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CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 36390/0056-8

LAY SUMMARY

On 21st September 2011, the MHRA granted STD Chemicals Limited a Marketing Authorisation (licence) for Carboplatin 10 mg/ml Concentrate for Solution for Infusion.

Carboplatin 10 mg/ml Concentrate for Solution for Infusion contains the active ingredient carboplatin. Carboplatin belongs to a group of medicines known as platinum compounds, which are used to treat cancer.

Carboplatin is used against advanced cancer of the ovary and small cell cancer of the lung.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Carboplatin 10 mg/ml Concentrate for Solution for Infusion outweigh the risks; hence these Marketing Authorisations have been granted.
CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 36390/0056-8

SCIENTIFIC DISCUSSION

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Clinical assessment (including statistical assessment) Page 9
Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal product Carboplatin 10 mg/ml Concentrate for Solution for Infusion (PL 36390/0056-8) to STD Chemicals Limited on 21st September 2011. This prescription only medicine (POM) is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:
   (a) First line therapy
   (b) Second line therapy, after other treatments have failed.

2. Small cell carcinoma of the lung.

These applications for Carboplatin 10 mg/ml Concentrate for Solution for Infusion were submitted according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Carboplatin 10 mg/ml Concentrate for Solution for Infusion, which was originally approved and licensed to Neolab Limited (PL 08137/0150-2) on 27th May 2011. These licences then underwent a change of ownership to Fannin (UK) Limited on 20th July 2011 (PL 20417/0011-3).

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance together with the necessary means for notification of any adverse reaction suspected of occurring.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

No new data were submitted nor were they necessary for this ‘simple’ application, as the data are identical to that of the previously granted cross-reference product.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0056-8
PROPRIETARY NAME: Carboplatin 10 mg/ml Concentrate for Solution for Infusion
ACTIVE(S): Carboplatin
COMPANY NAME: STD Chemicals Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC, as amended
LEGAL STATUS: POM

1. INTRODUCTION
These are informed consent (‘simple’) applications for Carboplatin 10 mg/ml Concentrate for Solution for Infusion (PL 36390/0056-8) submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed MA holder is STD Chemicals Limited, Hillbrow House, Esher, Surrey, KT10 9NW.

These applications cross-refer to Carboplatin 10 mg/ml Concentrate for Solution for Infusion, which was originally approved and licensed to Neolab Limited (PL 08137/0150-2) on 27th May 2011. These licences then underwent a change of ownership to Fannin (UK) Limited on 20th July 2011 (PL 20417/0011-3).

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 NAME(S)
The proposed name of the product is Carboplatin 10 mg/ml Concentrate for Solution for Infusion. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each ml of concentrate for solution for infusion contains 10mg carboplatin.
Each 5ml vial contains 50mg carboplatin.
Carboplatin 10 mg/ml Concentrate for Solution for Infusion is used by intravenous route only.

The finished product is packaged in clear vials of hydrolytic Type I glass, packed in a carton. Vials are closed with a fluororesin coated bromobutyl rubber stoppers with aluminium crimp caps with polypropylene flip-off lids.

The products are presented in packs of 1 vial containing 50 mg/5ml of carboplatin.

The proposed shelf-life for the unopened product is 24 months with the following storage conditions:
‘Do not store above 25°C. Do not store in a refrigerator. Store containers in the original carton. Protect from light’.
This is consistent with the details registered for the cross-reference product.

The shelf-life for the product after dilution is 24 hours under refrigeration (2 - 8°C).

2.3 Legal status
This is a prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
STD Chemicals Limited, Hillbrow House, Esher, Surrey, KT10 9NW.
The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size for each product is stated.

2.8 Finished product/shelf-life specification
The finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification
The drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
None of the excipients contain material of animal or human origin. This information is consistent with the cross-reference product.

3. EXPERT REPORTS
The applicant has included expert statements in Module 2 of the application. Signed declarations and copies of the experts’ curriculum vitae are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See Section 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON PIL
The patient information leaflet has been prepared in line with the details registered for the cross-reference product.

The results of consultations with target patient groups (‘user testingg’) are in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.
Labelling
The artwork is similar to the artwork registered for the cross-reference product and complies with statutory requirements.

7. CONCLUSIONS
The data submitted with the applications are acceptable. The grant of these Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

A satisfactory non-clinical expert statement has been provided and accepted in line with the reference product.

Satisfactory justification has been provided for the absence of an Environmental Risk Assessment.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.

A satisfactory clinical expert statement has been provided and accepted, in line with the reference product.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with the data for the previously approved cross-reference product and as such, are judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted application, Carboplatin 10 mg/ml Concentrate for Solution for Infusion, which was originally approved and licensed to Neolab Limited (PL 08137/0150-2) on 27th May 2011. These licences then underwent a change of ownership to Fannin (UK) Limited on 20th July 2011 (PL 20417/0011-3).

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product are identical to the cross-reference product. Extensive clinical experience with carboplatin is considered to have demonstrated the therapeutic value of the compound. The risk:benefit ratio is therefore considered to be positive.
## CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

**PL 36390/0056-8**

### STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Application on 14th June 2011.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 20th June 2011.</td>
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<td>3</td>
<td>Following assessment of the application further information was requested regarding the quality section of the dossier on 12th August 2011.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 24th August 2011 for the quality section.</td>
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<tr>
<td>5</td>
<td>The application was determined on 21st September 2011.</td>
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CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 36390/0056-8

**STEPS TAKEN AFTER ASSESSMENT**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Carboplatin 10 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of concentrate for solution for infusion contains 10mg carboplatin.
Each 5ml vial contains 50mg carboplatin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.

Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Carboplatin is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:
   (a) first line therapy
   (b) second line therapy, after other treatments have failed.

2. Small cell carcinoma of the lung.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Dosage and Administration:
Carboplatin should be used by the intravenous route only. The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m², given as a single short term intravenous infusion over 15 to 60 minutes. Alternatively, the Calvert formula shown below may be used to determine dosage:

\[
\text{Dose (mg)} = \text{target AUC (mg/ml x min)} \times \left[ \text{GFR ml/min} + 25 \right]
\]

<table>
<thead>
<tr>
<th>Target AUC</th>
<th>Planned chemotherapy</th>
<th>Patient treatment status</th>
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<tbody>
<tr>
<td>5-7 mg/ml/min</td>
<td>Single agent carboplatin</td>
<td>Previously untreated</td>
</tr>
<tr>
<td>4-6 mg/ml/min</td>
<td>Single agent carboplatin</td>
<td>Previously treated</td>
</tr>
<tr>
<td>4-6 mg/ml/min</td>
<td>Carboplatin plus cyclophosphamide</td>
<td>Previously untreated</td>
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Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m².
Calvert’s formula should not be used in patients who have received extensive pretreatment**.

**Patients are considered heavily pretreated if they have received any of the following:
- Mitomycin C
- Nitrosourea
- Combination therapy with doxorubicin/ cyclophosphamide/cisplatin,
- Combination therapy with 5 or more agents,
- Radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of non-tolerable side effects.

Therapy should not be repeated until four weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm³ and the platelet count is at least 100,000 cells/mm³.
Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80).

