SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CARBODEX 50 mg/5 ml solution for IV infusion
Sterile, Cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial:
Active substance:
Each 1 ml contains 10 mg carboplatin, 50 mg carboplatin in 5 ml (total volume).

Excipient(s):
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Vial containing solution for infusion.
5 ml clear, colorless-pale yellow concentrated particle-free solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Ovarian carcinoma,
- Germcell tumors,
- Small cell lung carcinoma,
- Other malignancies:

Non-small cell lung carcinoma, malign mesothelioma, breast carcinoma, head-neck carcinomas (Larynx carcinoma, nasopharynx carcinoma), esophagus carcinoma, stomach carcinoma, pancreas carcinoma, bladder carcinoma, soft tissue and bone sarcomas, lymphomas, malignancies of unknown primary, invasive squamous cell skin carcinoma, brain tumors, melanomas, neuroblastoma, myeloma, Wilm's tumor, hepatoblastoma.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The recommended dosage of carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m² as a single IV dose administered by a 15 to 60 minutes infusion. 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 carboplatin dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and/or radiotherapy and significantly low performance status (ECOG-Zubrod 2-4 or Karnofsky <80).

It is recommended that hematologic decline levels be determined by weekly blood counts during the initial courses of treatment with carboplatin injection for dosage adjustment in subsequent courses of treatment.

Combination chemotherapy:
The optimal use of carboplatin in combination with other myelosuppressive agents requires dosage adjustments according to the selected regimen and schedule.

Method of administration:
Carboplatin is for intravenous use only. The solution must be administered by a short-term intravenous infusion (15-60 minutes).

The solution may be diluted in either 5% glucose or 0.9% sodium chloride.

The safety measures for dangerous substances are to be complied with 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.

Needles or intravenous infusion 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.

Additional information on special populations

Renal/Hepatic impairment
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression (bone marrow suppression). The frequency of severe leucopoenia, neutropenia, or thrombocytopenia has been maintained at about 25% level with the following dosage recommendations:

Creatinine Clearance	Initial Dose (Day 1)
41-59 mL/min.	250 mg/m² IV
16-40 mL/min.	200 mg/m² IV

Insufficient data exist on the use of carboplatin 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.

Pediatric population:
There is insufficient experience available to recommend a dosage in the children.

Geriatric population:
In patients of more than 65 years of age, dosage adjustment may be necessary during the initial and the subsequent therapeutic courses depending on the physical condition of the patient.

4.3. Contraindications
CARBODEX is contraindicated in the following conditions.
- In patients with hypersensitivity to carboplatin and/or platinum-containing compounds and any other excipients.
- In patients with severe myelosuppression,

- In patients with pre-existing severe renal impairment (Creatinine clearance <30 mL/min),
- In pregnant women,
- During lactation,
- In patients with bleeding tumors,
- In children,
- Concomitant use with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Carboplatin for injection should be used by only 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:

Leucopoenia, neutropenia and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood count should be monitored during carboplatin injection treatment frequently and, in cases 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 carboplatin injection doses should not be repeated until leucocytes, 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 2000 cells/mm³ and the platelet count is at least 100.000 cells/mm³.

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 hematopoietic system is more pronounced and longer-acting than in patients with normal renal function. In this risk group, therapy with carboplatin must be administered with special caution (see section 4.2)

Neurologic toxicity:

Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia 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 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 pediatric patients. A long-term audiometric follow-up in this population is recommended.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. 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 anticoagulants, to increase frequency of the control of the INR (International Normalized Ratio) monitoring.

Concomitant use contraindicated
- Yellow fever vaccine: Risk of generalized fatal vaccine disease (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 patients who are already immunosuppressed by their underlying disease.

In this case (poliomyelitis), inactivated vaccine is used.
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions due to decreased absorption of phenytoin from the gastrointestinal tract by the cytotoxic drug, or increased toxicity or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism of phenytoin.

