

# **Public Assessment Report**

**Carboplatin 10mg/ml, solution for infusion**

**UK/H/0704/001**

**Pharmachemie BV**

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## Module 1

<b>Product Name</b>	Carboplatin 10mg/ml solution for infusion
<b>Type of Application</b>	Outgoing Mutual Recognition Procedure
<b>Active Substance</b>	Carboplatin
<b>Form</b>	Solution for infusion
<b>Strength</b>	10mg/ml
<b>MA Holder</b>	Pharmachemie BV
<b>RMS</b>	Germany
<b>CMS</b>	UK
<b>Procedure Number</b>	UK/H/704/01
<b>Timetable</b>	Day 90 16 <sup>th</sup> November 2005

## Module 2

### Summary of Product Characteristics

#### 1. NAME OF THE MEDICINAL PRODUCT

Carboplatin 10 mg/ml concentrate for solution for infusion.

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 10 mg of carboplatin.

One vial of 5/15/45 ml solution contains 50/150/450 mg of carboplatin.  
For excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Carboplatin 10 mg/ml concentrate for solution for infusion is a clear, colourless to faintly yellow solution, free from particles.

#### 4. CLINICAL PARTICULARS

##### 4.1. Therapeutic indications

Carboplatin is indicated for the treatment of

1. Advanced ovarian carcinoma of epithelial origin in:

- first line therapy
- second line therapy, after other treatments have failed.

2. Small cell carcinoma of the lung, in association with other chemotherapeutic agents.

##### 4.2. Posology and method of administration

Dosage and administration

Route of administration: intravenous use.

Carboplatin should be used by the intravenous route only. The recommended dosage of Carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m<sup>2</sup> as a single i.v. dose administered by a short term (15 to 60 minutes) infusion. Therapy should not be repeated until four weeks after the previous

Carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm<sup>3</sup> and the platelet count is at least 100,000 cells/mm<sup>3</sup>.

Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior chemotherapy and/ or radiotherapy, or 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.

In case of a glomerular filtration rate of  $\leq 20$  ml/min, carboplatin should not be administered at all.

Dose recommendations by AUC:

As an alternative, the initial dose can be calculated using the Calvert formula, which takes account of renal function (glomerular filtration rate [GFR]). This reduces the risk of over- or underdosage caused by individual variations in renal function.

Calvert formula :

$$\text{Dosage (mg)} = (\text{Target AUC}^*) \times (\text{GFR} + 25)$$

Note : With the Calvert's formula, the total carboplatin dose is calculated in mg, not in mg/m<sup>2</sup>.

*Target AUC	Planned chemotherapy	Patient treatment status
5-7 mg/ml min	Monotherapy with carboplatin	Previously untreated
4-6 mg/ml min	Monotherapy with carboplatin	Previously treated
4-6 mg/ml min	Carboplatin plus cyclophosphamide	Previously untreated

Calvert's formula should not be used in patients who have received extensive pre-treatment with the following therapy regimens:

- Mitomycin C
  - Nitrosourea
  - combination therapy with doxorubicin/cyclophosphamide/cisplatin
  - combination therapy with 5 or more agents
  - radiation therapy  $\geq 4500$  rad, focused on  $20 \times 20$  cm field or on more than one field.
- Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of not tolerable side effects.

#### 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.

Use in children and adolescents:

As no sufficient experience of carboplatin use in children and adolescents is available, no specific dosage recommendations can be given.

Elderly (over 65 years old)

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

Dilution

The product may be diluted with 5% Glucose for Injection to a concentration as low as 0.5 mg/ml (500 micrograms/ml).

#### **4.3. Contraindications**

Carboplatin is contra-indicated in patients with severe pre-existing renal impairment (creatinine clearance at or below 20 ml/minute).

Carboplatin is contra-indicated in severely myelosuppressed patients.

Carboplatin is also contra-indicated in patients with hypersensitivity to carboplatin or other platinum containing products, or to mannitol.

Carboplatin is contra-indicated in patients with bleeding tumours.

Carboplatin is contra-indicated during breast feeding.

#### **4.4. Special warnings and precautions for use**

Carboplatin should be administered by individuals experienced in the use of anti-neoplastic therapy.

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. Thombocytopenia, leucopenia 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. Pre-medication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects. Renal function impairment may be encountered with Carboplatin. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is

recommended not to combine Carboplatin with aminoglycosides or other nephrotoxic compounds.

As for other platinum co-ordination compounds, allergic reactions to Carboplatin have been reported. They may occur within minutes of administration and should be managed with appropriate supportive therapy. Anaphylactic-like reactions may also occur as with other platinum co-ordination compounds.

In patients pre-treated with platinum containing medicinal products, the risk of allergic reactions, including anaphylaxis, is increased.

In old age, renal function may be impaired, and should be taken into account for dosage, if necessary.

Neurotoxic effects, especially in patients older than 65 years and/or those previously treated with cisplatin, have been reported.

A relationship between visual transient disturbances and too high dosages in renally impaired patients has been reported.

