1. **TRADE NAME OF THE MEDICINAL PRODUCT**

Carboplatin "Ebewe"

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1ml contains 10mg carboplatin as active ingredient.
For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

4. **CLINICAL PARTICULARS**

4.1. Therapeutic Indications

Carboplatin is used alone or in combination with other antineoplastic agents in the treatment of epithelial ovarian carcinoma and small cell lung cancer.

4.2. Posology and Method of Administration

Dosage

Previously untreated adult patients with normal renal function receive 400mg carboplatin/m^2 body surfaces as i.v. short term infusion (15–60min), therapy cycles can be repeated after 4 weeks therapy free interval. Patients with risks (previously treated with myelosuppressive active drugs and/or radiation therapy or general poor conditions) should be treated with an initial dose of 300–320mg/m^2. In patients with impaired renal function the carboplatin dose must be reduced and adapted to the glomerular filtration rate.

A suggested dosage schedule based on creatinine clearance is as follows:

Creatinine Clearance (ml/min)	Dosage of Carboplatin
40ml per minute	400mg per square metre
20–39ml per minute	250mg per square metre
0–19ml per minute	150mg per square metre

An alternative formula for calculating dosage, based upon the patient glomerular filtration rate (GFR in ml/min) and the Carboplatin target area under the concentration versus time curve (AUC in mg/ml x min) see below (Calvert formula):

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min +25]		
Target AUC	**Planned Chemotherapy**	**Patient treatment status**
5–7mg/ml.min	single agent carboplatin	Previously untreated
4–6mg/ml.min	single agent carboplatin	Previously untreated
4–6mg/ml.min	carboplatin plus cyclophosphamide	Previously untreated

Note: With the Calvert formula, the total dose of caroplatin is calculated in mg, not mg/m^2.
For children no specific dosage recommendations can be made because of lack of experience in this field.

Route of Administration

Carboplatin is administered after preparation of the solution as i.v. short-time infusion over a period of 15–60min.

Dilution

The product may be diluted with 5% Glucose solution to concentrations as low as 0.4mg/ml (400 microgram/ml).
Since no antibacterial preservatives are contained in the formulation, it is recommended that any Carboplatin solution be discarded after 24 hours from dilution if stored at room temperature or refrigerated.

4.3. Contraindications

- Hypersensitivity to drug components or other platinum containing agents.
- Pregnancy and lactation period.
- Severe myelosuppression.
- Renal impairment (glomerular filtration rate < 30ml/min).
- Hearing impairment.

4.4. Special Warnings and Special Precautions for Use

Warnings:
This agent should only be administered under the direction of an oncologist, in specialist units under conditions permitting adequate monitoring and surveillance.
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, leukopenia and anaemia occur after administration of Carboplatin. Weekly monitoring of peripheral blood counts is recommended during the initial course of therapy with regular monitoring during 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 myelouppression.
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 function impairment may be encountered with Carboplatin. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine Carboplatin with aminoglycosides or other nephrotoxic compounds.
As for other platinum containing compounds, allergic reactions to Carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy.
Anaphylactic-like reactions may also occur as with other platinum containing compounds.
Its carcinogenic potential has not been studied but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

Precautions:

Peripheral blood counts, 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.
Cases of hepatic toxicity associated with renal toxicity have been reported with very high doses of Carboplatin.

4.5. Interactions

Myelosuppression is worsened by therapy combining Carboplatin with other compounds that are myelosuppressive.
Renal function impairment may occur with carboplatin. Therefore, carboplatin should not be combined with aminoglycosides or other agents with similar toxicity.

4.6. Pregnancy and Lactation

The safe use of Carboplatin during pregnancy has not been established.
Animal studies have shown Carboplatin to be embryotoxic and teratogenic in rats and it should not be used during pregnancy.
Carboplatin has been shown to be mutagenic in vivo and in vitro. The carcinogenic potential of Carboplatin has not been studied but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.
Nursing Mothers:
It is not known whether Carboplatin is excreted in human milk. Therefore it should not be administered to women who are breastfeeding infants.

4.7. Effects on ability to Drive and Use Machines

Depending on individual susceptibility, the patient's ability to drive a vehicle or operate machinery may be impaired.

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.
Infections and infestations
Uncommon:
Infectious complications have occasionally been reported.
Blood and the lymphatic system disorders:
Very common:
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 x 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.
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 usually reversible and not cumulative when Carboplatin is used as a single agent and at the recommended dosages and frequencies of administration.
Leukopenia has also occurred in approximately 14 % of patients but its recovery from the nadir day (day 14–28) may be slower and usually occurs within 42 days from the start of therapy. A haemoglobin decrease may be observed in some patients. Neutropenia with granulocyte counts below 1 x 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.
Immune system disorders
Common:
Allergic reactions to Carboplatin have been reported. These reactions are similar to those observed after administration of other platinum-containing compounds, i.e. erythematous rash, fever with no other apparent cause and pruritus and should be managed with appropriate supportive therapy.
Metabolism and nutrition disorders
Very common
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
Uncommon:
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.
Rare:
Cases of hyponatraemia have been reported.
Nervous system disorders
Common:

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 the 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.
Taste alteration.
Rare:
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.
Ear and labyrinth disorders
Very common:
Subclinical decrease in hearing acuity, consisting of high-frequency (4000–8000Hz) 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.
Vascular disorders
Uncommon:
Haemorrhagic complications, usually minor, have also been reported.
Gastrointestinal disorders
Very common:
Nausea without vomiting occurs in about 15% of the 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.
Skin and subcutaneous tissue disorders
Common
Alopecia
Musculoskeletal, connective tissue and bone disorders
Common
Asthenia
Renal and urinary disorders
Very common:
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 60ml/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 effect, but dosage reduction or discontinuation of therapy is required in the presence of severe alteration of renal function tests.
Rare:
Haemolytic-uraemic syndrome has been reported rarely.
General disorders and administration site conditions
Common
Fever and chills

4.9. Overdose

A specific antidote for overdosage is not available.
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".

5.2. Pharmacokinetic Properties

Carboplatin has biochemical properties similar to that 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.
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.
otal body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

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

Sodium dihydrogen phosphate anhydrous, water for injections.

6.2. Incompatibilities

Carboplatin may form a precipitate on contact with aluminium.

6.3. Shelf Life

36 months

6.4. Special Precautions for Storage

Do not store above 25°C. Keep container in the outer carton, in order to protect from light.
Following reconstitution in 5 % Glucose chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C and at room temperature. 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 (etc.) has taken place in controlled and validated aseptic conditions.

6.5. Nature and Contents of Containers

Type I Ph Eur glass vials with stoppers.

1 vial containing 50mg/5ml of carboplatin.
1 vial containing 150mg/15ml of carboplatin.
1 vial containing 450mg/45ml of carboplatin.

6.6. Instructions for Use/Handling

Handle according to the guidelines for cytostatics.

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG
A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF TEXT

December 2003