SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carboplatin Pfizer 10 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 10 mg carboplatin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As single-drug therapy or in combination with other antineoplastic drugs for the treatment of the following diseases:

Advanced epithelial ovarian cancer

Small-cell lung cancer.

4.2 Posology and method of administration

Posology
Adults not previously treated, whose renal function is normal, receive 400 mg carboplatin/m^2 body surface as a short (15 - 60 minutes) intravenous infusion. Alternatively, the dosage can be calculated using the formula given below.

Treatment with Carboplatin Pfizer at a dosage of 400 mg/m^2 body surface should only be carried out or repeated if a patient's haematopoietic system, kidneys and nervous system are functioning normally or after the function of these organs has been restored 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.

The initial dosage should be reduced to 300 – 320 mg carboplatin/m^2 body surface for patients with risk factors (previously treated with myelosuppressant drugs and/or radiotherapy, markedly reduced general state of health (ECOG-Zubrod 2-4 or Karnofsky below 80)).

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

Carboplatin can induce emesis. The incidence and severity of emesis may be reduced by pre-treatment with anti-emetics.

Elderly
In the case of patients aged over 65, the carboplatin dosage needs to be adjusted to their general state of health during the first and subsequent courses of treatment.

Paediatric population
The safety and efficacy of Carboplatin Pfizer in children has not yet been established. No data are available.

Renal impairment
In patients with renal impairment (creatinine clearance less than 60 ml/min), the carboplatin dose must be reduced and adjusted to the glomerular filtration rate (GFR). Close monitoring of hepatic and renal function, blood count, electrolytes and platelets is an essential requirement.

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 intravenous
16-40 ml/min	200 mg/m^2 intravenous

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.

Dosage based on AUC (Area Under The Curve)
As an alternative to the initial dosage given above, this can be calculated using the following mathematical formula, which includes renal function. This will reduce the risk of overdosing or underdosing because of individual differences in renal function.

Formula according to Calvert:
Total dose (mg) = (target AUC*) x (GFR + 25)

Note:
Calvert's formula calculates the total dose in mg, **not** in mg/m^2 body surface.

*Target AUC	Planned chemotherapy	Patient's treatment status
5- 7 mg/ml min	single-drug therapy with carboplatin	no previous treatment
4- 6 mg/ml min	single-drug therapy with carboplatin	previous treatment
4- 6 mg/ml min	carboplatin plus cyclophosphamide	no previous treatment

Calvert's formula should not be used for heavily pretreated patients who have previously been treated with any of the following regimens:

- mitomycin C,
- nitrosourea,

- combination therapy with doxorubicin / cyclophosphamide / cisplatin,
- chemotherapy with 5 or more different active substances, or
- radiotherapy ≥ 4500 rad, focused on one field measuring 20 x 20 cm or on more than one field.

Combination chemotherapy
In combination therapy with other bone marrow-depressant drugs, the carboplatin dose must be adjusted to the treatment regimen being used at the time.

There is no general time limit on treatment with carboplatin. The medication should be withdrawn if the tumour fails to respond, in the case of progressive disease and/or the appearance of side-effects that can no longer be tolerated.

Method of administration
Carboplatin is for intravenous use only.

The solution for infusion is given as a short intravenous infusion over 15 – 60 minutes.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or Intravenous administration sets that contain aluminium parts which may come into contact with carboplatin should not be used for the preparation or administration of the drug. Thus, aluminium containing equipment should not be used during preparation and administration of carboplatin.

Carboplatin is a mutagenic and potentially carcinogenic substance. The usual precautions for hazardous substances must be observed during preparation and administration of the drug. The solution must be prepared by suitably trained staff wearing protective gloves, mouth protection and protective clothing.

Note
The average body surface of an adult is 1.73 m^2.

Based on the recommended dosages of 400 mg/m^2 body surface and 300 – 320 mg/m^2, this means mg quantities of 680 mg and 480 – 520 mg carboplatin respectively.

The different pack sizes of this medication must be combined appropriately to make up these quantities. In order to minimize the amount of solution left over, the pack sizes containing 50 mg and 150 mg carboplatin should be used to achieve exactly the desired dosage.