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

**Impaired Renal Function:**
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression.

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

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

**Paediatrics:**
Sufficient usage of carboplatin in paediatrics has not occurred to allow specific dosage recommendations to be made.

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

**Dilution & Reconstitution:**
The product must be diluted prior to infusion, see section 6.6.

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

It should not be employed in severely myelosuppressed patients.

It is also contraindicated in patients with a history of severe allergic reactions to carboplatin or other platinum containing compounds.

Carboplatin is contraindicated in patients with bleeding tumours.

Breastfeeding.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
**Warnings:**
Carboplatin should be administered by individuals experienced in the use of anti-neoplastic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Carboplatin myelosuppression is closely related to its renal clearance. Patients with abnormal kidney function or receiving concomitant therapy with other drugs with nephrotoxic potential are likely to experience more severe and prolonged myelotoxicity. Renal function parameters should therefore be carefully assessed before and during therapy.

Carboplatin courses should not be repeated more frequently than monthly under normal circumstances. Thrombocytopenia, leukaemia and anaemia occur after administration of carboplatin. Frequent monitoring of peripheral blood counts is recommended throughout and following therapy with carboplatin. Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully respect to dosages and timing in order to minimise additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.
Renal and hepatic function impairment may be encountered with carboplatin. Very high doses of carboplatin (>5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and renal function. It is not clear whether an appropriate hydration programme might overcome effects on renal function. Dose reduction or discontinuation of therapy is required in the presence of moderate to severe alteration in renal or hepatic function test (see sections 4.2, 4.3 and 4.8).

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is also more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds.

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

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

Safety and effectiveness of carboplatin administration in children are not proven.

Precautions:
Peripheral blood counts and renal and hepatic function tests should be monitored closely. Blood counts at the beginning of the therapy and weekly to assess haematological nadir for subsequent dose adjustment are recommended.

Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose carboplatin. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with other platinum treatments and other ototoxic agents.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics is not recommended, since this may lead to increased or exacerbated toxicity due to carboplatin induced changes in renal clearance of these substances.

When combining carboplatin with other myelosuppressive compounds, the myelosuppressive effect of carboplatin and/or the other compounds may be more pronounced. Patients receiving concomitant therapy with other nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity due to decreased renal clearance of carboplatin.

Caution should be exercised when carboplatin is used concomitantly with warfarin, as cases of increased INR have been reported.

A decrease in phenytoin serum levels has been observed in cases of concurrent administration of carboplatin and phenytoin. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

The concurrent administration of carboplatin and chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin. However, the antineoplastic effect of carboplatin was not influenced by diethyl- dithiocarbamate in animal experiments or in clinical use.
4.6 PREGNANCY AND LACTATION

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

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

For women who are pregnant or become pregnant during therapy, genetic counselling should be provided.

Fertility
Women of childbearing potential should be advised to avoid becoming pregnant by using effective contraception during treatment and up to 6 months after therapy.

Carboplatin is genotoxic. Men being treated with carboplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with carboplatin.

Lactation
It is not known whether carboplatin is excreted in human milk. Breast feeding should be discontinued during carboplatin therapy (See section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Carboplatin has no or negligible influence on the ability to drive and use machines. However Carboplatin may cause nausea and vomiting, indirectly impairing the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS
Incidences of adverse reactions reported here under are based on cumulative data obtained in a large group of patients with various pretreatment prognostic features.

The following frequencies have been used:
- 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), including isolated reports

Cardiac disorders
Very rare: Cardiovascular events (cardiac failure, embolism) as well as cerebrovascular events (apoplexy) have been reported in single cases (causal relationship with carboplatin not established). Single cases of hypertension have been reported.

Blood and lymphatic system disorders
Very common: Myelosuppression is the dose-limiting toxicity of carboplatin. Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65. Myelosuppression is also worsened by therapy combining carboplatin with other compounds that are myelosuppressive. Myelosuppression is usually reversible and not cumulative when carboplatin is used as a single agent and at the recommended dosages and frequencies of administration.

At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than 50 x 10^9/l, occurs in about a third of the patients. The nadir usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy.

Leukopenia has also occurred in approximately 20% of patients but its recovery from the day of nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy.

Neutropenia with granulocyte counts below 1 x 10^9/l occurs in approximately one fifth of patients. Haemoglobin values below 9.5 mg/100ml have been observed in 48% of patients with normal baseline values. Anaemia occurs frequently and may be cumulative.
Common: Haemorrhagic complications, usually minor, have also been reported.

Uncommon: Infectious complications have occasionally been reported.

Rare: Cases of febrile neutropenia have been reported. Single cases of life-threatening infections and bleeding have occurred.

Respiratory, thoracic and mediastinal disorders
Very rare: Pulmonary fibrosis manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see General disorders below).

Nervous system disorders
Common: The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in elderly patients and those previously treated with cisplatin. Paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin.

Uncommon: Central nervous symptoms have been reported, however, they seem to be frequently attributed to concomitant antiemetic therapy.

Eye disorders
Rare: Transient visual disturbances, sometimes including transient sight loss, have been reported rarely with platinum therapy. This is usually associated with high dose therapy in renally impaired patients. Optic neuritis has been reported in post marketing surveillance.

Ear and labyrinth disorders
Very common: Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.

Common: Clinical otoxicity. Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen.

At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

Gastrointestinal disorders
Very common: Nausea without vomiting occurs in about a quarter of patients receiving carboplatin vomiting has been reported in over half of the patients and about one-third of these suffer severe emesis. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin, usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) anti-emetic medication. A quarter of patients experience no nausea or vomiting. Vomiting that could not be controlled by drugs was observed in only 1% of patients. Vomiting seems to occur more frequently in previously treated patients, particularly in patients pre-treated with cisplatin. Painful gastro-intestinal disorders occurred in 17% of patients.

Common: Diarrhoea (6%), constipation (4%), mucositis.

Rare: Taste alteration. Cases of anorexia have been reported.

Renal and urinary disorders
Very common: Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as high volume fluid hydration or forced diuresis. Nevertheless, increasing blood urea and blood urea nitrogen levels or serum creatinine levels can occur.

Common: Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min, may also be observed. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. It is not clear whether an
appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41-59 ml/min) or severe renal impairment (creatinine clearance 21-40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min.

Skin and subcutaneous tissue disorders
Common: Alopecia.

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

Rare: Cases of hyponatraemia have been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps) Uncommon: Secondary malignancies (including promyeloicytic leukaemia which occurred 6 years after monotherapy with carboplatin and preceeding irradiation) have been reported following administration of carboplatin as a single agent or in combination therapy (causal relationship not established).

General disorders and administration site conditions
Very common: Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allopurinol. Asthenia.

Common: Malaise, urticaria. flu-like syndrome, erythematous rash, pruritis.

Uncommon: Fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis

Rare: Haemolytic uraemic syndrome.

Immune system disorders
Common: Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus. These reactions are similar to those observed after administration of other platinum containing compounds and should be managed with appropriate supportive therapy.

Rare: Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial edema and facial flushing, dyspnea, hypotension, dizziness, wheezing, and tachycardia have occurred (See section 4.4).