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

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

Carboplatin can have genotoxic effects. Therefore, 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.

Women should not become pregnant during treatment with carboplatin and should use an effective method of contraception.

Peripheral blood counts, renal and liver function tests and serum electrolytes should be monitored closely.

#### Precautions

Peripheral blood counts and renal 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 evaluations should also be performed on a regular basis.

#### **4.5. Interactions with other medicinal products and other forms of interaction**

*Myelosuppression is worsened by therapy combining Carboplatin with other compounds that are myelosuppressive. Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosage and timing in order to minimise additive effects.*

*Patients receiving concomitant therapy with other nephrotoxic potential are likely to experience more severe and prolonged myelotoxicity. Although no clinical evidence on compounding nephrotoxicity has been accumulate, it is recommended not to combine Carboplatin with aminoglycosides or other nephrotoxic compounds.*

*Administration of nephrotoxic and/or ototoxic medicinal products (e.g. aminoglycosides, loop diuretics) during treatment with carboplatin may increase organ toxicity.*

*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.*

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

#### **4.6. Pregnancy and lactation**

##### **Pregnancy**

Carboplatin is suspected to cause serious birth defects when administered during pregnancy. Carboplatin was shown to be embryotoxic and teratogenic in rats. Carboplatin should not be used during pregnancy unless clearly necessary. The mother should be informed about the risk to the fetus. Women of child-bearing potential must use effective contraception during treatment. See also section 4.4 “Special warnings and precautions for use”.

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

##### **Lactation**

It is unknown whether Carboplatin is excreted in human breastmilk. Due to the risk of serious adverse effects of carboplatin, breastfeeding must be discontinued during treatment with carboplatin.

#### **4.7. Effects on ability to drive and use machines**

*Carboplatin may cause nausea and vomiting, indirectly impairing the ability to drive and use machines.*

#### **4.8. Undesirable effects**

Incidences of adverse reactions reported hereunder are based on cumulative data obtained in a large group of patients with various pre-treatment prognostic features.

The following frequencies have been used:

- Very common (>1/10)
- Common (>1/100, <1/10)
- Uncommon (>1/1,000, <1/1000)
- Rare (>1/10,000, <1/1,000)
- Very rare (<1/10,000) including isolated reports

Neoplasms benign and malignant (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).

#### Blood and lymphatic system disorders

##### Very common:

- Myelosuppression, which 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.
- Thrombocytopenia. At maximum tolerated dosages of Carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than  $50 \times 10^9/l$ , 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.
- Leucopenia. This has 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.
- A haemoglobin decrease ( $\leq 9.5$  mg/100 ml) has been observed in 48% of patients. 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.

#### Immune system disorders

##### Common:

- Allergic reactions to Carboplatin have been reported in less than 2% of patients. These reactions are similar to those observed after administration of other platinum-containing compounds, i.e. skin rash, urticaria, erythema, fever with no other apparent cause and pruritus.

##### Rare:

- Cases of bronchospasm, hypotension, and anaphylactic shock requiring adequate treatment (epinephrine, antihistamines, corticosteroids) may occur.

#### Metabolism and nutrition disorders

##### Very common:

- Decrease in serum electrolytes (magnesium, potassium, sodium and, rarely, 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:

- Isolated cases of hyponatremia have been reported, but a causal connection is not proven.

### 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 patients above the age of 65 years or patients 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.
- Central nervous symptoms have occasionally 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.

### 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:

- 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. Clinically significant hearing loss has occurred in children who received Carboplatin dosages higher than recommended and combined with other ototoxic drugs.

### Cardiovascular disorders

- 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.

### Gastrointestinal disorders

#### Very common:

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

#### Common:

- Diarrhoea and constipation have occurred in 6 % and 4 % of patients, respectively.
- Mucositis

## Rare:

- Taste alteration
- Isolated cases of anorexia have been reported.

## Hepato-biliary disorders

## Very common:

- Abnormalities of liver function tests (usually mild to moderate). These 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.

## Skin and subcutaneous disorders

## Common:

- Alopecia

## Renal and urinary disorders

## Very common:

- Elevation of blood urea or serum creatinine levels. Renal toxicity is usually not dose-limiting in patients receiving Carboplatin, nor does it require preventive measures such as a high volume fluid hydration or forced diuresis. Nevertheless increasing blood urea or serum creatinine levels can occur commonly.

## 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 to 59 ml/ min) or severe alteration (21 - 40 ml/ min). Carboplatin is contra-indicated in patients with a glomerular filtration rate at or below 20 ml/ min.

## General disorders and administration site conditions

## Very common:

- Hyperuricaemia, which is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allopurinol.
- Asthenia

## Common:

- Malaise

## Uncommon:

- Injection site reactions, such as pain, erythema, swelling, urticaria and necrosis, have been reported.
- Fever and chills without evidence of infection have occurred.

## Rare:

- Haemolytic uraemic syndrome occurred in single cases.

