Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin "Ebewe" 10 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the concentrate contains 10 mg Carboplatin.

Each vial of 5 ml of the concentrate contains 50 mg Carboplatin.
Each vial of 15 ml of the concentrate contains 150 mg Carboplatin.
Each vial of 45 ml of the concentrate contains 450 mg Carboplatin.
Each vial of 60 ml of the concentrate contains 600 mg Carboplatin.
Each vial of 100 ml of the concentrate contains 1000 mg Carboplatin.

Excipients with known effect :
For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Carboplatin is used alone or in combination with other antineoplastic agents in the treatment of advanced ovarian carcinoma and small cell (SCLC) and non-small cell lung carcinoma (NSCLC).

4.2 Posology and method of administration

Carboplatin injection should be used by the intravenous route only.

The recommended dosage of carboplatin injection in previously untreated adult patients with normal kidney function is 400 mg/m^2 as a single intravenous dose administered by a 15- to 60-minute infusion. Therapy should not be repeated until 4 weeks after the previous carboplatin injection course and/or until the neutrophil count is at least 2,000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

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

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

The safety measures for dangerous substances are to be complied with for preparation and administration. Preparation must be carried out by personnel who have been trained in the safe use while wearing protective gloves, face mask and protective clothes.

Renal Impairment:
Patients with creatinine clearance values below 60 mL/min are at increased risk of severe myelosuppression. The frequency of severe leukopenia, neutropenia, or thrombocytopenia has been maintained at about 25% with the following dosage recommendations:

Baseline Creatinine Clearance	Initial Dose (Day 1)
41-59 mL/min	250 mg/m^2 I.V.
16-40 mL/min	200 mg/m^2 I.V.

Insufficient data exist on the use of carboplatin 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 the acceptable level of myelosuppression.

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

Elderly patients
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.

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

4.3 Contraindications

Carboplatin injection is contraindicated in:

- Hypersensitivity to carboplatin.
- patients with 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.
- patients with severe myelosuppression.
- patients with bleeding tumors.
- Concomitant use with yellow fever vaccine (see section 4.5.)

4.4 Special warnings and precautions for use

Carboplatin injection should be used only by physicians experienced with cancer chemotherapeutic drugs. Blood counts as well as renal and hepatic function tests must be done regularly and the drug should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

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

carboplatin injection 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 injection course and/or until the neutrophil count is at least 2,000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

Anemia is frequent and cumulative requiring very rarely a transfusion.

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

Allergic Reactions:
As with other platinum-based drugs, allergic reactions appearing most often during perfusion may occur and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see section 4.3 and section 4.8).

Renal toxicity
In patients with impaired renal function, the effect of carboplatin on the haematopoietic system is more pronounced and longer-acting than in patients with normal renal function. In this risk group, therapy with Carboplatin must be performed with special caution (see section 4.2 Posology and method of administration).

Neurologic Toxicity:
Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decrease of osteotendionous 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 injection 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).

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

<u>Concomitant use contraindicated</u>
- Yellow fever vaccine**:** risk of generalised vaccinal disease mortal ((see section 4.3.).

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.
Use an inactivated vaccine where this exist (poliomyelitis).

- Phenytoin, fosphenytoin Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug or risk of toxicity enhancement or lose of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Concomitant use to tale into consideration
- Cyclosporin (and by extrapolation tacrolimus and sirolimus):
Excessive immunosuppression with risk of lymphoproliferation.
- Aminoglycosides:
The concomitant use of carboplatine with aminoglycosides antibiotics should be taken into account due to the cumulative nephrotoxicity and ear toxicity, particulary in renal failure patient.
- Loop diuretics
The concomitant use of carboplatine with loop diuretic should be taken into account due to the cumulative nephrotoxicity and ear toxicity.

4.6 Fertility, pregnancy and lactation

Carboplatin injection can cause fetal harm when administered to a pregnant woman. Carboplatin injection has been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. No controlled studies in pregnant women have been conducted. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women with child-bearing potential should be advised to avoid becoming pregnant.

It is not known whether carboplatin injection is excreted in human milk. If treatment becomes necessary during the lactation period, breastfeeding must be stopped.