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

Rare: Severe hepatic dysfunction (including acute liver necrosis) has been reported after administration of higher than recommended carboplatin dosages.

4.9 OVERDOSE
Symptoms of overdose
Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m² i.v. per course. At this dosage, life-threatening haematological side effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9-25 (median: days 12-17). The granulocytes had reached values of ≥ 500/µl after 8-14 days (median: 11) and the thrombocytes values of ≥ 25,000/µl after 3-8 days (median: 7).

The following non-haematological side effects also occurred: renal function disturbances with a 50% drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinemia, mucositis, diarrhoea, nausea and vomiting with headache, erythema, and severe infection. In the
majority of cases, hearing disturbances were transient and reversible.

Treatment of overdose
There is no known antidote for carboplatin over dosage. The anticipated complications of over dosage would be related to myelosuppression as well as impairment of hepatic and renal function. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological side effects.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: LO1X AO2

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

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of carboplatin, reported values for the terminal elimination half-lives of free ultrafilterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultrafilterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primarily in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

Carboplatin clearance has been reported to vary by 3- to 4- fold in paediatric patients. As for adult patients, literature data suggest that renal function may contribute to the variation in carboplatin clearance.

5.3 PRECLINICAL SAFETY DATA
Carboplatin has been shown to be embryotoxic and teratogenic in rats. (See para. 4.6, Pregnancy and Lactation.) It is mutagenic in vivo and in vitro and although the carcinogenic potential of carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Water for injections.

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

6.3 SHELF LIFE
24 months (unopened).

After dilution:
24 hours under refrigeration (2 - 8°C).
6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25 °C. Do not store in a refrigerator. Store containers in the original carton. Protect from light.

After dilution (see section 6.6.):

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for solutions with a final concentration of carboplatin 0.4 mg/ml or 2.0 mg/ml after dilution of the carboplatin 10 mg/ml with 5% Glucose Injection BP, or 0.9% Sodium Chloride Injection BP.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Clear vials of hydrolytic Type I glass, packed in a carton.

Vials are closed with a fluoro resin coated bromobutyl rubber stopper with an aluminium crimp cap with a polypropylene flip-off lid.

Packs of 1 vial containing 50 mg/5ml of carboplatin.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
This product is for single dose use only.

Solutions should only be used if clear and particle free.

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

Dilution:
The product must be diluted before use. It may be diluted with 5% Glucose Injection BP, or 0.9% Sodium Chloride Injection BP, to concentrations from 2.0 mg/ml to as low as 0.4 mg/ml (400 micrograms/ml).

Guidelines for the safe handling of anti-neoplastic agents:
1 Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents
2 This should be performed in a designated area.
3 Adequate protective gloves should be worn.
4 Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. In the event of contact with the eyes, wash with water and/or saline.
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 cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000 °C. Liquid waste may be flushed with copious amounts of water.
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.

7 MARKETING AUTHORISATION HOLDER
STD CHEMICALS LIMITED,
HILLBROW HOUSE,
HILLBROW ROAD,
ESHER,
SURREY,
KT10 9NW
8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/09/2011

10 DATE OF REVISION OF THE TEXT
21/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Carboplatin 10 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of concentrate for solution for infusion contains 10mg carboplatin.
Each 15ml vial contains 150mg carboplatin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Carboplatin is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:
   (a) first line therapy
   (b) second line therapy, after other treatments have failed.

2. Small cell carcinoma of the lung.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Dosage and Administration:
Carboplatin should be used by the intravenous route only.
The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m², given as a single short term intravenous infusion over 15 to 60 minutes. Alternatively, the Calvert formula shown below may be used to determine dosage:

\[
\text{Dose (mg)} = \text{target AUC (mg/ml x min)} \times \left[ \text{GFR ml/min} + 25 \right]
\]

<table>
<thead>
<tr>
<th>Target AUC</th>
<th>Planned chemotherapy</th>
<th>Patient treatment status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-7 mg/ml.min</td>
<td>Single agent carboplatin</td>
<td>Previously untreated</td>
</tr>
<tr>
<td>4-6 mg/ml.min</td>
<td>Single agent carboplatin</td>
<td>Previously treated</td>
</tr>
<tr>
<td>4-6 mg/ml.min</td>
<td>Carboplatin plus cyclophosphamide</td>
<td>Previously untreated</td>
</tr>
</tbody>
</table>

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m².
Calvert’s formula should not be used in patients who have received extensive pretreatment**.

**Patients are considered heavily pretreated if they have received any of the following:
- Mitomycin C
- Nitrosourea
- Combination therapy with doxorubicin/cyclophosphamide/cisplatin,
- Combination therapy with 5 or more agents,
- Radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of non-tolerable side effects.

Therapy should not be repeated until four weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm³ and the platelet count is at least 100,000 cells/mm³.
Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80).

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

*Impaired Renal Function:*
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression.

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

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

*Paediatrics:*
Sufficient usage of carboplatin in paediatrics has not occurred to allow specific dosage recommendations to be made.

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

*Dilution & Reconstitution:*
The product must be diluted prior to infusion, see section 6.6.

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

It should not be employed in severely myelosuppressed patients.

It is also contraindicated in patients with a history of severe allergic reactions to carboplatin or other platinum containing compounds.

Carboplatin is contraindicated in patients with bleeding tumours.

Breastfeeding.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
*Warnings:*
Carboplatin should be administered by individuals experienced in the use of anti-neoplastic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Carboplatin myelosuppression is closely related to its renal clearance. Patients with abnormal kidney function or receiving concomitant therapy with other drugs with nephrotoxic potential are likely to experience more severe and prolonged myelotoxicity. Renal function parameters should therefore be carefully assessed before and during therapy.

Carboplatin courses should not be repeated more frequently than monthly under normal circumstances. Thrombocytopenia, leukopenia and anaemia occur after administration of carboplatin. Frequent monitoring of peripheral blood counts is recommended throughout and following therapy with carboplatin. Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosages and timing in order to minimise additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.
Renal and hepatic function impairment may be encountered with carboplatin. Very high doses of carboplatin (>5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and renal function. It is not clear whether an appropriate hydration programme might overcome effects on renal function. Dose reduction or discontinuation of therapy is required in the presence of moderate to severe alteration in renal or hepatic function test (see sections 4.2, 4.3 and 4.8).

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is also more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds.

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

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

Safety and effectiveness of carboplatin administration in children are not proven.

Precautions:
Peripheral blood counts and renal and hepatic function tests should be monitored closely. Blood counts at the beginning of the therapy and weekly to assess haematological nadir for subsequent dose adjustment are recommended.

Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose carboplatin. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and otoxicity are more likely seen in patients previously treated with other platinum treatments and other ototoxic agents.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics is not recommended, since this may lead to increased or exacerbated toxicity due to carboplatin induced changes in renal clearance of these substances.

When combining carboplatin with other myelosuppressive compounds, the myelosuppressive effect of carboplatin and/or the other compounds may be more pronounced. Patients receiving concomitant therapy with other nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity due to decreased renal clearance of carboplatin.

Caution should be exercised when carboplatin is used concomitantly with warfarin, as cases of increased INR have been reported.