## 4.9. Overdose

Since no known antidote exists for Carboplatin, every possible measure should be undertaken to avoid an overdose.

### Symptoms of intoxication

Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m<sup>2</sup> 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  $\geq 500/\mu\text{l}$  after 8-14 days (median: 11) and the thrombocytes values of  $\geq 25.000/\mu\text{l}$  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.

### Therapy of intoxication

There is no specific antidote. Symptomatic measures should be taken to sustain the patient through any period of toxicity that might occur. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological side effects.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, platinum compounds.  
ATC code: L01XA02.

Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks.

### 5.2. Pharmacokinetic properties

Following administration of Carboplatin in man, linear relationship exists between dose and plasma concentrations of total and free ultra-filterable platinum. The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of Carboplatin reported values for the terminal elimination half-lives of free ultrafilterable platinum and Carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultra-filterable 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 clearance of free ultra-filterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

### 5.3. Preclinical safety data

In animals, symptoms of acute toxicity consisted of emesis, anorexia, adipsia, postural changes, troubled respiration and diarrhoea. Symptoms of long term toxicity included myelosuppression, depression of the immune system, necrosis of the mucosae of the gastrointestinal system, reduction in body weight, increases in the levels of enzymes of the liver and blood urea nitrogen, bleeding, bacterial infection, bronchitis, damage to the retinae, mild ototoxicity and damage to the kidneys. Carboplatin induces cytogenetic effects suggesting that it is likely to be mutagenic/carcinogenic. Reproduction and teratology: increases in toxicity to the mother and foetus were observed in a dose dependent fashion. Changes to the foetuses included alterations to the weight and length of the body, increases in the incidences and severity of abnormalities to the skeleton and internal organs. At doses higher than 4mg/kg/day, spontaneous abortion of most of the foetuses and severe deformities to the skeletons of surviving foetuses were observed.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Mannitol, Water for Injection.

### 6.2. Incompatibilities

This medicinal product should not be mixed with other medical products except those mentioned under 4.2. "Dilution".

This product should not be used with aluminium-containing infusion assemblies, syringes and injection needles. The antineoplastic activity can be reduced.

### 6.3. Shelf life

2 years

After first opening/dilution  
Immediate and single use.

Chemical and physical in-use stability has been demonstrated for three hours at room temperature (15-25°C) and for 24 hours at 2-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

### 6.4. Special precautions for storage

Do not store above 25 °C.  
Keep container in the outer carton in order to protect from light.  
Storage conditions after first opening/dilution  
Do not store above 25 °C.  
Protect from light.

#### **6.5. Nature and contents of container**

Amber coloured glass vials, USP type I with chlorobutyl, black teflon-coated, grey stoppers with an aluminium seal covered with a polypropylene snap-cap.

Pack sizes:

Box of 1 vial of 5 ml, 15 ml and 45 ml

Boxes of 5 and 10 vials of 5 ml, 15 ml and 45 ml (each packed separately in a box, wrapped together with transparent shrink foil).

Not all pack sizes may be marketed

#### **6.6. Instruction for use and handling (, and disposal)**

Dilution: The product may be diluted with 5% Glucose for Injection to concentrations as low as 0.5 mg/ml (500 micrograms/ml).

When diluted as directed, Carboplatin is chemically and physically stable for three hours at room temperature (15-25°C) and for 24 hours at 2-8°C.

The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

For single use only. Any unused solution should be discarded.

Guidelines for safe handling of anti-neoplastic agents:

1 Trained personnel should handle the drug

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 1000°C. Liquid waste may be flushed with copious amounts of water.

Dilution:

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**

Pharmachemie B.V.  
Swensweg 5  
PO Box 562  
2003 RN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER**

PL 04946/0028

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

17 March 2004

**10. DATE OF REVISION OF THE TEXT**

May 2005

## **Module 3**

# **Product Information Leaflet**

APP 5

Patient Information Leaflet  
Carboplatin 10 mg/ml Concentrate For Infusion

Please read this leaflet carefully before you receive this medicine. It briefly outlines the most important things you need to know. If you want to know more about this medicine, or you are not sure about anything, ask your doctor or nursing staff.

The name of your medicine is Carboplatin 10 mg/ml Concentrate for Infusion.

WHAT IS CARBOPLATIN?

Each 5 ml vial contains 50 mg of the active ingredient carboplatin.  
Each 15 ml vial contains 150 mg of the active ingredient carboplatin.  
Each 45 ml vial contains 450 mg of the active ingredient carboplatin.

The other ingredients are mannitol and water for injection.

The product is available in packs containing a single 5 ml, 15 ml or 45 ml vial.

The Marketing Authorisation holder and the company responsible for manufacture is Pharmachemie BV, The Netherlands, Haarlem, Holland (Teva Group logo).

WHAT IS CARBOPLATIN USED FOR ?

Carboplatin is a platinum containing compound. It is an anti-cancer agent which is used either alone or in combination with other drugs for the treatment of certain kinds of ovarium cancer and lung cancer.