4.3 Contraindications

Carboplatin must not be used in the following circumstances:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- hypersensitivity to other platin compounds
- severe kidney damage (GFR <30 ml/min), unless in the judgment of the physician and patient, the possible benefits of treatment outweigh the risks
- pre-existing severe bone marrow depression
- bleeding tumours
- concomitant use with yellow fever vaccine (see section 4.5)

The effect of carboplatin on the haematopoietic system is more pronounced and more prolonged in patients with renal impairment than in patients with normal renal function. Treatment with carboplatin must be undertaken with particular caution in this at-risk group (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

Carboplatin should only be administered by doctors who are experienced in cancer therapy. 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 drug should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Myelosuppression
Severity of myelosuppression is increased in patients with renal impairment (see section 4.3) or patients with extensive prior treatment in particular with cisplatin. Initial carboplatin dosages in these groups of patients should be appropriately reduced and the effects carefully monitored through frequent blood counts between courses. Myelosuppressive effects may be additive to those of concomitant chemotherapy. Carboplatin 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. Patients with poor performance status or aged over 65 years, or who were receiving concomitant therapy with nephrotoxic drugs, may also experience more severe or prolonged myelosuppression.

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 should be interrupted and dose modification or discontinuation should be considered.

Haematologic toxicity
Leucopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. The peripheral blood count, electrolytes and platelets, as well as hepatic and renal function, should be checked before the start of therapy and before each course of treatment and, in cases of toxicity, until recovery is achieved. Peripheral blood counts should be performed at weekly intervals during therapy. This will monitor toxicity and help determine the nadir and recovery of haematological parameters, and assist in subsequent dosage adjustments. 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. Lowest levels of platelets are generally seen between Days 14 and 21 of initial therapy. A greater reduction is seen in patients who previously received extensive myelosuppressive chemotherapy. Lowest levels of white cells occur generally between Days 14 and 28 of initial therapy. Transfusions may be necessary and dosage reductions recommended for subsequent treatment.

In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. Treatment with carboplatin should not be started or resumed after previous courses of treatment until 4 weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm^3, the platelet count is at least 100,000 cells/mm^3 and the leucocyte count is ≥ 4,000 cells/mm^3. This recovery usually takes 5 to 6 weeks.

Close monitoring of the blood count and platelets during the treatment-free interval is recommended, particularly in the case of combination therapy with bone marrow depressant drugs, so that dose adjustments can be made, if necessary.

Anaemia is frequent and cumulative, however it rarely requires a transfusion.

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

Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/acute myeloid leukemia (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 Lactate Dehydrogenase (LDH). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Allergic reactions
As with other platinum-based drugs, allergic reactions appearing most often during perfusion may occur and necessitate discontinuation of the infusion. An appropriate symptomatic treatment must also be initiated in such cases. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

The risk of allergic reactions, including anaphylaxis, is higher in patients who have previously been treated with medicines containing platinum.

The vial stopper for Carboplatin 50mg, 150mg and 450mg presentations contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

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). Kounis syndrome can develop in patients with and without cardiac risk factors, and may be presented with a combination of cardiac and allergic symptoms, or as standalone. Coronary vasospasm may be treated with steroids and antihistamines in addition to spasmolytics treatment.

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).

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 in renal function tests.

Renal function tests should be done regularly.

Neurologic toxicity
Although peripheral neurologic toxicity is generally common and mild, limited to paraesthesia and decreases in osteotendinous reflexes, its frequency is increased in patients older than 65 years and/or in patients previously treated with cisplatin.

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.

Neurological investigations, including an assessment of hearing, should be done regularly. The frequency and intensity of any neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity increases in elderly patients and those previously treated with cisplatin.

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).

Gastrointestinal
The gastrointestinal absorption of phenytoin may be reduced during chemotherapy. During treatment with carboplatin, serum levels of phenytoin should therefore be checked regularly, in order to prevent the occurrence of convulsions by prompt adjustment of the phenytoin dosage. After completion of the treatment, the phenytoin must be re-adjusted, as required.

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.

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.

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. As 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

No interaction studies have been performed.

When carboplatin is used with myelosuppressant substances, the effect of carboplatin and/or the additional medication on the bone marrow may be increased (see section 4.2).

Due to the increase of thrombotic risk in cases of tumoural 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, may require an increase in frequency of INR monitoring if a patient is treated with oral anticoagulants.

Concomitant use contraindicated
- Yellow fever vaccine: risk of generalized 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 loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration
- Cyclosporine (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.

- If nephrotoxic and/or ototoxic drugs (e.g. aminoglycosides, loop diuretics) are administered during treatment with carboplatin, the organotoxicity of these medicines may be increased. Concomitant use should be approached with caution due to the cumulative nephrotoxicity and ototoxicity, particular caution is required with aminoglycosides in renal failure patients.

A case was reported in the literature where concurrent use of phenytoin and carboplatin led to a considerable decrease in the serum phenytoin level, which resulted in the recurrence of convulsions and necessitated an increase in the phenytoin dosage.