A decrease in phenytoin serum levels has been observed in cases of concurrent administration of carboplatin and phenytoin. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

The concurrent administration of carboplatin and chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin. However, the antineoplastic effect of carboplatin was not influenced by diethyl- dithiocarbamate in animal experiments or in clinical use.
4.6 PREGNANCY AND LACTATION

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

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

For women who are pregnant or become pregnant during therapy, genetic counselling should be
provided.

Fertility
Women of childbearing potential should be advised to avoid becoming pregnant by using effective
contraception during treatment and up to 6 months after therapy.

Carboplatin is genotoxic. Men being treated with carboplatin are advised not to father a child during
and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment
because of the possibility of irreversible infertility due to therapy with carboplatin.

Lactation
It is not known whether carboplatin is excreted in human milk. Breast feeding should be discontinued
during carboplatin therapy (See section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Carboplatin has no or negligible influence on the ability to drive and use machines. However
Carboplatin may cause nausea and vomiting, indirectly impairing the ability to drive and use
machines

4.8 UNDESIRABLE EFFECTS

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

The following frequencies have been used:
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), including isolated reports

Cardiac disorders
Very rare: Cardiovascular events (cardiac failure, embolism) as well as cerebrovascular events
(apoplexy) have been reported in single cases (causal relationship with carboplatin not established).
Single cases of hypertension have been reported.

Blood and lymphatic system disorders
Very common: Myelosuppression is the dose-limiting toxicity of carboplatin. Myelosuppression
may be more severe and prolonged in patients with impaired renal function, extensive prior
treatment, poor performance status and age above 65. Myelosuppression is also worsened by
therapy combining carboplatin with other compounds that are myelosuppressive. Myelosuppression
is usually reversible and not cumulative when carboplatin is used as a single agent and at the
recommended dosages and frequencies of administration.

At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia,
with nadir platelet counts of less than 50 x 10⁹/l, occurs in about a third of the patients. The nadir
usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy.

Leukopenia has also occurred in approximately 20% of patients but its recovery from the day of
nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy.

Neutropenia with granulocyte counts below 1 x 10⁹/l occurs in approximately one fifth of patients.
Haemoglobin values below 9.5 mg/100ml have been observed in 48% of patients with normal base-
line values. Anaemia occurs frequently and may be cumulative.
**Common:** Haemorrhagic complications, usually minor, have also been reported.

**Uncommon:** Infectious complications have occasionally been reported.

**Rare:** Cases of febrile neutropenia have been reported. Single cases of life-threatening infections and bleeding have occurred.

**Respiratory, thoracic and mediastinal disorders**

*Very rare:* Pulmonary fibrosis manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see General disorders below).

**Nervous system disorders**

*Common:* The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in elderly patients and those previously treated with cisplatin. Paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin.

**Uncommon:** Central nervous symptoms have been reported, however, they seem to be frequently attributed to concomitant antiemetic therapy.

**Eye disorders**

*Rare:* Transient visual disturbances, sometimes including transient sight loss, have been reported rarely with platinum therapy. This is usually associated with high dose therapy in renally impaired patients. Optic neuritis has been reported in post marketing surveillance.

**Ear and labyrinth disorders**

*Very common:* Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.

*Common:* Clinical ototoxicity. Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen.

At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

**Gastrointestinal disorders**

*Very common:* Nausea without vomiting occurs in about a quarter of patients receiving carboplatin vomiting has been reported in over half of the patients and about one-third of these suffer severe emesis. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin, usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) anti-emetic medication. A quarter of patients experience no nausea or vomiting. Vomiting that could not be controlled by drugs was observed in only 1% of patients. Vomiting seems to occur more frequently in previously treated patients, particularly in patients pre-treated with cisplatin. Painful gastro-intestinal disorders occurred in 17% of patients.

*Common:* Diarrhoea (6%), constipation (4%), mucositis.

**Renal and urinary disorders**

*Very common:* Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as high volume fluid hydration or forced diuresis. Nevertheless, increasing blood urea and blood urea nitrogen levels or serum creatinine levels can occur.

*Common:* Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min, may also be observed. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. It is not clear whether an
appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41-59 ml/min) or severe renal impairment (creatinine clearance 21-40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min.

Skin and subcutaneous tissue disorders
Common: Alopecia.

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

Rare: Cases of hyponatraemia have been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Secondary malignancies (including promyelocytic leukaemia which occurred 6 years after monotherapy with carboplatin and preceding irradiation) have been reported following administration of carboplatin as a single agent or in combination therapy (causal relationship not established).

General disorders and administration site conditions
Very common: Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allopurinol. Asthenia.

Common: Malaise, urticaria. flu-like syndrome, erythematous rash, pruritis.

Uncommon: Fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis

Rare: Haemolytic uraemic syndrome.

Immune system disorders
Common: Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus. These reactions are similar to those observed after administration of other platinum containing compounds and should be managed with appropriate supportive therapy.

Rare: Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial oedema and facial flushing, dyspnoea, hypotension, dizziness, wheezing, and tachycardia have occurred (See section 4.4).

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

Rare: Severe hepatic dysfunction (including acute liver necrosis) has been reported after administration of higher than recommended carboplatin dosages.

4.9 OVERDOSE
Symptoms of overdose
Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m² i.v. per course. At this dosage, life-threatening haematological side effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9-25 (median: days 12-17). The granulocytes had reached values of ≥ 500/µl after 8-14 days (median: 11) and the thrombocytes values of ≥ 25,000/µl after 3-8 days (median: 7).

The following non-haematological side effects also occurred: renal function disturbances with a 50% drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, erythema, and severe infection. In the
majority of cases, hearing disturbances were transient and reversible.

Treatment of overdose
There is no known antidote for carboplatin over dosage. The anticipated complications of over dosage would be related to myelosuppression as well as impairment of hepatic and renal function. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological side effects.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: LO1X AO2

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

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of carboplatin, reported values for the terminal elimination half-lives of free ultrafilterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultrafilterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primarily in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

Carboplatin clearance has been reported to vary by 3- to 4-fold in paediatric patients. As for adult patients, literature data suggest that renal function may contribute to the variation in carboplatin clearance.

5.3 PRECLINICAL SAFETY DATA
Carboplatin has been shown to be embryotoxic and teratogenic in rats. (See para. 4.6, Pregnancy and Lactation.) It is mutagenic in vivo and in vitro and although the carcinogenic potential of carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Water for injections.

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

6.3 SHELF LIFE
24 months (unopened).

After dilution:
24 hours under refrigeration (2 - 8°C).
6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
Do not store above 25 °C. Do not store in a refrigerator. Store containers in the original carton. 
Protect from light.

After dilution (see section 6.6.):

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for solutions with a final concentration of carboplatin 0.4 mg/ml or 2.0 mg/ml after dilution of the carboplatin 10 mg/ml with 5% Glucose Injection BP, or 0.9% Sodium Chloride Injection BP.

From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 **NATURE AND CONTENTS OF CONTAINER**
Clear vials of hydrolytic Type I glass, packed in a carton.

Vials are closed with a fluoro resin coated bromobutyl rubber stopper with an aluminium crimp cap with a polypropylene flip-off lid.