Concomitant use to take into consideration
- Cyclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Aminoglycosides: The concomitant use of carboplatin with aminoglycosides should be approached with caution particularly in renal failure patients due to the cumulative nephrotoxicity and ototoxicity
- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

Additional information on special population

Renal/hepatic impairment:
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression (bone marrow suppression). The frequency of severe leucopoenia, neutropenia, or thrombocytopenia has been maintained at about 25% level with the following dosage recommendations:

Creatinine Clearance	Initial Dose (Day 1)
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Insufficient data exist on the use of carboplatin 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.

Pediatric population:
There is insufficient experience available to recommend a dosage in the children.

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is D.

Women of child-bearing potential/Birth control (Contraception)
Women of childbearing potential should be warned to avoid becoming pregnant during treatment and should use effective contraceptive methods.

Pregnancy
Carboplatin has harmful pharmacologic effects on pregnancy and/or the fetus/new born.
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.
CARBODEX should not be used in pregnancy unless necessary.

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

Reproductive ability/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. Male patients should also be advised to seek counseling on

spermatic preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.
Women with child-bearing potential should be advised to avoid becoming pregnant during their treatment 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, CARBODEX 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 (≥1/1,000, <1/100); rare (≥1/10,000, <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*
Neoplasms, benign and malignant (including cysts and polyps)	Not known	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leucopoenia, anemia
	Common	Hemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, hemolytic-uremic syndrome
Immunity system disorders	Common	Hypersensitivity, anaphylactoid reaction
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatremia
Nervous system disorders	Common	Neuropathy peripheral, paresthesia, 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	Diarrhea, 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 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 injection. 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 leucopoenia with WBC counts below 2000/mm³ in 14% of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin injection with other myelosuppressive compounds or forms of treatment.
Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired renal function. Patients with poor performance status have also experienced increased leucopoenia 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.
Anemia with hemoglobin values below 8 g/dL has been observed in 15% of patients with normal baseline values. The incidence of anemia is increased with increasing exposure to carboplatin injection.

Immunity system disorders
Anaphylactic-type reactions, sometimes fatal, may occur in the minutes following injection of the product: facial edema, dyspnea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm.

Nervous system disorders
Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4% of patients administered carboplatin injection. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin injection, appear to be at increased risk.
Clinically significant sensory disturbances (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.

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.
In patients who have been previously treated with cisplatin and have a hearing organ pre-damaged due to cisplatin, a further exacerbation in the hearing function sometimes occurs during treatment with carboplatin.

Gastrointestinal disorders
Vomiting occurs in 65% of patients, in one-third of whom it is severe. Additionally, nausea occurred in 15% of patients. Previously treated patients (in particular patients treated with cisplatin) appear to be more prone to vomiting. Nausea and vomiting usually disappear within 24 hours after treatment and are generally responsive to and 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, diarrhea, and constipation in 6% of patient.

Renal and urinary disorders
When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin injection has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6% of patients, elevation of blood urea nitrogen in 14%, and of uric acid in 5% of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven to be the most sensitive renal function in patients receiving carboplatin injection. 27% of patients who have a baseline value of 60 ml/min or greater, experience a reduction in creatinine clearance during carboplatin injection 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 hyponatremia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.
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 changes were generally mild and reversible in approximately half of 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.

Other undesired effects:
Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.
Rarely, alopecia, fever with chills, mucositis, asthenia, malaise, and dysgeusia have been reported.
In isolated cases, a hemolytic-uremic 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:
Injection site reactions (Burning, pain, redness, swelling, hives, and necrosis with extravasation) were reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose
There is no specific antidote for carboplatin. Overdose may lead to impaired renal, hepatic and auditory functions as well as myelosuppression. Use of higher than recommended doses of carboplatin injection may cause loss of vision (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents (Platinum compounds)
ATC code: L01XA02

Carboplatin is a cytotoxic, inorganic heavy metal complex. Carboplatin binds to DNA to produce intra- and interstrand crosslinks which inhibit DNA synthesis. Cross-resistance was developed by continuous cisplatin in animal studies.

5.2. Pharmacokinetic properties
Absorption:
After intravenous administration the highest plasma concentrations as well as the area under the curve (AUC) value of unchanged carboplatin, ultrafiltrated platinum and total platinum content corresponds linearly with the administered dose.