Fertility
Gonadal suppression resulting in amenorrhea or azospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.
Men of sexually mature age treated with Carboplatin are recommended not to father a child during treatment and up to 6 month afterwards 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 on the potential effect of these events on the ability to drive or to use machines.

4.8 Undesirable effects

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single agent carboplatin 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, < 1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (< 1/10000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Neoplasms, benign and malignant(including cysts and polyps)	Not known	Treatment related secondary malignancy
Infections and infestations	Common	Infections*
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, hemolytic-uraemic syndrome
Immune System Disorders	Common	Hypersensitivity, anaphylactoid type reaction
Metabolism and Nutrition Disorders	Not known	Dehydration, anorexia, hyponatraemia
Nervous System Disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Not known	Cerebrovascular accident*
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
Skin and Subcutaneous Tissue Disorders	Common	Alopecia, skin disorder
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal, Connective Tissue and Bone 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, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver funtion 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.

Haematologic:
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/mm^3 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.

Gastrointestinal:
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 injection is given in combination with other emetogenic compounds.

The other gastro-intestinal complaints corresponded to pain in 8% of patients, diarrhoea, and constipation in 6 % of patients.

Neurologic:
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.

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.

Ototoxicity
Auditory defects out of the speech range with impairments in the high-frequency range (4,000-8,000 Hz) were found in serial audiometric investigations with a frequency of 15%. Very rare cases of hypoacusia have been reported.

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

Renal:
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.

Electrolytes:
Decreases in serum sodium, potassium, calcium, and magnesium occur in 29%, 20%, 22%, and 29% of patients,

respectively. In particular, cases of early hyponatraemia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.

Hepatic:
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 occurred after high-dosed administration of carboplatin.

Allergic Reactions:

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

Other undesirable effects:
Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.

Alopecia, fever and chills, mucositis, asthenia, malaise as well as dysgeusia have occasionally been observed.

In isolated cases, a haemolytic-uraemic syndrome occurred.

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

Cases of hypertension have been reported.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no known antidote for carboplatin injection overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal and auditory function. Use of higher than recommended doses of carboplatin injection has been associated with loss of vision (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, ATC-Code: L01XA02

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.

Total 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

Water for injections

6.2 Incompatibilities

Carboplatin may form a precipitate on contact with aluminium.
This medicinal product must not be mixed with other medicinal products other than those mentioned in section 4.2.

6.3 Shelf life

As packaged for sale: 18 months

Remove solution from vial immediately before use.

Shelf life after dilution: Chemical and physical in use stability has been demonstrated in 5 % Glucose at concentrations of 0.4mg/ml and 2mg/ml for
24 hours at 2-8°C and 25°C.

In-use: 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.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

Vials of Type I Ph. Eur. glass with bromobutyl stopper and aluminium crimp cap. Vials are packed with or without a protective plastic overwrap (ONCO-SAFE) in a carton.

Package sizes:
5 ml Carboplatin “Ebewe” 10 mg/ml: 1, 5 or 10 vials are packed in one carton.
15 ml Carboplatin “Ebewe” 10 mg/ml: each vial is packed in a cardboard box.
45 ml Carboplatin “Ebewe” 10 mg/ml: each vial is packed in a cardboard box.
60 ml Carboplatin “Ebewe” 10 mg/ml: each vial is packed in a cardboard box.
100 ml Carboplatin “Ebewe” 10 mg/ml: each vial is packed in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Carboplatin "Ebewe" should only be prepared for administration by personnel who have been trained in the safe handling of cytotoxics.

Pregnant personnel should not handle cytotoxic agents.

Operations such as dilution of the concentrate should be carried out only in the designated area. Detailed instructions on the dilution of the concentrate are listed in section 4.2.

Personnel handling the product should be adequately protected with appropriate personal protective equipment, e.g. clothing, mask, gloves, eye shield.

Unused solution should be discarded.

Destruction of drug or contaminated articles:
Incineration: 1000°C
Chemical: Dilute in large volumes of water; allow to stand for 48 hours.
Contact with skin: Wash with water.
Liquid waste may be flushed with copious amounts of water.

Observe guidelines for the handling of cytotoxic drugs.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0789/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 1999
Date of last renewal: 22 February 2009

10 DATE OF REVISION OF THE TEXT

August 2014