SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carbomedac 10 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg carboplatin.

1 vial of 5 ml concentrate for solution for infusion contains 50 mg of carboplatin.
1 vial of 15 ml concentrate for solution for infusion contains 150 mg of carboplatin.
1 vial of 45 ml concentrate for solution for infusion contains 450 mg of carboplatin.
1 vial of 60 ml concentrate for solution for infusion contains 600 mg of carboplatin.
1 vial of 100 ml concentrate for solution for infusion contains 1000 mg of carboplatin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Carbomedac 10 mg/ml concentrate for solution for infusion is a clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carbomedac concentrate for solution for infusion, alone or in combination with other antineoplastic medicinal products, is indicated for the treatment of the following malignant tumours:

- advanced ovarian carcinoma of epithelial origin
  a. first line therapy
  b. second line therapy, after other treatments have failed.
- small-cell carcinoma of the lung

4.2 Posology and method of administration

Posology

The recommended dose of carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m² as a single intravenous dose administered by a 15 to 60 minutes infusion.
Alternatively, see Calvert formula below:
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	monotherapy carboplatin	previously untreated
4 – 6 mg/ml min	monotherapy carboplatin	previously treated
4 – 6 mg/ml min	carboplatin plus cyclophosphamide	previously untreated

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m².

Calvert's formula should not be used in patients who have received extensive pre-treatment with the following therapy regimens:
- mitomycin C,
- nitrosourea,
- combination therapy with doxorubicin/cyclophosphamide/cisplatin,
- combination therapy with 5 or more agents,
- radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of non-tolerable undesirable effects.

Therapy should not be repeated until four weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm³ and the platelet count is at least 100,000 cells/mm³ (see section 4.4).

Reduction of the initial dose by 20 – 25 % is recommended for those patients who present with risk factors such as prior myelosuppressive treatment (see also section 4.4) and low performance status (ECOG-Zubrod 2 – 4 or Karnofsky below 80).

Determination of the haematological nadir by weekly blood counts during the initial courses of treatment with carboplatin is recommended for future dose adjustment.

Elderly
Dose adjustment, initially or subsequently, may be necessary, dependent on the physical condition of the patient (see section 4.4).

Renal impairment
The optimal use of carboplatin in patients presenting with impaired renal function requires adequate dose adjustments and frequent monitoring of both haematological nadirs and renal function (see section 4.4).

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 dose recommendations:

Baseline creatinine clearance	Initial dose (Day 1)
41 – 59 ml/min	250 mg/m² IV
16 – 40 ml/min	200 mg/m² IV

In patients with creatinine clearance below 30 ml/min, an individual benefit-risk assessment should be performed before initiating therapy with carboplatin.

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 doses 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 dose adjustments according to the regimen and schedule to be adopted (see section 4.4).

Paediatric population
As no sufficient experience of carboplatin use in children is available, no specific dose recommendations can be given.

Method of administration
Carboplatin should be used by intravenous route only.

Precautions to be taken before handling or administering the medicinal product

Dilution:
The product may be diluted with glucose 50 mg/ml (5 %) solution for infusion to concentrations between 0.4 – 2 mg/ml or sodium chloride 9 mg/ml (0.9 %) solution for infusion to a concentration of 2 mg/ml.

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 medicinal product (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance 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 (see section 4.2).
- Severe myelosuppression.
- Bleeding tumours.
- Concomitant use with yellow fever vaccine (see section 4.5).
- Patients with a history of severe allergic reaction to platinum-containing components.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Carboplatin should be used only by physicians in equipped centers who are experienced in the use of cancer chemotherapeutic active substances. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications. Blood counts as well as renal and hepatic function tests must be done regularly and the medicinal product should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Haematological 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/mm³ and the platelet count is at least 100,000 cells/mm³. Transfusions may be necessary and dosage reductions recommended for subsequent treatment.

Anaemia is frequent and cumulative requiring very rarely 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.

Severity of myelosuppression, especially thrombocytopenia, is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial carboplatin doses 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. 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 occur, carboplatin dosing should be interrupted and dose modification or discontinuation should be considered. Carboplatin combination therapy with other myelosuppressive forms of treatment must be planned very carefully with respect to doses and timing in order to minimise additive effects.
Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS) / acute myeloid leukaemia (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.

Allergic reactions

As with other platinum-based active substances, allergic reactions appearing most often during infusion may occur and necessitate discontinuation of the infusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see section 4.3 and section 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

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 dose reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function.
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 paraesthesia 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.

Gastrointestinal effects

Carboplatin induces emesis. The incidence and severity of emesis may be reduced by pre-treatment with antiemetics or by continuous infusion of carboplatin over 24 hours, or by infusion of separate doses over 5 days rather than in a single dose. Selective type 3 (5-HT3) serotoninergic receptor inhibitors (e.g. ondansetron) or substituted benzamides (e.g. metoclopramide) can be particularly effective antiemetics, and, in patients who have refractory or severe emetic effects, combination therapy may be considered.