Packs of 1 vial containing 50 mg/5ml of carboplatin.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
This product is for single dose use only.

Solutions should only be used if clear and particle free.

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

**Dilution:**
The product must be diluted before use. It may be diluted with 5% Glucose Injection BP, or 0.9% Sodium Chloride Injection BP, to concentrations from 2.0 mg/ml to as low as 0.4 mg/ml (400 micrograms/ml).

Guidelines for the safe handling of anti-neoplastic agents:
1. Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents
2. This should be performed in a designated area.
3. Adequate protective gloves should be worn.
4. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes.
   In the event of contact with the eyes, wash with water and/or saline.
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 cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000 °C. Liquid waste may be flushed with copious amounts of water.
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.

7 **MARKETING AUTHORISATION HOLDER**
STD CHEMICALS LIMITED,
HILLBROW HOUSE,
HILLBROW ROAD,
ESHER,
SURREY,
KT10 9NW
8 MARKETING AUTHORISATION NUMBER(S)
   PL 36390/0057

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   21/09/2011

10 DATE OF REVISION OF THE TEXT
    21/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Carboplatin 10 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of concentrate for solution for infusion contains 10mg carboplatin.
Each 45ml vial contains 450mg carboplatin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.

Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Carboplatin is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:
   (a) first line therapy
   (b) second line therapy, after other treatments have failed.

2. Small cell carcinoma of the lung.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Dosage and Administration:
Carboplatin should be used by the intravenous route only. The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m², given as a single short term intravenous infusion over 15 to 60 minutes. Alternatively, the Calvert formula shown below may be used to determine dosage:

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

<table>
<thead>
<tr>
<th>Target AUC</th>
<th>Planned chemotherapy</th>
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<tbody>
<tr>
<td>5-7 mg/ml.min</td>
<td>Single agent carboplatin</td>
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</tr>
<tr>
<td>4-6 mg/ml.min</td>
<td>Single agent carboplatin</td>
<td>Previously treated</td>
</tr>
<tr>
<td>4-6 mg/ml.min</td>
<td>Carboplatin plus cyclophosphamide</td>
<td>Previously untreated</td>
</tr>
</tbody>
</table>

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m². Calvert’s formula should not be used in patients who have received extensive pretreatment**.

**Patients are considered heavily pretreated if they have received any of the following:
- Mitomycin C
- Nitrosourea
- Combination therapy with doxorubicin/ cyclophosphamide/cisplatin,
- Combination therapy with 5 or more agents,
- Radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of non-tolerable side effects.

Therapy should not be repeated until four weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm³ and the platelet count is at least 100,000 cells/mm³.
Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80).

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

**Impaired Renal Function:**
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression.

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

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

**Paediatrics:**
Sufficient usage of carboplatin in paediatrics has not occurred to allow specific dosage recommendations to be made.

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

**Dilution & Reconstitution:**
The product must be diluted prior to infusion, see section 6.6.

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

It should not be employed in severely myelosuppressed patients.

It is also contraindicated in patients with a history of severe allergic reactions to carboplatin or other platinum containing compounds.

Carboplatin is contraindicated in patients with bleeding tumours.

Breastfeeding.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
**Warnings:**
Carboplatin should be administered by individuals experienced in the use of anti-neoplastic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Carboplatin myelosuppression is closely related to its renal clearance. Patients with abnormal kidney function or receiving concomitant therapy with other drugs with nephrotoxic potential are likely to experience more severe and prolonged myelotoxicity. Renal function parameters should therefore be carefully assessed before and during therapy.

Carboplatin courses should not be repeated more frequently than monthly under normal circumstances. Thrombocytopenia, leukopenia and anaemia occur after administration of carboplatin. Frequent monitoring of peripheral blood counts is recommended throughout and following therapy with carboplatin. Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosages and timing in order to minimise additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.
Renal and hepatic function impairment may be encountered with carboplatin. Very high doses of carboplatin (>5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and renal function. It is not clear whether an appropriate hydration programme might overcome effects on renal function. Dose reduction or discontinuation of therapy is required in the presence of moderate to severe alteration in renal or hepatic function test (see sections 4.2, 4.3 and 4.8).

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is also more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds.

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

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

Safety and effectiveness of carboplatin administration in children are not proven.

Precautions:
Peripheral blood counts and renal and hepatic function tests should be monitored closely. Blood counts at the beginning of the therapy and weekly to assess haematological nadir for subsequent dose adjustment are recommended.

Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose carboplatin. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with other platinum treatments and other ototoxic agents.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics is not recommended, since this may lead to increased or exacerbated toxicity due to carboplatin induced changes in renal clearance of these substances.

When combining carboplatin with other myelosuppressive compounds, the myelosuppressive effect of carboplatin and/or the other compounds may be more pronounced. Patients receiving concomitant therapy with other nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity due to decreased renal clearance of carboplatin.

Caution should be exercised when carboplatin is used concomitantly with warfarin, as cases of increased INR have been reported.

A decrease in phenytoin serum levels has been observed in cases of concurrent administration of carboplatin and phenytoin. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

The concurrent administration of carboplatin and chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin. However, the antineoplastic effect of carboplatin was not influenced by diethyl- dithiocarbamate in animal experiments or in clinical use.
4.6 PREGNANCY AND LACTATION

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

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

For women who are pregnant or become pregnant during therapy, genetic counselling should be
provided.

Fertility
Women of childbearing potential should be advised to avoid becoming pregnant by using effective
contraception during treatment and up to 6 months after therapy.

Carboplatin is genotoxic. Men being treated with carboplatin are advised not to father a child during
and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment
because of the possibility of irreversible infertility due to therapy with carboplatin.

Lactation
It is not known whether carboplatin is excreted in human milk. Breast feeding should be discontinued
during carboplatin therapy (See section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Carboplatin has no or negligible influence on the ability to drive and use machines. However
Carboplatin may cause nausea and vomiting, indirectly impairing the ability to drive and use
machines

4.8 UNDESIRABLE EFFECTS
Incidences of adverse reactions reported here under are based on cumulative data obtain in a large
group of patients with various pretreatment prognostic features.

The following frequencies have been used:
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), including isolated reports

Cardiac disorders
Very rare: Cardiovascular events (cardiac failure, embolism) as well as cerebrovascular events
(apoplexy) have been reported in single cases (causal relationship with carboplatin not established).
Single cases of hypertension have been reported.

Blood and lymphatic system disorders
Very common: Myelosuppression is the dose-limiting toxicity of carboplatin. Myelosuppression
may be more severe and prolonged in patients with impaired renal function, extensive prior
treatment, poor performance status and age above 65. Myelosuppression is also worsened by
therapy combining carboplatin with other compounds that are myelosuppressive. Myelosuppression
is usually reversible and not cumulative when carboplatin is used as a single agent and at the
recommended dosages and frequencies of administration.

At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia,
with nadir platelet counts of less than 50 x 10⁹/l, occurs in about a third of the patients. The nadir
usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy.

Leukopenia has also occurred in approximately 20% of patients but its recovery from the day of
nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy.

