CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 08137/0150-2

UKPAR

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CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Neolab Limited Marketing Authorisations (licences) for the medicinal product Carboplatin 10mg/ml Concentrate for Solution for Infusion (PL 08137/0150) and its duplicate licences (PL 08137/0151-2) on 27 May 2011. These are prescription-only medicines (POM).

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 these applications and it was, therefore, judged that the benefits of taking Carboplatin 10mg/ml Concentrate for Solution for Infusion outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal product Carboplatin 10 mg/ml Concentrate for Solution for Infusion (PL 08137/0150) and its duplicate licences of the same product name (PL 08137/0151-2) to Neolab Limited on 27 May 2011. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The applications refer to the innovator product, Paraplatin Solution Injection 10mg/ml (PL 00125/0201), authorised to Bristol-Myers Squibb Holdings Ltd, on 27 February 1991. The reference product have been authorised in the EEA for over 10 years.

Carboplatin is an analogue of cisplatin with similar actions and uses. It is used in the treatment of advanced ovarian cancers and of small-cell lung cancer, both alone and combined with other antineoplastic agents. It has also been tried as an alternative to cisplatin in other solid tumours.

Carboplatin is indicated for the treatment of advanced cancer of the ovary and small cell cancer of the lung.

No new pre-clinical or clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of the reference product that have been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder (MAH) and it was, therefore, judged that the benefits of taking product Carboplatin 10mg/ml Concentrate for Solution for Infusion outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Carboplatin
INN: Carboplatin
Chemical name: (SP-4-2)-diammine [cyclobutan-1,1-dicarboxylato(2-)-O,O’]platin

Structure:

\[
\begin{array}{c}
\text{NH}_2 \\
\text{HO} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{F} \\
\text{OH} \\
\text{F}
\end{array}
\]

, HCl

Molecular mass: 371.3

Molecular formula: C₆H₁₂N₂O₄Pt

General Properties

Description: Colourless, crystalline powder

Carboplatin is the subject of a European Pharmacopoeia monograph (Ph Eur).

Manufacture

All aspects of the manufacture and control of the active substance carboplatin are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Description and Composition

Carboplatin 10 mg/ml Solution for Infusion is presented as a clear colourless or almost colourless solution. Each ml of concentrate for solution for infusion contains 10mg carboplatin and each 5 ml vial contains 50 mg carboplatin.

Other ingredients consist of pharmaceutical excipients, namely water for injections). Appropriate justification for the inclusion of this excipient has been provided and is in compliance with its Ph.Eur monograph. A satisfactory Certificates of Analysis have been provided for this excipient. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for, the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of the drug product.
Pharmaceutical Development
The aim of the pharmaceutical development programme was to produce a stable, robust, reproducible and pharmaceutically equivalent product that could be considered a generic medicinal product of Paraplatin 10 mg/ml Injection (Bristol Myers Squibb Holdings Ltd). Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug product have been compared with the originator product. These data demonstrate that the proposed product can be considered a generic medicinal product to Paraplatin 10 mg/ml Injection (PL 00125/0201).

Compatibility and stability studies have been carried with the finished product diluted in 5% glucose injection BP as well as 0.9% sodium chloride injection BP. The studies show that the product is chemically stable.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted.

Finished Product Specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The finished product is presented in clear, hydrolytic, Type I glass vials sealed with flororesin coated brombutyl rubber stoppers with aluminium crimp caps and polypropylene flip-off lids. Each vial contains 50 mg/5 ml of carboplatin. Each vial is packaged with the patient information leaflet into outer cardboard cartons.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for parenteral preparations.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set for the unopened vial which is satisfactory. Storage conditions are “Do not store above 25°C”, “Do not store in a refrigerator”, “Store containers in the original carton” and “Protect from light”.

For full details of shelf-life and storage conditions for diluted medicinal product, refer to Section 6.3 and 6.4 of the SmPC. Please also refer to Section 6.6 of the SmPC for information on proper handling and disposal of the product and contaminated materials.
Bioequivalence Study
Bioequivalence studies are not necessary to support this application for parenteral products.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The approved SmPCs, PILs and labelling are pharmaceutically acceptable. Mock-ups of the package leaflet and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier. The CV of the expert has been provided.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications were submitted as abridged applications, according to Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of carboplatin are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The curriculum vitae of the expert has been provided.

A suitable justification has been provided for the non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

Carboplatin 10 mg/ml Solution for Infusion is a generic version of the originator product Paraplatin 10 mg/ml Concentrate solution for Infusion, (Bristol Eli Lilly and Company Limited). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, carboplatin. Thus, in accordance with the “Guideline on the Investigation of Bioequivalence”, the applicant is not required to submit a bioequivalence study, if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
No new safety data have been submitted or required for these generic applications. As carboplatin is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs and PILs are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA forms are medically satisfactory.

Conclusion
There are no objections to approval of Carboplatin 10 mg/ml Solution for Infusion from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Carboplatin 10mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The applicant’s Carboplatin 10mg/ml Concentrate for Solution for Infusion has been demonstrated to be a generic version of the reference product, Paraplatin Solution Injection 10mg/ml (PL 00125/0201), authorised to Bristol-Myers Squibb Holdings Limited, dated 27 February 1991.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs and PILs are acceptable, and consistent with those for the reference products. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Carboplatin 10mg/ml Concentrate for Solution for Infusion and the reference product Paraplatin Solution Injection 10mg/ml (Bristol-Myers Squibbs Holdings Limited) are interchangeable. Extensive clinical experience with carboplatin is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk is, therefore, considered to be positive.
STEPS TAKEN FOR ASSESMENT

<table>
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 7th June 2005.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 30th August 2005.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 12th June 2006 and 10th November 2010.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 6th April 2010 and 11th February 2011.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 27th May 2011.</td>
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CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 08137/0150-2

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Carboplatin 10 mg/ml Concentrate for Solution for Infusion (PL 08137/0150) is as follows:

Please note that the SmPC for PL 08137/0151-2 are identical except for the PL numbers.