Ask your doctor or nursing staff if you need additional information.

BEFORE YOU RECEIVE CARBOPLATIN

Do you have a history of severe allergic reactions to Carboplatin or any other platinum containing compounds; or to mannitol?

Are you pregnant or breast-feeding?

Do you have any kidney problems?

Do you have any bone marrow problems?

Do you have a tumour that bleeds?

Are you taking phenytoin?

Have you received cisplatin in the past?

Are you taking or being given any drugs which can cause damage to either your kidneys or inner ears e.g. aminoglycosides such as gentamicin, streptomycin or diuretics such as bumetanide, furosemide?

If the answer to any of these questions is YES, you should not receive Carboplatin before talking to your doctor or nursing staff.

Carboplatin may cause you to feel or be sick. Do not drive or operate machinery until you are sure you are not affected.

### RECEIVING CARBOPLATIN

The usual adult dose is 400 mg/m<sup>2</sup> given as a single intravenous (into the vein) dose over a period of 15 to 60 minutes.

For elderly patients (over 65 years old), the dosage may need adjusting depending on your physical condition.

If you have received treatment previously or have kidney problems your dosage will be adjusted to suit you.

- Carboplatin should only be administered by specifically qualified doctors.
- Carboplatin will be diluted and then administered to you by the intravenous route only.
- You will have regular tests performed to monitor your condition.

You should use an effective method of contraception during therapy. Male patients should continue to use contraception for at least six months after their therapy has ended. If you become pregnant or suspect that you may be pregnant during therapy, you must tell your doctor immediately.

### AFTER RECEIVING CARBOPLATIN

You may experience some side effects with Carboplatin. Tell your doctor if you experience any of the following:

- Nausea, vomiting, abdominal pain, diarrhoea, constipation or if you have a rash, fever, chill, sore throat, ulcers in your mouth or throat, itching, taste alteration, ringing in the ears or hearing loss, sight problems or hair loss.
- Unusual bleeding or unexplained bruising, infections, anaemia (unusual tiredness or weakness), gout, kidney problems, slow reflexes, pins-and-needles and numbness.
- Injection site reactions such as pain, redness, swelling, nettle rash and dead skin.

In addition the following have been reported:

- Single cases of wheezing, low blood pressure, and severe allergic reaction shortly after receiving the drug.
- Cases of abnormal liver function tests, liver problems and changes in blood chemistry.
- Single cases of high blood pressure, heart problems, stroke and blood clots.
- Single cases of secondary malignancies (cancerous tumour that spreads from its original location to establish secondary tumours in other parts of the body). Although, it has not been established that Carboplatin was the cause of this effect.

Tell your doctor, if you have any other unusual problems.

Your doctor may give you blood or urine tests to check your blood composition, kidney or liver function before, during and after treatment with Carboplatin.

### STORING CARBOPLATIN

Do not store above 25°C. Keep the container in the outer carton.

After dilution in 0.9% NaCl solution or 5% glucose solution, storage should be restricted to three hours at room temperature protected from light or 24 hours at 2 - 8°C when carried

out under validated aseptic conditions. The storage times relate to the commencement of drug administration.

Only use this product if it is a clear, colourless to faintly yellow solution, free from fibres and particles of foreign matter.

FURTHER INFORMATION

This leaflet only gives a brief outline of some of the more important points about Carboplatin. If you want to know more about this medicine or its effects, please ask your doctor or nursing staff.

Keep out of reach of children.

April 2005

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## **Module 4**

## **Labelling**

PL 04946/0028

PHARMACHEMIE B.V.			
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004	
	Replaces:	-	
IB2 Packaging and labelling texts	Page:	1	
	Doc.name:	PL 04946/0028	

**Label text for 5 ml vial**

Carboplatin concentrate for infusion 10 mg/ml ✓  
 1 ml contains 10 mg of carboplatin  
 5 ml vial contains 50 mg carboplatin  
 Excipients: mannitol and water for injections  
 For intravenous infusion only ✓  
 Vials should be disposed of safely after use  
 To be used as directed by a medical practitioner  
 MA Holder: Pharmachemie B.V., the Netherlands ✓

Do not store above 25°C ✓  
 Keep container in the outer carton ✓  
 Keep all medicines out of the reach and sight of children ✓  
 PL 04946/0028 ✓

P.M.

