SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin 10mg/ml Concentrate for Solution for Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Carboplatin 150mg in 15ml (10mg/ml)

For excipients see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection.

Clear, colourless or almost colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carboplatin is indicated for the treatment of:

1. - Advanced ovarian carcinoma of epithelial origin in:

(a) first line therapy

(b) second line therapy, after other treatments have failed.

2. - Small cell carcinoma of the lung.

4.2 Posology and method of administration

Dosage and Administration:

Carboplatin should be used by the intravenous route only. The recommended dosage of carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m² as a single i.v. 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]

Patient treatment status	**Planned chemotherapy**	**Target AUC**
Previously untreated	Single agent carboplatin	5-7 mg/ml.min
Previously treated	Single agent carboplatin	4-6 mg/ml.min
Previously untreated	Carboplatin plus cyclophosphamide	4-6 mg/ml

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

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

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

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

Impaired Renal Function:
The optimal use of carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs 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.

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

Elderly:

Dosage adjustment, initially or subsequently, may be necessary, dependent on the physical condition of the patient.

Dilution & Reconstitution:
See 6.6 Instructions for Use / Handling

4.3 Contraindications

Carboplatin should not be used in patients with severe pre-existing renal impairment (creatinine clearance at or below 20ml/minute).

It should not be employed in severely myelosuppressed patients. It is also contraindicated in patients with a history of severe allergic reactions to carboplatin or other platinum containing compounds.

4.4 Special warnings and precautions for use

Carboplatin should be administered by individuals experienced in the use of anti-neoplastic therapy.

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

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

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

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).

Carboplatin myelosuppression is closely related to its renal clearance. Patients with abnormal kidney function or receiving concomitant therapy with other drugs with nephrotoxic potential are likely to experience more severe and prolonged myelotoxicity. Renal function parameters should therefore be carefully assessed before and during therapy. Carboplatin courses should not be repeated more frequently than monthly under normal circumstances. Thrombocytopenia, leucopenia and anaemia occur after administration of carboplatin. Frequent monitoring of peripheral blood counts is recommended throughout and following therapy with carboplatin. Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosages and timing in order to minimise additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

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

Tumour lysis syndrome (TLS)
In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.

Renal and hepatic function impairment may be encountered with carboplatin. Very high doses of carboplatin (>5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and renal function. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds.

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.

Infrequent allergic reactions to carboplatin have been reported, e.g. erythematous rash, fever with no apparent cause or pruritus. Rarely anaphylaxis, angio-oedema and anaphylactoid reactions including bronchospasm, urticaria and facial oedema have occurred. These reactions are similar to those observed after administration of other platinum containing compounds and may occur within minutes. The incidence of allergic reactions may increase with previous exposure to platinum therapy; however, allergic reactions have been observed upon initial exposure to carboplatin. Patients should be observed carefully for possible allergic reactions and managed with appropriate supportive therapy.

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

Precautions:

Peripheral blood counts and renal and hepatic function tests should be monitored closely. Blood counts at the beginning of the therapy and weekly to assess haematological nadir for subsequent dose adjustment are recommended. Neurological evaluations should also be performed on a regular basis.

4.5 Interaction with other medicinal products and other forms of interaction

The use of carboplatin with nephrotoxic compounds is not recommended.

4.6 Pregnancy and lactation

The safe use of carboplatin during pregnancy has not been established: carboplatin has been shown to be an embryotoxin and teratogen in rats. If carboplatin is used during pregnancy the patient should be appraised of the potential hazard to the foetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

Carboplatin has been shown to be mutagenic in vivo and in vitro.

Nursing Mothers:

It is not known whether carboplatin is excreted in human milk.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Incidences of adverse reactions reported hereunder are based on cumulative data obtained in a large group of patients with various pretreatment prognostic features.

Haematological toxicity:

Myelosuppression is the dose-limiting toxicity of carboplatin. At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than 50×10^9/L, occurs in about a quarter 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 14% 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 1×10^9/L occurs in approximately one fifth of patients. Anaemia with haemoglobin values below 11g/dL has been observed in more than two-thirds of patients with normal base-line values.

Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65. Myelosuppression is also worsened by therapy combining carboplatin with other compounds that are myelosuppressive.

Myelosuppression is usually reversible and not cumulative when carboplatin is used as a single agent and at the recommended dosages and frequencies of administration.

Infectious complications have occasionally been reported. Haemorrhagic complications, usually minor, have also been reported.

Nephrotoxicity:

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 dosage reduction or discontinuation of therapy is required in the presence of severe alteration of renal function tests.

Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) have been reported after treatment with carboplatin but have not been reported to be severe enough to cause the appearance of clinical signs or symptoms.

Cases of hyponatraemia have been reported. Haemolytic uraemic syndrome has been reported rarely.

Gastrointestinal toxicity:

Nausea without vomiting occurs in about 15% of patients receiving carboplatin; vomiting has been reported in over half of the patients and about one-fifth of these suffer severe emesis. Nausea and vomiting usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) anti-emetic medication. A fifth of patients experience no nausea or vomiting.

frequency unknown: pancreatitis

Cases of anorexia have been reported.

Allergic reactions:

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Infrequent allergic reactions to carboplatin have been reported, e.g., erythematous rash, fever with no apparent cause or pruritus. Rarely, anaphylaxis, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria and facial oedema have occurred. (See Warnings.)

Ototoxicity:

Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin. However, only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen.

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 solution was administered.

Neurotoxicity:

The incidence of peripheral neuropathies after treatment with carboplatin is 4%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in elderly patients and those previously treated with cisplatin.

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

Ocular toxicity:

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

Nervous system disorders

frequency unknown: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Metabolism and Nutrition Disorders :

frequency unknown: Tumor lysis syndrome

Infection and infestation

frequency unknown: pneumonia

Other:

Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about one-third of the patients with normal baseline values. The alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment.

Infrequent events consisting of taste alteration, asthenia, alopecia, fever and chills without evidence of infection have occurred.

4.9 Overdose

There is no known antidote for carboplatin overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Carboplatin exhibited comparable activity to cisplatin against a wide range of tumours regardless of implant site.

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 patients:

Safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties

Carboplatin has biochemical properties similar to those of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks. Following administration of carboplatin in man, linear relationships exist between dose and plasma concentrations of total and free ultrafilterable platinum. The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose when creatinine clearance exceeds 60ml/min.

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 ultrafilterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primarily in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultrafilterable 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

Carboplatin has been shown to be embryotoxic and teratogenic in rats. (See para. 4.6, Pregnancy and Lactation.) 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

Nitrogen

6.2 Incompatibilities

Needles or intravenous sets containing aluminium parts that may come into contact with carboplatin should not be used for preparation or administration of carboplatin.

6.3 Shelf life

18 months (unopened)

After dilution:

24 hours under refrigeration (2 – 8°C)

6.4 Special precautions for storage

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

After dilution (see section 6.6.):

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for solutions with a final concentration of carboplatin 0.4mg/ml or 2.0mg/ml after dilution of the carboplatin 10mg/ml with glucose solution 5%.

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 dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Amber vials of hydrolytic type I glass, packed in a carton.

Vials are closed with a rubber stopper with an aluminium crimp cap with flip-off.

Packs of 1 vial containing 150mg/5ml of carboplatin.

6.6 Special precautions for disposal

This product is for single dose use only.

Solutions should only be used if clear and particle free.

Trained personnel should prepare carboplatin for infusion in designated areas. Protective clothing (including gloves) should be worn. The eyes should be protected. In the event of contact with the eyes, wash with water and/or saline.

Pregnant staff should not handle cytotoxics.

Any unused product, syringes, containers, absorbent material or other waste material should be disposed of using adequate care and precautions. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1000ºC. Liquid waste may be flushed with copious amounts of water.

Carboplatin for infusion may be prepared by dilution with Glucose 5% Solution.

7 MARKETING AUTHORISATION HOLDER

EBEWE Pharma

Ges.m.b.H. Nfg.KG

A-4866 Unterach, AUSTRIA

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