The simultaneous administration of carboplatin and complex formers should be avoided because this can theoretically lead to weakening of the antineoplastic potency of carboplatin. In animal studies and in clinical practice, however, the antineoplastic efficacy of carboplatin was unaffected by diethyldithiocarbamate.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should be advised to avoid becoming pregnant and must use effective contraception during treatment and for at least 7 months after last dose.

Pregnancy
Carboplatin is suspected to cause serious birth defects when administered during pregnancy (see section 4.4). Carboplatin can have genetically damaging effects and has embryotoxic and teratogenic properties. Carboplatin was shown to be embryotoxic and teratogenic in rats (see section 5.3). No controlled studies in pregnant women have been conducted. Carboplatin Pfizer 10 mg/ml concentrate for solution for infusion should not be used during pregnancy unless clearly necessary. The mother should be informed about the risk to the foetus.

Breast-feeding
Carboplatin and its active metabolites have been identified in human milk of treated mothers. Due to the risk of serious adverse effects of carboplatin, breast-feeding must be discontinued during treatment and for 1 month following last dose or discontinue treatment with Carboplatin Pfizer 10 mg/ml concentrate for solution for infusion, taking into account the importance of the drug to the mother.

Fertility
Male and female fertility may be impacted by treatment with carboplatin (see section 5.1). Both men and women should seek advice for fertility preservation before treatment with carboplatin.

Gonadal suppression resulting in amenorrhea or azospermia may occur in patients receiving antineoplastic therapy and patients receiving carboplatin should be warned of this potential.

Although not reported with carboplatin, this has been reported with other platinum agents. These effects appear to be related to dose and length of therapy and may be irreversible.

Prediction of the degree of testicular or ovarian functional impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.

Sexually mature males who are treated with carboplatin are advised not to father a child during the treatment and for at least 4 months thereafter. Contraceptive measures or abstinence are recommended. If a pregnancy does happen during the treatment, use should be made of genetic counselling.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, carboplatin can cause nausea and vomiting, vision abnormalities and ototoxicity; and thus indirectly impair the fitness to drive or ability to operate machinery. Patients should be warned of 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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**MedDRA Term**
Infections and infestations	Common	Infections*
	Not known	Pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Not known	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, hemolytic-uraemic syndrome, hemolytic anemia
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
	Rare	Angioedema
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia, Tumor lysis syndrome

System Organ Class	Frequency	MedDRA Term
Nervous system disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Not known	Cerebrovascular accident*, encephalopathy, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Eye disorders	Common	Visual disturbance (incl. rare cases of loss of vision)
	Not known	Cortical blindness
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Not known	Cardiac failure*, Kounis syndrome (vasospastic allergic angina)
Vascular disorders	Not known	Embolism*, hypertension, hypotension, venoocclusive disease (fatal)
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
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder
	Not known	Urticaria, rash, exfoliative dermatitis, erythema, erythematous rash, pruritus
Musculoskeletal and connective tissue 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.

System Organ Class	Frequency	MedDRA Term
	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 the 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/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.

Platelet and WBC counts are usually restored to baseline after 28 days.

Platelet and WBC recovery sometimes takes as long as 35 or 42 days respectively. In such cases, the treatment with carboplatin should not be repeated until the platelet count is ≥100,000 cells/mm^3 and the white cell count ≥4,000 cells/mm^3.

The depression of bone marrow function is more severe and more prolonged in patients with impaired renal function, intensive previous treatment, in particular in patients previously treated with cisplatin a reduced general state of health or aged over 65 than in patients without these risk factors. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia.

The disturbances of bone marrow function are usually reversible and non-cumulative, provided carboplatin is used according to the recommendations in the dosage guidelines.

These effects, although usually reversible, have resulted in infectious and haemorrhagic 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.

In exceptional cases, erythrocyte substitution may be necessary.

Neoplasms, benign and malignant (including cysts and polyps)
Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.

After cytostatic combination treatments containing carboplatin there have been uncommon cases of myelodysplastic syndromes and acute myeloid leukemia. Very rarely, acute promyelocytic leukemia occurred.

Immune system disorders
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, angioeodema.

These reactions can be controlled with anti-histamine, adrenaline and/or glucocorticoids. 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 and there are reports of cross-sensitivity with other platinum compounds; however, allergic reactions have been observed upon initial exposure to carboplatin. Patients should be observed carefully for possible allergic reactions and managed with appropriate therapy.

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.

Paraesthesia as a consequence of cisplatin treatment can sometimes be further aggravated by subsequent treatment with carboplatin.