Neutropenia with granulocyte counts below 1 x 10⁹/l occurs in approximately one fifth of patients.
Haemoglobin values below 9.5 mg/100ml have been observed in 48% of patients with normal base-
line values. Anaemia occurs frequently and may be cumulative.
**Common:** Haemorrhagic complications, usually minor, have also been reported.

**Uncommon:** Infectious complications have occasionally been reported.

**Rare:** Cases of febrile neutropenia have been reported. Single cases of life-threatening infections and bleeding have occurred.

**Respiratory, thoracic and mediastinal disorders**

**Very rare:** Pulmonary fibrosis manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see General disorders below).

**Nervous system disorders**

**Common:** The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in elderly patients and those previously treated with cisplatin. Paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin.

**Uncommon:** Central nervous symptoms have been reported, however, they seem to be frequently attributed to concomitant antiemetic therapy.

**Eye disorders**

**Rare:** Transient visual disturbances, sometimes including transient sight loss, have been reported rarely with platinum therapy. This is usually associated with high dose therapy in renally impaired patients. Optic neuritis has been reported in post marketing surveillance.

**Ear and labyrinth disorders**

**Very common:** Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.

**Common:** Clinical otoxicity. Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen.

At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

**Gastrointestinal disorders**

**Very common:** Nausea without vomiting occurs in about a quarter of patients receiving carboplatin vomiting has been reported in over half of the patients and about one-third of these suffer severe emesis. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin, usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) anti-emetic medication. A quarter of patients experience no nausea or vomiting. Vomiting that could not be controlled by drugs was observed in only 1% of patients. Vomiting seems to occur more frequently in previously treated patients, particularly in patients pre-treated with cisplatin. Painful gastrointestinal disorders occurred in 17% of patients.

**Common:** Diarrhoea (6%), constipation (4%), mucositis.

**Rare:** Taste alteration. Cases of anorexia have been reported.

**Renal and urinary disorders**

**Very common:** Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as high volume fluid hydration or forced diuresis. Nevertheless, increasing blood urea and blood urea nitrogen levels or serum creatinine levels can occur.

**Common:** Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min, may also be observed. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. It is not clear whether an
appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41-59 ml/min) or severe renal impairment (creatinine clearance 21-40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min.

Skin and subcutaneous tissue disorders
*Common:* Alopecia.

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

*Rare:* Cases of hyponatraemia have been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
*Uncommon:* Secondary malignancies (including promyelocytic leukaemia which occurred 6 years after monotherapy with carboplatin and preceeding irradiation) have been reported following administration of carboplatin as a single agent or in combination therapy (causal relationship not established).

General disorders and administration site conditions
*Very common:* Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allopurinol. Asthenia.

*Common:* Malaise, urticaria. flu-like syndrome, erythematous rash, pruritis.

*Uncommon:* Fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis

*Rare:* Haemolytic uraemic syndrome.

Immune system disorders
*Common:* Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus. These reactions are similar to those observed after administration of other platinum containing compounds and should be managed with appropriate supportive therapy.

*Rare:* Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial oedema and facial flushing, dyspnoea, hypotension, dizziness, wheezing, and tachycardia have occurred (See section 4.4).

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

*Rare:* Severe hepatic dysfunction (including acute liver necrosis) has been reported after administration of higher than recommended carboplatin dosages.

4.9 **OVERDOSE**

Symptoms of overdose
Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m² i.v. per course. At this dosage, life-threatening haematological side effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9-25 (median: days 12-17). The granulocytes had reached values of $\geq 500/\mu l$ after 8-14 days (median: 11) and the thrombocytes values of $\geq 25.000/\mu l$ after 3-8 days (median: 7).

The following non-haematological side effects also occurred: renal function disturbances with a 50% drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, erythema, and severe infection. In the
majority of cases, hearing disturbances were transient and reversible.

Treatment of overdose
There is no known antidote for carboplatin over dosage. The anticipated complications of over
dosage would be related to myelosuppression as well as impairment of hepatic and renal function.
Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of
managing haematological side effects.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: LO1X AO2
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 those of cisplatin, thus producing predominantly
interstrand and intrastrand DNA crosslinks. Following administration of carboplatin in man, linear
relationships exist between dose and plasma concentrations of total and free ultrafilterable platinum.
The area under the plasma concentration versus time curve for total platinum also shows a linear
relationship with the dose when creatinine clearance exceeds 60 ml/min.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in
plasma. Following the administration of carboplatin, reported values for the terminal elimination
half-lives of free ultrafilterable platinum and carboplatin in man are approximately 6 hours and 1.5
hours respectively. During the initial phase, most of the free ultrafilterable platinum is present as
carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of
plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted
primarily in the urine, with recovery of approximately 70% of the administered platinum within 24
hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultra
filterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

Carboplatin clearance has been reported to vary by 3- to 4- fold in paediatric patients. As for adult
patients, literature data suggest that renal function may contribute to the variation in carboplatin
clearance.

5.3 PRECLINICAL SAFETY DATA
Carboplatin has been shown to be embryotoxic and teratogenic in rats. (See para. 4.6, Pregnancy and
Lactation.) It is mutagenic in vivo and in vitro and although the carcinogenic potential of carboplatin
has not been studied, compounds with similar mechanisms of action and mutagenicity have been
reported to be carcinogenic.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Water for injections.

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

6.3 SHELF LIFE
24 months (unopened).

After dilution:
24 hours under refrigeration (2 - 8°C).
6.4  SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25 °C. Do not store in a refrigerator. Store containers in the original carton. Protect from light.

After dilution (see section 6.6.):

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for solutions with a final concentration of carboplatin 0.4 mg/ml or 2.0 mg/ml after dilution of the carboplatin 10 mg/ml with 5% Glucose Injection BP, or 0.9% Sodium Chloride Injection BP.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5  NATURE AND CONTENTS OF CONTAINER
Clear vials of hydrolytic Type I glass, packed in a carton.

Vials are closed with a fluoro resin coated bromobutyl rubber stopper with an aluminium crimp cap with a polypropylene flip-off lid.

Packs of 1 vial containing 50 mg/5ml of carboplatin.

6.6  SPECIAL PRECAUTIONS FOR DISPOSAL
This product is for single dose use only.

Solutions should only be used if clear and particle free.

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

Dilution:
The product must be diluted before use. It may be diluted with 5% Glucose Injection BP, or 0.9% Sodium Chloride Injection BP, to concentrations from 2.0 mg/ml to as low as 0.4 mg/ml (400 micrograms/ml).

Guidelines for the safe handling of anti-neoplastic agents:
1  Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents
2  This should be performed in a designated area.
3  Adequate protective gloves should be worn.
4  Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. In the event of contact with the eyes, wash with water and/or saline.
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 cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000 °C. Liquid waste may be flushed with copious amounts of water.
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.

7  MARKETING AUTHORISATION HOLDER
STD CHEMICALS LIMITED,
HILLBROW HOUSE,
HILLBROW ROAD,
ESHER,
SURREY,
KT10 9NW
8 MARKETING AUTHORISATION NUMBER(S)
   PL 36390/0058

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   21/09/2011

10 DATE OF REVISION OF THE TEXT
     21/09/2011
UKPAR Carboplatin 10 mg/ml Concentrate for Solution for Infusion
PL 36390/0056-8

PACKAGE LEAFLET: INFORMATION FOR THE USER

Carboplatin 10 mg/ml Concentrate for Solution for Infusion

Carboplatin

Read all of the leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Carboplatin is and what it is used for.
2. Before you are given Carboplatin.
3. How Carboplatin will be used.
4. Possible side effects.
5. How to store Carboplatin.
6. Further information.