Batch no:  
 Exp. date:

final 13.1.2004

PHARMACHEMIE B.V.			
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004	
	Replaces:	-	
IB2 Packaging and labelling texts	Page:	2	
	Doc.name:	PL 04946/0028	

**Label text for 15 ml vial**

Carboplatin concentrate for infusion 10 mg/ml

1 ml contains 10 mg of carboplatin

15 ml vial contains 150 mg carboplatin

Excipients: mannitol and water for injections

For intravenous infusion only

Vials should be disposed of safely after use

To be used as directed by a medical practitioner

MA Holder: Pharmachemie B.V., the Netherlands

Do not store above 25°C

Keep container in the outer carton

Keep all medicines out of the reach and sight of children

PL 04946/0028



Batch no:

Exp. date:

PHARMACHEMIE B.V.			
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004	
	Replaces:	-	
IB2 Packaging and labelling texts	Page:	3	
	Doc.name:	PL 04946/0028	

**Label text for 45 ml vial**

Carboplatin concentrate for infusion 10 mg/ml

1 ml contains 10 mg of carboplatin

45 ml vial contains 450 mg carboplatin

Excipients: mannitol and water for injections

For intravenous infusion only

Vials should be disposed of safely after use

To be used as directed by a medical practitioner

MA Holder: Pharmachemie B.V., the Netherlands

Do not store above 25°C

Keep container in the outer carton

Keep all medicines out of the reach and sight of children

PL 04946/0028

Batch no:

Exp. date:

100M

PHARMACHEMIE B.V.			
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004	
	Replaces:	-	
IB2 Packaging and labelling texts	Page:	4	
	Doc.name:	PL 04946/0028	

**Outer carton packaging for 5 ml vial**

Carboplatin concentrate for infusion 10 mg/ml

Each 5 ml vial contains 50 mg of carboplatin

Excipients: mannitol and water for injections

For intravenous infusion only

One 5 ml vial

To be used as directed by a medical practitioner

Please read the enclosed package insert

Special warning: Vials should be disposed of safely after use

Keep all medicines out of the reach and sight of children

Do not store above 25°C

Keep container in the outer carton

10 ml

Batch no.:

Exp. date:

PL 04946/0028

MA Holder:

Pharmachemie B.V.,

Haarlem

The Netherlands

<b>PHARMACHEMIE B.V.</b>		
<b>Carboplatin 10 mg/ml concentrate for infusion</b>	Version date:	January, 2004
	Replaces:	-
<b>IB2 Packaging and labelling texts</b>	Page:	5
	Doc.name:	PL 04946/0028

**Outer carton packaging for 15 ml vial**

Carboplatin concentrate for infusion 10 mg/ml ✓  
 Each 15 ml vial contains 150 mg of carboplatin ✓  
 Excipients: mannitol and water for injections ✓  
 For intravenous infusion only ✓

One 15 ml vial ✓

To be used as directed by a medical practitioner ✓

Please read the enclosed package insert ✓

Special warning: Vials should be disposed of safely after use ✓

Keep all medicines out of the reach and sight of children ✓

Do not store above 25°C ✓

Keep container in the outer carton ✓

*fo M*

Batch no.: ✓

Exp. date: ✓

PL 04946/0028

MA Holder:

Pharmachemie B.V.,

Haarlem

The Netherlands

PHARMACHEMIE B.V.		
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004
	Replaces:	-
IB2 Packaging and labelling texts	Page:	6
	Doc.name:	PL 04946/0028

**Outer carton packaging for 45 ml vial**

Carboplatin concentrate for infusion 10 mg/ml  
 Each 45 ml vial contains 450 mg of carboplatin  
 Excipients: mannitol and water for injections  
 For intravenous infusion only  
 One 45 ml vial  
 To be used as directed by a medical practitioner  
 Please read the enclosed package insert  
 Special warning: Vials should be disposed of safely after use  
 Keep all medicines out of the reach and sight of children

Do not store above 25°C  
 Keep container in the outer carton

*(cm)*

Batch no.:  
 Exp. date:  
 PL 04946/0028

MA Holder:  
 Pharmachemie B.V.,  
 Haarlem  
 The Netherlands

PHARMACHEMIE B.V.			
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004	
	Replaces:	-	
IB2 Packaging and labelling texts	Page:	7	
	Doc.name:	PL 04946/0028	

**Hospital packaging labels**10 vials of 5 ml

Carboplatin 50 mg

Concentrate for infusion 10 mg/ml

10 vials, each vial contains 5 ml concentrate for infusion

For intravenous infusion only



Do not store above 25°C

Keep container in the outer carton

Batch no.:

Exp. date:

PHARMACHEMIE B.V.			
Carboplatin 10 mg/ml concentrate for infusion	Version date:	January, 2004	
	Replaces:	-	
IB2 Packaging and labelling texts	Page:	8	
	Doc.name:	PL 04946/0028	

10 vials of 15 ml

Carboplatin 150 mg

Concentrate for infusion 10 mg/ml

10 vials, each vial contains 15 ml concentrate for infusion

For intravenous infusion only

Do not store above 25°C

Keep container in the outer carton

Batch no.:

Exp. date:

## Module 5

### Scientific discussion during initial procedure

#### OVERALL CONCLUSION ON THE MEDICINAL PRODUCT

##### *Executive Summary*

##### Introduction

##### Market Authorisations Granted

The Market Authorisation holder is Pharmachemie BV and a National Licence was granted in the UK on 17<sup>th</sup> March 2004 . In addition, Market Authorization have been granted in Germany and Poland under Article 10.1 (a) (iii) of Directive 2001/83/EC as amended, for Carboplatin Concentrate for Infusion 10 mg/ml, and is classed as a hybrid.

