risks to which it is subject and is expected to remain in constant supervision. Diagnostic and treatment facilities should be readily available to management and possible complications. Blood counts should be performed regularly, as well as renal and hepatic function tests and the drug should be discontinued an abnormal depression of the bone marrow or abnormal renal or liver function is detected.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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.

Concomitant use contraindicated

- Yellow fever vaccine: risk of mortal disease associated to the administration of the vaccine (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), 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.
- Aminoglycosides: concomitant use of Carboplatin with aminoglycosides should be approached with caution because of nephrotoxicity and ototoxicity, particularly in patients with kidney failure.
- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

The concomitant use with nephrotoxic or ototoxic substances may increase or exacerbate renal toxicity of carboplatin, inducing changes in renal clearance.

The combination with other myelosuppressive agents may require changes in dose or in dosing regimens in order to minimize the potentiation of hematological toxicity of carboplatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use of carboplatin in pregnancy has not been established. Carboplatin can cause foetal harm when administered to a pregnant woman. Both men and women receiving carboplatin should be informed of the potential risk of adverse effects on reproduction. Carboplatin has been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis (see section 5.3). No controlled studies in pregnant women have been conducted. 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.

If the medicine is used during pregnancy, or if the patient becomes pregnant while using the medicine, the patient should be advised of the potential risk to the fetus. Women with childbearing potential should avoid pregnancy.

Lactation

It is not known whether carboplatin/metabolites are excreted in breast milk, therefore breast-feeding is not recommended for mothers under therapy with carboplatin, in order to avoid possible harmful effects in the infant. If treatment becomes necessary during the lactation period then breast-feeding must be stopped.

Fertility

Most forms of chemotherapy have been associated with reduction of oogenesis and spermatogenesis and patients using carboplatin should be warned of this possibility. 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 due to 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 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.

Although not reported with carboplatin, this has been reported with other platinum agents. The recovery of fertility after exposure can occur, but is not guaranteed.

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 1893 patients receiving single 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, (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (< 1/10000), and not known (cannot be estimated from the available data).

System Organ Class MedDRA	Frequency	MedDRA Term
Infections and infestations	Common	Infections*
	Not known	Pneumonia
Neoplasms, benign and malignant (including cysts and polyps)	Not known	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Leukopenia, neutropenia,
	Common	thrombocytopenia, anaemia

			Haemorrhage*
		Not known	Haemolytic-uraemic syndrome, bone marrow failure, febrile neutropenia
	Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
		Rare	Angioedema
	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*
	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 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.
		Frequentes	Blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test
			Blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased
			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.

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/mm3 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.

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 immune diseases).

Gastrointestinal disorders:

Vomiting occurs in 65% of patients, in one-third of whom it is severe. Nausea occurs in an additional 15%. 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.Previously treated patients (in particular patients previously treated with cisplatin) appear to be more prone to vomiting. 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.

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.

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. Parasthesias, especially if caused by cisplatin, may persist or worsen during carboplatin therapy (see section 4.4 Special warnings and precautions for use).

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.

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 (4,000-8,000 Hz), determined by audiogram, occurred in 15% of patients. Very rare cases of hypoacusia have been reported.

Tinnitus was also commonly reported. In patients with damaged hearing organs due to cisplatin sometimes occurs a higher rebound in auditory function during treatment with carboplatin. 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, significant hearing loss has been reported in paediatric patients when carboplatin is administered.

Cardiac disorders:

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

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.

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

Immune system disorders:

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

These reactions can be controlled with antihistamines, adrenalin, and/or glucocorticoids. These reactions are similar to those observed after administration of other platinum compounds and may occur minutes after administration. The incidence of allergic reactions may increase with prior exposure to treatment with platinum; however, allergic reactions have been observed upon initial exposure to carboplatin. Patients should be observed closely to detect possible allergic reactions and to control allergic reactions with proper treatment.

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

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

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.

General disorders and administration site conditions:

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

Fever, chills and mucositis have occasionally been observed.

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after authorization of the medicinal product is important, since it allows continuous monitoring of the drug benefit-risk balance. Healthcare professionals are asked to report any suspected adverse reactions via 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

There is no known antidote for carboplatin overdosage. 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 has been associated with loss of vision (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC Code: 16.1.2. Antineoplastic drugs and immunomodulators, cytotoxic alkylating cytotoxic related.

ATC code: L01XA02 Carboplatin

Mechanism of action

Carboplatin is an antineoplastic agent analogue of cisplatin and interferes with DNA intrastrand and interstrand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.

Paediatric population

The safety and efficacy in children has not yet been determined.

5.2 Pharmacokinetic properties

After a 1-hour infusion (20-520 mg/m^2), plasma levels of total platinum and free (ultrafilterable) platinum decay biphasically following first order kinetics. For free platinum, the initial phase (t-α) half life is approximately 90 minutes and the later phase (t-ß) 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 six 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.

Paediatric population

Carboplatin clearance in children has been reported as 3 to 4 times the clearance in adults.

5.3 Preclinical safety data

Carboplatin is embryotoxic and teratogenic in rats. It has been observed adverse effects on male rats fertility, with impaired spermatogenesis. Carboplatin showed mutagenic potential in vivo and in vitro. Although the carcinogenic potential of carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been described as carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Hydrochloric acid (pH adjustment)

Sodium hydroxide (pH adjustment)

6.2 Incompatibilities

Aluminium-containing equipment should not be used with carboplatin (see Section 4.5).

This medicine should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

In use:

Carboplatin may be diluted in Dextrose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. These solutions for infusion are chemically stable for up to 24 hours when stored at 2-8ºC and up to 8 hours when stored at 22ºC. From a microbiological point of view, however, the product should be used immediately.

6.4 Special precautions for storage

Store below 25°C.

Store in the original package in order to protect from light.

Do not freeze.

6.5 Nature and contents of container

Colorless solution packaged in amber glass vials type I of 6, 20, 50 or 100 ml with bromobutyl stopper and aluminum cap.

The medicine is provided in one vial packaging containing 5 ml, 15 ml, 45 ml or 60 ml of solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling:

Carboplatin should be prepared and administered only by professionals who have been trained in the safe use of chemotherapeutic agents.

Contamination

In the event of accidental 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.

In the event of a spillage, it should be asked for support to another specialized person, and with adequate protective measures, the contaminated areas should be cleaned with a sponge kept for that purpose. After the decontamination put all solutions and sponges in a plastic bag, seal and label with the words 'CYTOTOXIC WASTE' and incinerate at 1000ºC.

All the syringes, bottles and materials which have come into contact with carboplatin should be placed in a bag and incinerated as indicated above.

7 MARKETING AUTHORISATION HOLDER

Hikma Farmacêutica (Portugal) S.A.

Estrada do Rio da Mó, nº8, 8A e 8B, Fervença

2705-906 Terrugem SNT

Portugal

8 MARKETING AUTHORISATION NUMBER(S)

PL 15413/0068

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/08/2018

10 DATE OF REVISION OF THE TEXT

10/05/2019