1. WHAT CARBOPLATIN IS AND WHAT IT IS USED FOR

Carboplatin belongs to a group of medicines known as platinum compounds, which are used to treat cancer. Carboplatin is used against advanced cancer of the ovary and small cell cancer of the lung.

2. BEFORE YOU ARE GIVEN CARBOPLATIN

Do not use Carboplatin
- If you are allergic (hypersensitive) to carboplatin.
- If you are allergic to another drug that belongs to the group of platinum containing compounds.
- If you have severe problems with your kidneys.
- If you have an imbalance of your blood cells (severe myelosuppression).
- If you have a tumour that bleeds.
- If you are pregnant or trying to get pregnant.

If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do so as soon as possible and before receiving an infusion. Carboplatin is usually given to patients in hospital. Normally you should not handle this medicine. Your doctor or nurse will administer the medicine and will carefully and frequently monitor you during and after treatment. You will normally have blood tests before each administration.

Take special care with Carboplatin
- If your kidneys are not working properly the effects of carboplatin on the blood (haematopoietic system) are increased and prolonged compared to patients with normal kidney function. Your doctor will want to monitor you more regularly if your kidneys are not working properly.
- Carboplatin can cause serious allergic reactions (difficulty in breathing and dizziness). If you had previously received a platinum medicine, Carboplatin may cause severe depression of your bone marrow and a decrease of blood cells. This is more pronounced if you are also receiving other myelosuppressive medicines or your kidneys are not working properly.
- Carboplatin may cause severe sickness and you may receive premedication with anti-emetics to reduce this side effect.
- Carboplatin may cause abnormalities in your nervous system, such as pain and weakness or hearing problems, especially if you have received platinum treatments in the past. Your doctor may regularly assess you.

If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do as soon as possible and before receiving Carboplatin. Using other medicines

You should tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should tell your doctor if you are taking any of the following medicines as they may interact with Carboplatin.
- other medicines that are known to affect blood cell formation in the bone marrow.
- other medicines that are known to be toxic to your kidneys (e.g. aminoglycoside antibiotics).
- other medicines that are known to damage the hearing or balance functions of the ears (e.g. aminoglycoside antibiotics; furosemide used to treat heart failure and oedema).
- chemotherapeutic agents (substances binding to carboplatin thereby decreasing the effect of carboplatin).
- phenytoin used to treat epilepsy.
- warfarin used to prevent the formation of blood clots.

Pregnancy and breast-feeding
Tell your doctor if you are trying to become pregnant, are already pregnant, or are breast-feeding before being treated with Carboplatin. If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do as soon as possible and before receiving Carboplatin. Pregnancy

You must not be treated with Carboplatin during pregnancy unless clearly indicated by your doctor. Animal studies have shown a possible risk of abnormalities in the developing fetus. If you are being treated with carboplatin whilst pregnant, you should discuss with your doctor the possible risk of effects on your unborn child. Women of child-bearing potential must use an effective method of contraception both before and during treatment with carboplatin. Since carboplatin can cause genetic damage, if pregnancy occurs during treatment with carboplatin, genetic counselling is recommended. Genetic counselling is also recommended for patients wishing to have children after treatment with Carboplatin.

Breast-feeding

It is not known whether carboplatin is excreted into the breast milk. Therefore, during treatment with Carboplatin you should discontinue breast-feeding.

Fertility

Carboplatin can cause genetic damage. Women of child-bearing potential should be advised to avoid becoming pregnant by using effective contraception both before and during treatment. Women who are pregnant or become pregnant during therapy, gene counselling should be provided.

Men treated with carboplatin are advised not to father a child during, and up to 6 months after treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility.

Ask your doctor or nurse for advice before using any medicine.

Driving and using machines

Carboplatin does not affect your ability to drive and use machines. However, you should take extra care when you are first given carboplatin, especially if you feel dizzy or unwell.

3. HOW CARBOPLATIN WILL BE USED

Carboplatin will always be administered by a nurse or doctor experienced in the use of cancer treatment.

It is usually given in a drip by slow injection into a vein and will usually take between 15 and 60 minutes to be administered. You will be kept for this time.

Your dose will be dependent on your height and weight, function of your blood system and your kidney function.

Your doctor will choose the best dose for you. Carboplatin will be diluted before use.

Adult

The usual dose is 400 mg/m2 of your body surface area (calculated from your height and weight).

Elderly

The usual adult doses may be used although the doctor may choose to use a different dose.

Kidney problems

The amount given may vary, according to how well your kidneys are working. If you suffer from kidney problems your doctor may reduce the dose and may perform frequent blood tests as well as monitoring your kidney function.

Children

There has not been enough usage of carboplatin in children to allow the recommendation of specific dose.
UKPAR  Carboplatin 10 mg/ml Concentrate for Solution for Infusion  PL 36390/0056-8

You may feel sick while you are being treated with Carboplatin. Your doctor may give you another medicine to reduce these effects before you are treated with Carboplatin.

There will be usual gap of 4 weeks between each dose of Carboplatin. Your doctor will want to perform some blood tests each week after giving you Carboplatin. So he/she can decide on the correct next dosage for you. You may receive Carboplatin in combination with other medicines and your dose may be adjusted.

If you receive more Carboplatin than you should
It is unlikely that you will be given too much carboplatin. However in the event that this occurs you may have some problems with your kidneys. If you are worried that too much has been administered or you have any questions about the dose being given you should talk to the doctor.

If you miss a dose of Carboplatin
It is very unlikely that you will miss a dose of your medicine, as your doctor will have instructions on when to give it to you. If you think you have missed a dose please talk to your doctor.

If you stop using Carboplatin
Do not stop treatment before talking to your doctor. If you have any further question on the use of this product ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Carboplatin can have side effects although not everybody gets them.