Carboplatin Concentrate for Infusion 10mg/ml is essentially similar to Paraplatin lyophilised powder for injection (50 mg, 150 mg and 450 mg), which contains the same active and inactive ingredient (carboplatin and mannitol in equal amounts). Marketing Authorisation PL 0125/0179-0181 was granted to Bristol-Myers Squibb, 13 March 1986. Carboplatin 10 mg/ml solution for infusion and Paraplatin® has the same qualitative and quantitative composition after reconstitution and before dilution for intravenous infusion. The pharmaceutical forms are different (injection versus lyophilised powder for infusion), the MA status being the hybrid one.

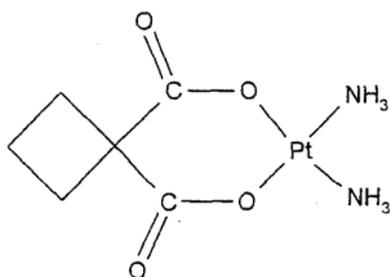
The expert reports confirm the similarity between the comparator and Carboplatin 10mg/ml solution for infusion and, therefore, there is no need to submit any additional toxicological or clinical data.

##### **b) Chemical and pharmacokinetic properties of the active ingredient**

##### Chemical structure of the active ingredient:

Platinum compound.

Teva Carboplatin has biochemical properties similar to that of cisplatin.



Pharmacokinetic properties of carboplatin:

Following administration of carboplatin in man, a linear relationship exists between dose and plasma concentrations of total and free ultra-filterable platinum. The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of carboplatin, reported values for the terminal elimination half-lives of free ultra-filterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours, respectively. During the initial phase, most of the free ultra-filterable 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 clearance of free ultra-filterable platinum correlate with the rate of glomerular filtration, but not tubular secretion.

Physico-chemical properties of the active ingredients and characteristics of the pharmaceutical form which could have an effect on the pharmacokinetic parameters and clinical efficacy:

Carboplatin 10 mg/ml solution for infusion is exclusively injected by the intravenous route. Therefore, the bioavailability of the active ingredient is total.

**c) Therapeutic Indications**

Carboplatin is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:
  - First-line therapy
  - Second-line therapy, after other treatments have failed.
2. Small cell carcinoma of the lung, in association with other chemotherapeutic agents.

**Posology**

Carboplatin should be used by the intravenous route only. The recommended dosage of carboplatin in previously untreated adult patients with normal kidney function is 400mg/m<sup>2</sup> as a single i.v. dose administered by a short-term (15 to 60 minutes) infusion. Therapy should not be repeated until 4 weeks after the previous carboplatin course.

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 of severe 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.

The onset of severe leucopenia, neutropenia or thrombocytopenia may be controlled using the following posology:

- 250 mg/m<sup>2</sup> i.v. on day 1, in patients with creatinine clearance base values from 41-59ml/min.
- 200 mg/m<sup>2</sup> i.v. on day 1, in patients with creatinine clearance base values from 21-40ml/min.

Carboplatin should not be administered to patients with a GFR < 20 ml/min.

*Dose recommendations according to AUC.*

*Alternatively, the initial dose can be calculated using the Calvert formula. This is based on renal function (glomerular filtration rate [GFR]). Thereby, the risk of underdosing or overdosing due to individual differences in renal function is reduced.*

Calvert formula : total dose (mg) = (target AUC\*) x (GFR + 25)

Note : With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m<sup>2</sup>.

<b>*target AUC</b>	<b>planned chemotherapy</b>	<b>pre-treatment status</b>
5-7 mg/ml min	Single-agent carboplatin	no prior therapy
4-6 mg/ml min	Single-agent carboplatin	prior therapy
4-6 mg/ml min	Carboplatin plus cyclophosphamide	no prior therapy

The Calvert formula should not be used in heavily pre-treated patients who have already received one of the following regimens :

- mitomycin C
- nitrosourea
- doxorubicin/cyclophosphamide/cisplatin combination chemotherapy
- combination therapy including five or more cytostatic agents
- radiation therapy > 5000 rad focused on a field of 20 x 20 cm or more than one field.

#### 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 (over 65 years old)

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

#### Dilution

The product may be diluted with 5% Glucose for Injection BP or 0.9% Sodium Chloride for Injection BP to concentrations as low as 0.5 mg/ml (500 micrograms/ml).

#### *Pharmacological and therapeutic classification of the active ingredient, defining the mode of action:*

Cytostatic drug, platinum compound.

Teva Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks.

### **d) Contraindications and precautions for use**

#### Contraindications

Carboplatin should not be used in patients with severe pre-existing renal impairment (creatinine clearance < 20 ml/minute).

Carboplatin should not be employed in severely myelosuppressed patients.

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

Carboplatin is contraindicated in patients with bleeding tumours.

#### Special Warnings and Precautions for Use

Carboplatin should be administered by individuals experienced in the use of anti-neoplastic therapy.