Distribution:
After IV administration as short term infusion (<1 hour) the plasma concentrations decreases biphasically following first order kinetics.
Initial half-life ($T_{\alpha½}$) for free, unchanged carboplatin and platinum is 90 minutes, for total platinum 100 minutes. Terminal half-life ($T_{\alpha½}$) for free platinum is 6 hours and for total platinum 24-40 hours.
After repeated administrations (5 days of single intravenous carboplatin doses) accumulation of platinum in plasma is not found. Pharmacokinetic parameters on first day of administration are almost same as those after 2-5 days of administration.

Elimination:
Plasma protein binding rate of carboplatin is 20-25% after 4 hours, and >90% after 24 hours.
Carboplatin is mainly eliminated by the kidneys. 60-80% of administered dose found in urine after 24 hours.
Elimination rate of carboplatin mainly depends on glomerular filtration rate. In patients with impaired renal function the carboplatin dosage must be reduced according to the reduced clearance otherwise the myelosuppressive activity of carboplatin increases.

5.3. Preclinical safety data
Carboplatin has been shown to be cytotoxic, mutagenic and embryotoxic in the preclinical studies. The product is essentially similar to other products authorized in EU countries. Use of this medicinal product is well-known and its efficiency was established by several publications.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Water for Injections

6.2 Incompatibilities
In order to reduce risk of decreased antineoplastic activity of carboplatin and precipitate formation; needles, syringes, catheters or intravenous sets containing aluminum parts that may come into contact with carboplatin should not be used for preparation or administration of carboplatin.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at room temperature below 25°C.
Store in its original package to protect from light.
See section 6.6 for storage conditions and shelf life after dilution.

6.5 Nature and contents of container
Each box contains one amber colored Type I glass single-use vial with rubber stopper sealed flip-off aluminum cap with plastic disc.

6.6 Special precautions for disposal and other handling
For single use only.
CARBODEX and other cytotoxic drugs should be avoided from contact with pregnant women and from being administered or handled by pregnant personnel.

Infusion solution should be prepared and disposed by personnel who have been trained in the safe use of cytotoxics. A dedicated preparation area must be allocated for the application. Appropriate clothing, masks, protective eyewear, and gloves must be provided for personnel.

Any unused solution should be discarded.

Disposal of medication or contaminated materials:
Incineration: 1000°C
Chemical: Dilute with large volumes of water; let stand for 48 hours.
Skin contact: Wash with water.
Liquid waste should be washed with plenty of water.

When preparing CARBODEX infusion solution and disposing of both the remaining medical product and all remaining solvents and solutions, the standard procedures used for cytotoxic drugs and the legal requirements in force for the disposal of hazardous waste must be taken into account, and they must be disposed of in accordance with these requirements.
Any unused product or waste material should be disposed of in accordance with local disposal regulations.

Instructions for dilution:
CARBODEX should not be used undiluted.

The solution may be diluted with either 5% glucose or 0.9% sodium chloride.
From a microbiological point of view, the diluted solution should be used immediately. If not planned to be used immediately, in-use storage conditions are the responsibility of the user (would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place under controlled and validated aseptic conditions).

The following stability data (physical and chemical) is valid for diluted solution when that process is performed under aseptic conditions:

Carrier solution	Carboplatin Concentration (mg/ml)	Conditions	Stability Duration (hours)
5% glucose solution	0.4-2	Room temperature/ protect from light	72
0.9% sodium chloride solution	2	2-8°C/ protect from light	24

However, infusion solution diluted with 0.9% sodium chloride solution is recommended to be used immediately after preparation.
Carboplatin is for intravenous use only. The solution must be administered by a short-term intravenous infusion (15-60 minutes).
Since carboplatin reacts with aluminum, infusion materials, syringes, and injection needles containing aluminum should not be used. When used, it causes precipitation, leading to a decrease in antineoplastic activity.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

225/31

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization: 24.06.2010
Date of renewal :

10. DATE OF REVISION OF THE TEXT