Clinically significant-sensory disturbances (i.e., 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.

Central nervous symptoms which frequently appear to be attributable to anti-emetic treatment are uncommonly reported.

Eye disorders
Inflammation of the optic nerves with visual disturbances, including rare cases of loss of vision have occurred. Cortical blindness has been reported in patients with impaired renal function receiving high-dose carboplatin.

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.

Tinnitus was also commonly reported.

Where a patient’s auditory organ is already damaged by cisplatin, treatment with carboplatin can sometimes cause a further deterioration in auditory function. Clinically significant decreases in hearing acuity have occurred in children receiving higher carboplatin doses than recommended, in combination with other ototoxic drugs.

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.

Vomiting started roughly six hours after administration of carboplatin. It lasted a relatively short time and usually subsided. These effects usually disappear within after 24 hours. Vomiting seems to occur in previously treated patients, especially if previously treated with cisplatin. Vomiting is more likely when carboplatin injection is given in combination with other emetogenic compounds. Nausea and vomiting can generally be controlled by anti-emetics and can often be avoided by their prophylactic administration.

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

In some cases there has been vomiting which could not be controlled by medication.

Hepato-biliary 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.

A rise in liver enzymes (including alkaline phosphatase and aspartate aminotransferase), usually reversible, which could not be clearly attributed to the malignancy, after administration of carboplatin at the dosages recommended here. However, these changes in laboratory results did not lead to withdrawal of treatment in any patient.

Fulminating liver cell necrosis occurred after high-dose administration of carboplatin. In a limited series of patients. severe elevation in liver function values occurred following very high doses of Carboplatin and autologous bone marrow transplants.

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 of 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.

Hyperuricaemia – the raised serum levels of uric acid can be effectively reduced by administration of allopurinol.

Disturbances of renal function were more common and more pronounced in patients with renal impairment before the start of therapy than in patients with normal organ function. Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

It is uncertain at present whether a further deterioration in organ function can be avoided by hydration programmes in patients with renal impairment. In the case of moderate disturbances of renal function (creatinine clearance <60 to 30 ml/min) the carboplatin dose must be reduced as a function of the decrease in the GFR or the drug should be withdrawn (see section 4.2). Carboplatin is contraindicated where the GFR is <30 ml/min.

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

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 minimal and are not usually accompanied by any clinical symptoms.

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.

Fever and chills as well as mucositis have occasionally been observed.

In animal studies carboplatin exhibits embryotoxic and teratogenic properties. Mutagenicity and chromosome aberrations were demonstrated in cell culture. Based on these findings, it must be assumed that carboplatin has some carcinogenic potential.

Pulmonary fibrosis has been reported, manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see Immune system disorders above).

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

Life-threatening haematological side effects involving granulocytopenia, thrombocytopenia and anaemia have been observed with a dosage of up to 1600 mg carboplatin/m^2 body surface intravenous per course.

The nadir counts for granulocytes, platelets and haemoglobin were observed between Days 9 and 25, the median between Days 12 and 17. The granulocytes had recovered to levels of ≥0.5 x10^9/l after 8-– 14 (median 11) days and the platelets to ≥25 x10^9/l after 3 – 8 (median 7) days.

In addition, the following non-haematological side-effects occurred:

disturbances of renal function with a 50% fall in the GFR, neuropathies, ototoxicity, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headaches, reddening of the skin, serious infections and alopecia. The hearing disturbances were usually transient and reversible.

There is no specific antidote available. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal and auditory function. Death may follow. Use of higher than recommended doses of carboplatin has been associated with loss of vision (see section 4.4). Signs and symptoms of overdosage should be managed with supportive measures. Bone marrow transplantation and transfusions (platelets, blood) can be used to deal with haematological side-effects. Supportive treatment may also be required for renal and hepatic impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, ATC code: L01X A02

Carboplatin has an antineoplastic and cytocidal action.

Its cytocidal action is based on cross-linking of the single and double DNA strands by means of platinization and disruption of the matrix function of DNA.

5.2 Pharmacokinetic properties

Distribution
It is not carboplatin itself but its platin-containing degradation products that are bound to plasma proteins. During the first four hours post-infusion the proportion of the platin bound to plasma proteins is 24% and reaches 87% within 24 hours.

Elimination
After intravenous administration, the peak plasma level and the area under the concentration time curve for unchanged substance, filterable platin and total platin are linear and dependent on the dose of carboplatin administered.

After intravenous administration of carboplatin as a short infusion (< 1 hour) the plasma level falls in a biphasic exponential fashion.