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 them 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 tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Carboplatin dosing

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

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 the dose (see section 4.2).

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 longterm 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.

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

Appropriate measures to prevent pregnancy should be taken during and for at least 6 months after treatment. Men should also take contraceptive measures during and for at least 3 months after treatment, as chromosomes in human spermatozoa may be destroyed due to the mutagenic potential of carboplatin.
If childbearing is desired, a consultation about sperm preservation is recommended prior to initiation of therapy. Pregnant women should avoid handling carboplatin.

Paediatric population

Safety and efficacy in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Carboplatin is mostly used in combination with antineoplastic drugs with similar cytotoxic effects. Under these circumstances additive toxicity may occur.
When carboplatin is combined with other myelosuppressive drugs, the effect of carboplatin and/or the additionally prescribed drugs on the bone marrow may be enhanced. In patients receiving concomitant treatment with other nephrotoxic substances, there is a higher possibility of a more pronounced and prolonged myelotoxicity due to the decreased renal clearance of carboplatin.
Due to the increase of thrombotic risk in case of tumoural 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 mortality (see section 4.3).

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of systemic, possibly fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis).
- Phenytoin, fosphenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic active substance or risk of toxicity enhancement or loss of efficacy of the cytotoxic active substance due to increased hepatic metabolism by phenytoin.
- Administration together with nephrotoxic or ototoxic drugs, such as aminoglycosides, vancomycin, capreomycin, and diuretics, is not recommended because co-administration could result in increased or enhanced toxicity due to carboplatin-induced changes in renal clearance of these agents, especially in patients with renal insufficiency.

Concomitant use to take into consideration
- Cyclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Loop diuretics: the concomitant use of carboplatin with loop diuretic should be taken into account due to the cumulative nephrotoxicity and ear toxicity.
- The concurrent administration of carboplatin and chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin. However, the antineoplastic effect of carboplatin was not influenced by diethyl-dithiocarbamate in animal experiments or in clinical use.

4.6 Fertility, pregnancy and lactation

Pregnancy

Carboplatin can cause foetal harm when administered during pregnancy. Carboplatin has been shown to be embryotoxic and teratogenic in rats receiving the medicinal product 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 using this medicinal product, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential have to use effective contraception during and for at least 6 months after treatment.

Breast-feeding

It is not fully understood whether carboplatin or its platinum-containing metabolites are excreted in human milk. However, due to the possibility of serious adverse reactions in infants in the event of transfer to human milk, breast-feeding must be discontinued during treatment with carboplatin (see section 4.3).

Fertility

Gonadal suppression resulting in amenorrhoea or azoospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.
Carboplatin is genotoxic. Men of sexually mature age treated with carboplatin are recommended not to father a child during and for at least 3 months after treatment, and to ask advice about spermatic preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

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 about the potential effect of these events on the ability to drive or 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.

Tabulated list of adverse reactions

The following undesirable effects have been observed and reported during treatment with carboplatin with the following frequencies:

Very common (≥ 1/10);
Common (≥ 1/100 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (< 1/10,000);
Not known (cannot be estimated from the available data).

System organ class	Frequency	MedDRA term
Infections and infestations	Common	Infections*
	Not known	Pneumonia

System organ class	Frequency	MedDRA term
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Very rare	Acute promyelocytic leukaemia
	Not known	Treatment-related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Rare	Febrile neutropenia, sepsis/septic shock
	Not known	Haemolytic anaemia (including fatal outcomes), bone marrow failure, haemolytic-uraemic syndrome
Immune system disorders	Common	Hypersensitivity (e.g. skin rash, urticaria, erythema, fever with no apparent cause or pruritus), anaphylactoid type reaction (angiooedema, facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm)
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia, tumour lysis syndrome
Nervous system disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Uncommon	Central nervous symptoms (often associated with antiemetics)
	Not known	Cerebrovascular accident*, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), encephalopathy
Eye disorders	Common	Visual disturbance
	Rare	Loss of vision
	Not known	Optic neuritis
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Not known	Cardiac failure*, ischaemic coronary heart diseases (e.g. myocardial infarction, cardiac arrest, angina pectoris, myocardial ischaemia), 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
Hepatobiliary disorders	Not known	Severe hepatic dysfunction (including acute liver necrosis)

System organ class	Frequency	MedDRA term
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder
	Rare	Exfoliative dermatitis
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal disorder
	Uncommon	Myalgia, arthralgia
Renal and urinary disorders	Very common	Renal impairment
	Common	Urogenital disorder, hyperuricaemia
General disorders and administration site conditions	Common	Asthenia
	Uncommon	Fever and chills without evidence of infection
	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.

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/mm³ occurs in 25 % of patients, neutropenia with granulocyte counts below 1,000/mm³ 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 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 haemorrhagic 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. 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/100 ml have been observed in 48% of patients with normal base-line values.