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:

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

<table>
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<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>
</tr>
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</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 apprised 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 child-bearing 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

Incidence 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 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 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.

**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 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 fluoroelastic 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.

MARKETING AUTHORIZATION HOLDER
Neolab Limited
57 High Street
Odiham
Hants
RG29 1LF

MARKETING AUTHORIZATION NUMBER(S)
PL 08137/0150

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
27/05/2011

DATE OF REVISION OF THE TEXT
27/05/2011
# PATIENT INFORMATION LEAFLET

## PACKAGE LEAFLET INFORMATION FOR THE USER

**Carboplatin 10 mg/ml Concentrate for Solution for Infusion**

Read all of this leaflet carefully before you start taking this medicine.

- **Keep the leaflet.** You may need it again.
- **Show this leaflet to anyone else who will be taking the medicine.
- **Tell your doctor about this leaflet.**
- **You may have a prescription for this medicine.** Do not pass it on to someone else, even if they seem to have the same problem.
- **If you are not sure of the side effects, or if you notice any unusual effects, telephone your doctor or pharmacist immediately.

### WARNING

- 1. What carboplatin is and what it is for.
- 2. Before you use carboplatin.
- 3. How carboplatin should 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 USE CARBOPlatin

- You are contraindicated to receive this medicine if you:
  - Have an allergy to carboplatin or another platinum compound.
  - Have severe kidney problems.
  - Have severe liver problems.

### 3. HOW TO USE CARBOPLATIN

- The condition and severity of your disease will determine the correct dosage of carboplatin.

### 4. POSSIBLE SIDE EFFECTS

- A rare side effect is a reaction to the medication.

### 5. HOW TO STORE CARBOPlatin

- Keep the product in the original container.

### 6. FURTHER INFORMATION

- For more information about carboplatin, contact your doctor or pharmacist.

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### TABLE: CARBOPlatin 10 mg/ml Concentrate for Solution for Infusion

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
<th>Volume (ml)</th>
<th>Total Solution (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>10 mg/ml</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

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### Note

- Carboplatin is to be administered by a nuclear or other suitable radiopharmaceutical service.
- Carboplatin should be given in a hospital setting, preferably within the Nuclear Medicine Department of the hospital.
- Carboplatin should be given as a single intravenous injection or as a slow intravenous infusion over a period of 1 to 2 hours.
- Carboplatin should be given within 1 hour of mixing with the appropriate diluent.
- Carboplatin should be stored at room temperature.
- Carboplatin should be used within 24 hours of preparation.

---

### Author Note

- Carboplatin is a cytotoxic drug that is highly toxic to rapidly dividing cells, such as those found in the bone marrow, gastrointestinal tract, and urinary tract.
- Carboplatin is a platinum-based antineoplastic drug that is used to treat a variety of cancers, including ovarian, lung, and breast cancer.
- Carboplatin is administered intravenously and is given as a single dose or as a slow intravenous infusion.
- Carboplatin is a nephrotoxic agent, and monitoring of renal function is essential during therapy.
- Carboplatin is a myelosuppressive agent, and hematopoietic growth factors may be necessary to prevent complications.

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### Author's Signature

[R. Singh]

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### References

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 marked with Carboplatin.

There is a risk of you getting a severe allergy, which may include a rash, fever, or swelling of the face or throat. Your doctor may give you another medicine to reduce this risk.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Carboplatin can cause side effects in some patients. Tell your doctor immediately if you notice any of the following side effects:

- Feeling sick
- Headache
- Dizziness
- Nausea
- Vomiting
- Diarrhea
- Blurred vision
- Changes in taste
- Changes in hearing
- Skin rash
- Swelling of limbs

If any of the above side effects persist, please see your doctor or nurse.

5. COMMON SIDE EFFECTS

Some common side effects of Carboplatin include:

- Feeling sick or vomiting
- Nausea
- Diarrhea
- Headache
- Dizziness
- Drowsiness
-เลือ(6,10),(991,992)
CARBOPLATIN 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 08137/0150- CARTON

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 container. 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.

POM

PL 08137/0150

PL, Hodler

NEOLAB LTD,

67 High Street, Otham

Kent ME29 1LF

1 Vial of 5 ml

NLT 5pt

This product is a concentrate and MUST be diluted before use.

Do not store above 25°C. Do not store in refrigerator. Store container in the original container. Protect from light.

When diluted as directed use within 24 hours when stored at 2°C - 8°C (in a refrigerator). Read the package leaflet before use.

NEOLAB LTD, Otham, ME29 1LF

PL 08137/0150

POM

Code No.: 81

EXP.
### Carboplatin 10 mg/ml Concentrate for Solution for Infusion

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each vial contains 450 mg carboplatin. Other ingredients: water for injections. This product is a concentrate and MUST be diluted before use. Use only one 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 aluminum, contact with aluminum should be avoided. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</td>
<td></td>
</tr>
<tr>
<td>450 mg in 45 ml</td>
<td></td>
</tr>
</tbody>
</table>

**For intravenous infusion only.**

**CYTOSTATIC**