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, leucopenia 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. Pre-medication with anti-emetics and slower drug administration have been reported to be useful in reducing the incidence and intensity of these effects.

Renal function impairment may be encountered with carboplatin. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds.

As for other platinum co-ordination compounds, allergic reactions to carboplatin have been reported. They may occur within minutes of administration and should be managed with appropriate supportive therapy. Anaphylactic-like reactions may also occur as with other platinum co-ordination compounds.

Neurotoxic effects, especially in patients older than 65 years and/or those previously treated with cisplatin, have been reported.

A relationship between visual transient disturbances and too high dosages in renally impaired patients has been reported.

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

Peripheral blood counts, renal and liver function tests and serum electrolytes should be monitored closely.

Safety and efficacy of carboplatin in paediatric patients have not been established.

#### Precautions

Peripheral blood counts and renal 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 evaluations should also be performed on a regular basis.

#### Pregnancy:

Carboplatin may cause embryonic/foetal harm when administered to a pregnant woman. Carboplatin has been shown to be a teratogen, embryotoxin and mutagen in several experimental systems.

Therefore, all patients of reproductive age should be advised to use an effective contraceptive method for themselves and/or their sexual partners during therapy. Male patients are advised to practice contraception for at least 6 months after therapy.

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

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breastfeeding be discontinued if the mother is treated with carboplatin.

Drug interactions:

Administration of nephrotoxic and/or ototoxic drugs (e.g. aminoglycosides, loop diuretics) during treatment with carboplatin may increase organ toxicity of the drugs.

Concomitant administration of carboplatin and complex-forming compounds should be avoided as, theoretically, the antineoplastic effects of carboplatin might be decreased. However, in animals and clinically, the antineoplastic effects of carboplatin were not influenced by diethylthiocarbamate. A decrease in phenytoin serum level has been reported following concomitant administration of carboplatin and phenytoin.

Background

Carboplatin is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:
  - first line therapy
  - second line therapy, after other treatments have failed.
2. Small cell carcinoma of the lung, in association with other chemotherapeutic agents.

*Overall Benefit/Risk Assessment*

No new preclinical studies were conducted, which is acceptable given that these applications were based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that these applications were based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

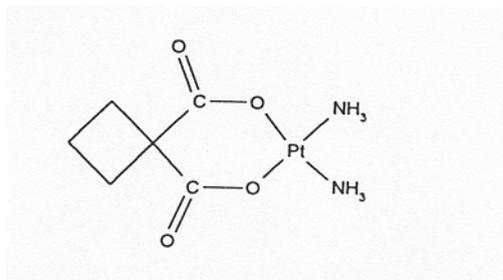
The RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All product related texts (SPC, PIL and labels) are satisfactory from the clinical, preclinical and pharmaceutical point of view for a product of this nature.

The quality of the product is satisfactory in relation to its safety and efficacy. The data have demonstrated the efficacy and safety of the product to the extent that the overall risk/benefit of the product is favourable for the proposed indications.

**PART II PHARMACEUTICAL ASSESSMENT****1. DRUG SUBSTANCE**

Carboplatin Ph.Eur./BAN/INN is



cis-Diammine(cyclobutane-1,1-dicarboxylato)platinum  
 $C_6H_{12}N_2O_4Pt(II) = 371.26$

It is a white crystalline powder, soluble in water (18g/L).

The manufacture of Carboplatin Ph.Eur. is covered by a Certificate of Suitability.

A satisfactory account has been provided of the synthetic process. All reactants, solvents, etc are defined and controlled. Evidence for the chemical structure of carboplatin is derived from elemental analysis, NMR, MS, IR, spectroscopy and X-ray diffraction, and is confirmed by literature. There are no chiral centres in carboplatin. X-ray crystallography shows that carboplatin is a square-planar cyclobutane ring. Adequate information is provided on the physico-chemical properties of carboplatin. These include appearance, odour, melting point/thermal decomposition, bulk density and aqueous solubility (~18g/l).

The related substance impurities arising from synthesis are considered to be cyclobutanidacarboxylic acid, cyclobutanmonocarboxylic acid and cisplatin. Other impurities arising from the synthesis include silver, potassium and nitrate, and the methanol and water solvents.

The drug substance complies with Ph.Eur specification, with additional in-house controls on related substances, particle size, bacterial endotoxin, microbial count, potassium, nitrate, methanol and platinum content. The limits for named impurities and single unknown impurities are tighter than those specified in the Ph.Eur monograph. Limits proposed for methanol (Class 2 solvent), the residual solvent, are considered satisfactory.

Based on satisfactory stability data, the proposed retest period of 24 months (in polyethylene containers) is justified.

The limits for named individual, unknown individual and total impurities are considered satisfactory. Apart from the Ph.Eur method, two in-house methods (HPLC and UV) are also used for assay. Cross-validation shows good agreement

between the two methods, but the alternate UV method has not been shown to be suitable for monitoring drug substance stability. Satisfactory analytical validation data is also provided for the HPLC method for related substances. Limits of detection for related substances are also provided.