Respiratory, thoracic and mediastinal disorders

Very rare: Pulmonary fibrosis manifested by tightness of the chest and dyspnoea. 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. 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 gastrointestinal complaints corresponded to pain in 8 % of patients, diarrhoea and constipation in 6 % of patients.

Nervous system disorders

Peripheral neuropathy (mainly paraesthesias 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. Paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin.

Clinically significant sensory disturbances (i.e. visual disturbances and taste modifications) have occurred in 1 % of patients.

Central nervous symptoms have been reported uncommonly, however, they seem to be frequently attributed to concomitant antiemetic therapy.

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.

Eye disorders

Transient visual disturbances, sometimes including transient sight loss, have been reported with platinum therapy. This is usually associated with high dose therapy in renally impaired patients.

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. Only 1 % of patients present with clinical symptoms, manifested in the majority of cases by tinnitus.

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

At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

Renal and urinary disorders

Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as high volume fluid hydration or forced diuresis. Nevertheless, increasing blood urea or serum creatinine levels can occur.
Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min, may also be observed. 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 dose reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 30 – 59 ml/min). Carboplatin is contraindicated in patients with a creatinine clearance < 30 ml/min (see sections 4.2 and 4.3).

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 half of 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.

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.

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 of the patients.
In a limited series of patients receiving very high doses 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

Allergic reactions to carboplatin have been reported in less than 2 % of patients, e.g. skin rash, urticaria, erythema, fever with no apparent cause or pruritus.
Anaphylactic-type reactions, sometimes fatal, may occur in the minutes following injection of the product: angiooedema, 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.

Acute promyelocytic leukaemia 6 years after monotherapy with carboplatin and previous radiotherapy has 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.

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.

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose

Carboplatin was administered in phase I studies at a dose of up to 1600 mg/m² intravenous per course. At this dose, life-threatening haematological undesirable effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9 – 25 (median: days 12 – 17). The granulocytes had reached values of ≥ 500/µl after 8 – 14 days (median: 11) and the thrombocytes values of ≥ 25.000/µl after 3 – 8 days (median: 7). The following non-haematological undesirable effects also occurred: renal function disturbances with a 50 % drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, erythema and severe infection. In the majority of cases, hearing disturbances were transient and reversible. Use of higher than recommended doses of carboplatin has been associated with loss of vision (see section 4.4).

Treatment of overdose

There is no known antidote for carboplatin overdose. The anticipated complications of overdose would be related to myelosuppression as well as impairment of hepatic and renal and auditory function. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological undesirable effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platinum compounds, ATC code: L01X A02.

Mechanism of action

Carboplatin is an antineoplastic agent. Its activity has been demonstrated against several murine and human cell lines.

Pharmacodynamic effects

Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks. Carboplatin exhibited comparable activity to cisplatin against a wide range of tumours regardless of implant site. Alkaline elution techniques and DNA binding studies have demonstrated the qualitatively similar modes of action of carboplatin and cisplatin. Carboplatin, like cisplatin, induces changes in the superhelical conformation of DNA which is consistent with a "DNA shortening effect".

Paediatric population

Safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties

Distribution

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.
Protein binding of carboplatin reaches approximately 87% within 24 hours following administration, although during the first 4 hours, only up to 29% of the dose is protein bound.

Elimination

Carboplatin is excreted primarily in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the substance is excreted in the first 6 hours. Approximately 32% of a given dose of carboplatin is excreted unchanged.
Total body and renal clearance of free ultrafilterable platinum correlates with the rate of glomerular filtration but not tubular secretion.

Renal impairment

Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin.

Linearity/non-linearity

Following administration of carboplatin in humans, 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.

Paediatric population

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 (see section 4.6). 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

Carboplatin should not be administered by using aluminium-containing infusion assemblies, syringes and injection needles as carboplatin reacts with aluminium. This can lead to precipitation and thus to reduced antineoplastic activity.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

2 years.

Shelf life after opening the container and preparing the solution for infusion ready-to-use

Chemical and physical in-use stability has been demonstrated in glucose 50 mg/ml (5 %) solution for infusion for 72 hours at room temperature and in sodium chloride 9 mg/ml (0.9 %) solution for infusion for 24 hours at 2 to 8 °C, when stored protected from light. However it is recommended to use solution for infusion reconstituted with sodium chloride 9 mg/ml (0.9 %) solution for infusion immediately after reconstitution.

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 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Cardboard carton containing one amber glass vial with a bromobutyl rubber fluoropolymer film-coated stopper and aluminium crimping cap with plastic top.

Pack sizes:
Packs of 1 vial of 5 ml, 15 ml, 45 ml, 60 ml and 100 ml concentrate for solution for infusion.
Packs of 10 vials of 5 ml, 15 ml, 45 ml, 60 ml and 100 ml concentrate for solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Carboplatin is a mutagenic and potentially carcinogenic substance. Precautions for safe handling of hazardous substances are to be taken for preparation and application. Preparation must be carried out by trained personal wearing adequate protective gloves, disposable gowns and masks.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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