Tell your doctor immediately if you notice any of the following:
- abnormal bruising, bleeding, or signs of infection such as a sore throat and high temperature
- severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat which may cause difficulty in swallowing or breathing (angio-oedema)
- stomatitis (mouth ulcers) (e.g. sore lips or mouth ulcers)

Other side effects:
- if any of the following side effects gets serious, please tell your doctor or nurse.
- very common side effects (affects more than 1 user in 10)
  - changes in your red and white blood cells and platelets (myelosuppression). Your doctor may want to monitor you.
  - anaemia (a condition in which there is a decrease number of red blood cells which lead to tiredness)
  - increase in the level of creatinine and urea in your blood. Your doctor may want to monitor you.
  - shortness of breath
  - abnormal liver enzymes levels. Your doctor may want to monitor you.
  - increased uric acid levels in your blood which may lead to gout.
  - feeling or being sick
  - abdominal pain and cramp
  - unusual feelings of tiredness or weakness
  - decrease in the levels of salts in your blood. Your doctor may want to monitor you.
  - damage to the kidneys (renal toxicity)
- common side effects (affects 1 to 10 users in 100)
  - unusual bruising or bleeding (haemorrhagic complications)
  - reduced function of your kidneys
  - diarrhoea, constipation, sore lips or mouth ulcers (mucositis)
  - allergic reactions including rash, urticaria, skin reddening, itching, high temperature
  - ringing in the ears (dizziness), hearing impairment and hearing loss
  - pins and needles (peripheral neuropathy)
  - hair loss
  - feeling unwell
  - decreased serum levels of calcium
  - flu-like symptoms
  - loss or lack of body strength
  - fever
- uncommon side effects (affects 1 to 10 users in 1,000)
  - secondary malignancies
  - central nervous symptoms
  - fever and chills without evidence of infection
  - redness, swelling and pain or dead skin around the injection site (injection site reaction)
  - infection

Rare side effects (affects 1 to 10 users in 10,000)
- feeling tired with a high temperature due to low levels of white blood cells (febrile neutropenia)
- life-threatening infections and bleeding
- taste alteration
- loss of appetite (anorexia)
- severely impaired liver function, damage or death of liver cells. Your doctor may want to monitor you.
- temporary visual disturbances including temporary sight loss
- inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- haematological/oncological syndrome (a disease characterised by acute renal failure, decreased number of red blood cells (microangiopathic haemolytic anaemia) and a low platelet count)
- severe allergic reactions (anaphylaxis/anaphylactic reactions)
- symptoms of a severe allergic reaction include sudden wheezing or tightness of chest, swelling of the eyelids, face or lips, facial flushing, hypotension, tachycardia, urticaria, dyspnoea, dizziness and anaphylactic shock
- low sodium levels in your blood leading to cramps, fits and coma

Very rare side effects (affects less than 1 user in 10,000)
- heart failure, blockage in blood vessels of your heart, high blood pressure
- bleeding in the brain, which may result in a stroke or loss of consciousness
- scarring of the lungs which causes shortness of breath and/or cough (pulmonary fibrosis).

If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE CARBOPLAIN

Keep out of the reach and sight of children.

Do not store above 25 °C. Do not store in a refrigerator.

Keep the vial in the outer carton in order to protect from light. Do not use this medicinal product after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

The product should be diluted and used immediately after opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Carboplatin 10 mg/ml Concentrate for Solution for Infusion contains
The vials contain:
- The active substance Carboplatin.
- Each ml of concentrate for solution for infusion contains: 10mg of carboplatin. Each 5ml vial contains 50mg of carboplatin. Each 15ml vial contains 150mg of carboplatin and each 45ml vial contains 450mg of carboplatin.
- The other ingredients is water for injections

What Carboplatin 10 mg/ml Concentrate for Solution for Infusion looks like and contents of the pack
Carboplatin 10 mg/ml Concentrate for Solution for Infusion is a clear, colourless or almost colourless solution. It is presented in clear vials of hydrolytic Type I glass, packed in a carton.

Vials are closed with a fluororesin coated bromobutyl rubber stopper with an aluminium crimp cap with a polypropylene flip-off lid.

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

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder is STD Chemicals Ltd., Hibbleworth House, Hibbleworth Road, Exeter, Devon, EX2 0SY.

The manufacturer responsible for batch release is Nootlab Ltd, 57 High Street, Oadham, Hants, B22 9LF.

This leaflet was last revised in June 2011.
Carboplatin 10 mg/ml Concentrate for Solution for Infusion

The following information is intended for medical or healthcare professionals only: instructions for use

Dosage and Administration:
Carboplatin should be used by the intravenous route only. The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m² given as a single short term intravenous infusion over 15 to 60 minutes. Alternatively, the Carver formula shown below may be used to determine dosage:

Dose (mg) = Target AUC (mg/m² x min) x (GFR min/min + 25)

<table>
<thead>
<tr>
<th>Target AUC</th>
<th>Planned chemotherapy</th>
<th>Patient treatment status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-7 mg/m²/min</td>
<td>Single-agent carboplatin</td>
<td>Previously untreated</td>
</tr>
<tr>
<td>4-6 mg/m²/min</td>
<td>Single-agent carboplatin</td>
<td>Previously treated</td>
</tr>
<tr>
<td>4-6 mg/m²/min</td>
<td>Carboplatin plus cyclophosphamide</td>
<td>Previously untreated</td>
</tr>
</tbody>
</table>

Note: With the Carver formula, the total dose of carboplatin is calculated in mg, not mg/m². Carver's formula should not be used in patients who have received other platinum compounds.

**Patients are considered heavily pretreated if they have received any of the following:**
- Mitomycin C
- Nitrosourea
- Combination therapy with doxorubicin/cyclophosphamide/carboplatin.
- Combination therapy with 5 or more agents.
- Radiotherapy 24 Gy/6 weeks, focused on a 20 x 20 cm field or on more than half of field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponder tumour, progressive disease and/or occurrence of non-tolerable side effects.

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

Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG 2-4 or Karnofsky below 50).

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

Impaired Renal Function:
Patients with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression.

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

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

Pediatrics:
Sufficient usage of carboplatin in pediatrics has not occurred to allow specific dosage recommendations to be made.

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

Please turn the page.
Carboplatin 10 mg/ml Concentrate for Solution for Infusion

50 mg in 5 ml

Each vial contains 50 mg carboplatin.
Other ingredients: water for injections.
This product is a concentrate and MUST be diluted before use.
Read the package leaflet before use.
Use once only and dispose of any unused product or waste material in accordance with local requirements.
Do not store above 25°C. Do not store in refrigerator. Store container in the original carton. Protect from light.
When diluted as directed use within 24 hours when stored at 2°C - 8°C (in a refrigerator).
Carboplatin reacts with aluminium; contact with aluminium should be avoided.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

For intravenous infusion only.

1 Vial of 5 ml
Carboplatin
10 mg/ml
Concentrate for
Solution for Infusion
150 mg in 15 ml

For intravenous infusion only.
CYTOSTATIC

Each vial contains 150 mg carboplatin.
Other ingredients: water for injections.
This product is a concentrate and MUST be diluted before use.
Read the package leaflet before use.
Use once only and dispose of any unused product or waste material in accordance with local requirements.
Do not store above 25°C. Do not store in refrigerator. Store container in the original carton. Protect from light.
When diluted as directed use within 24 hours when stored at 2°C - 8°C (in a refrigerator).
Carboplatin reacts with aluminium; contact with aluminium should be avoided.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Carboplatin 10 mg/ml Concentrate for Solution for Infusion
450 mg in 45 ml

Each vial contains 450 mg carboplatin. Other ingredients: water for injections. This product is a concentrate and MUST be diluted before use. Read the package leaflet before use. Use once only and dispose of any unused product or waste material in accordance with local requirements. Do not store above 25°C. Do not store in refrigerator. Store container in the original carton. Protect from light. When diluted as directed use within 24 hours when stored at 2°C - 8°C (in a refrigerator). Carboplatin reacts with aluminium; contact with aluminium should be avoided.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

For intravenous infusion only.

CYTOSTATIC

1 Vial of 45 ml