The $t_{1/2}$ α is 90 minutes for unchanged carboplatin and filterable platin, 100 minutes for platin. The $t_{1/2}$ ß is 6 hours for filterable platin and approximately 5 days for total platin in plasma.

No accumulation of platin in plasma is found after multiple administration of carboplatin repeated over 5 days and given as a short intravenous infusion. The pharmacokinetic parameters on the first day of administration are largely identical to those on days 2 – 5.

Carboplatin is excreted primarily in urine. Urinary recovery is 60 – 80% of the platin dose administered after 24 hours.

In the case of carboplatin, total body clearance, renal clearance and excretion of filterable platin in urine correlate with creatinine clearance. The elimination of carboplatin is thus largely dependent on the GFR.

For patients with renal impairment, the carboplatin dose must therefore be reduced, depending on the reduction in clearance. This is because its myelosuppressant effect is dependent on the area of filterable platin under the concentration time curve. (see section 4.2)

5.3 Preclinical safety data

Carboplatin has been shown to be mutagenic *in vitro* and *in vivo*. The carcinogenic potential of carboplatin has not been studied but compounds with a similar mode of action have been reported to be carcinogenic. Carboplatin is embryotoxic and teratogenic in rats. When rats were treated with carboplatin during organogenesis, there was an increased incidence of abnormalities of the skeleton and internal organs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Carboplatin should not be administered with giving sets, syringes and injection needles containing aluminium because, based on theoretical considerations, the possibility that its antineoplastic potency may be reduced cannot be ruled out.

6.3 Shelf life

2 years.

In use
Chemical and physical in-use stability has been demonstrated in undiluted Carboplatin Pfizer concentrate for solution for infusion in pierced vials for 14 days at 2 to 8°C when protected from light.

From a microbiological point of view, the concentrate 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 opening/piercing has taken place in controlled and validated aseptic conditions.

Stability following reconstitution/dilution
Carboplatin Pfizer 10 mg/ml concentrate for solution for infusion may be further diluted in Glucose 5% and administered as an intravenous infusion. Chemical and physical in-use stability has been demonstrated for 56 days to final concentrations of 0.2 mg/ml and 3.5 mg/ml when stored at 2-8ºC in non-PVC (polyolefin) infusion bags when protected from light.

Carboplatin Pfizer 10 mg/ml concentrate for solution for infusion may be further diluted in Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution is chemically stable for up to 24 hours when stored at 2-8ºC and up to 8 hours when stored at 22ºC.

From a microbiological point of view, the diluted solution 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 for the concentrate, after opening/piercing and for the diluted solution, not be longer than 24 hours at 2 to 8°C, unless opening/piercing of the vials and dilution have taken place in controlled and validated aseptic conditions.

The solution contains no preservative and any unused portion of the clear glass or Onco-Tain vial should be discarded immediately.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original pack in order to protect the contents against light.
For storage conditions after first opening and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Carboplatin Pfizer 10 mg/ml concentrate for solution for infusion is presented in Type 1 glass vials with natural or butyl rubber stoppers.

Vial containing
1 x 5 ml concentrate for solution for infusion
10 x 5 ml concentrate for solution for infusion
1 x 15 ml concentrate for solution for infusion
10 x 15 ml concentrate for solution for infusion
1 x 45 ml concentrate for solution for infusion
10 x 45 ml concentrate for solution for infusion

1 x 60 ml concentrate for solution for infusion
10 x 60 ml concentrate for solution for infusion

Not all pack sizes may be marketed.

Vials may be sheathed in protective ONCO-TAIN Sleeves.

6.6 Special precautions for disposal and other handling

Parenteral drugs should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If particulate matter is observed, shake and re-inspect. Vials with visible particulate matter should not be used.

Carboplatin Pfizer concentrate for solution for infusion can be further diluted with 5% glucose solution or 0.9% saline to a final concentration of 0.2 -3.5 mg/ml. Normally the calculated dose of carboplatin is diluted with infusion solution up to a volume of 500 ml. For storage conditions after first opening and dilution of the medicinal product, see section 6.3.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. Trained personnel should prepare the infusion solution under aseptic conditions.

2. This should be performed in a designated area.

3. Adequate protective gloves should be worn.

4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution.

5. The cytotoxic preparation should not be handled by pregnant staff.

6. Adequate care and precautions should be taken in the disposal of items (syringes needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7. The work surface should be covered with disposable plastic-backed absorbent paper.

8. Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

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

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 04.December.1997
Date of latest renewal: 28.October.2009

10 DATE OF REVISION OF THE TEXT

18 October 2023

Detailed information on this medicinal product is available on the website of: {name of MS/Agency}