## **2. FINISHED PRODUCT**

### **2.1 Formulation & Pharmaceutical Development**

The product is intended to be essentially similar to the Bristol-Myers-Squibb product Paraplatin Injection, but in the form of a ready-to-use solution rather than a freeze-dried powder for reconstitution. However, the two products have the same concentration prior to administration and, therefore, there are no preclinical or clinical issues here. Mannitol has been included in the applicant's product, like the freeze-dried reference product, as a tonicity-adjuster. The ratio of carboplatin : mannitol is 1:1, again, like the reference product. The product is not isotonic (it is stated to be about 'one-third physiological'), nor does it need to be because it is further diluted 1:20 with isotonic saline or dextrose infusions before use. The osmolality of the applicant's solution has been measured and found to be about 86mOsm/kg water. The product developed has a pH of 5.0-7.0, which is the same as that of a 1% solution of Carboplatin Injection USP.

To support the claim of essential similarity with the brand leader, the physicochemical properties of aged test (up to 18 months) and reference samples (near expiry date) have been compared. Comparative analytical data and chromatograms with the BMS product indicate qualitative similarity with the UK brand leader product, in terms of impurity profile. However, levels of total impurities and single unknown impurities are slightly higher in the applicant's product, but still well within the specification.

### **2.2 Manufacture/In-process Controls/Process Validation**

Three consecutive production batches were manufactured and involved in the validation program. Results fall within the upper and lower specification limits.

A satisfactory description of the manufacturing process has been provided both in descriptive and flow chart form. The data provided on aseptic process validation confirm that an acceptance criteria of 0.1% will be achieved with 95% confidence levels for medial fill as suggested in the GMP guideline.

### **2.3 Excipients**

Water-for-injections Ph.Eur. and Mannitol Ph.Eur. are used. Certificates of Analysis provided confirm compliance with the appropriate monographs. The applicant has also confirmed that no TSE-specified risk materials are used.

### **2.4 Immediate Packaging Materials**

The packaging complies with Type I requirements of both USP and Ph.Eur.

## 2.5 Finished Product Specifications

No control tests on intermediate products are applicable, as there are no intermediate products.

The limits (but not necessarily the methods used) for assay, sterility, bacterial endotoxins, pH and cyclobutanedicarboxylic acid are consistent with those required for Carboplatin Injection USP, though it is a lyophilised powder. These limits are considered satisfactory.

## 2.6 Analytical Methods

Satisfactory analytical validation data have been provided for the HPLC methods for the assay and for the determination of related substance impurities (in drug substance as well as product solutions).

Validation of the bacterial endotoxin test (LAL Test – QCL kinetic assay) is provided. Absence of carboplatin inhibition over the range 0.025 to 0.20 mg/ml was shown. A satisfactory validation report for application of the Ph.Eur. Test for Sterility to this product is provided, and shows the absence of bacteriostatic or fungistatic properties of carboplatin solution.

## 2.7 Finished Product Stability

A shelf-life of 24 months when the product is stored below 25°C and protected from light has been validated.

## 3. BIOAVAILABILITY & BIOEQUIVALENCE

As the product is a solution for intravenous infusion, bioavailability of the active from this product is considered to be immediate and bioequivalence with the cross-reference product can be assumed.

### 4.1 GMP Statement

The manufacturing and batch release site has been found to be satisfactory for the purposes nominated and is currently used for a licenced product (PL 14776/0019). Current manufacturing/GMP certificates are provided for this site

### 4.2 Product Labelling and Leaflets

Contain satisfactory pharmaceutical details.

### 4.3 Summary of Product Characteristics

Satisfactory pharmaceutical details.

## 5. PHARMACEUTICAL CONCLUSIONS

The Pharmaceutical Assessment supported granting of a Marketing Authorisation.

## **PART III PRECLINICAL ASSESSMENT**

These applications for a generic product claim essential similarity to Paraplatin 10mg/ml concentrate for infusion (Bristol-Myers-Squibb), which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

For further preclinical information relevant to this product, the reader is referred to the preclinical assessment report for the innovator product.

## **PART IV CLINICAL ASSESSMENT**

### **1. BACKGROUND**

Carboplatin has a spectrum of activity similar to that of cisplatin, with myelosuppression being the major dose-limiting toxicity. It is, therefore, supplanting cisplatin in oncological practice.

### **2. INDICATIONS**

Consistent with originator: Satisfactory.

### **3. DOSE & DOSE SCHEDULE**

Consistent with originator: Satisfactory.

### **4. TOXICOLOGY**

No new data has been submitted and none required for this application.

### **5. CLINICAL PHARMACOLOGY**

This formulation of carboplatin is proposed for intravenous route of administration and its bioavailability is, therefore, 100% and consequently no bioequivalence demonstration is required. No new data has been submitted

### **6. SAFETY**

No new data have been submitted and none are required for this application

### **7. EXPERT REPORTS**

A comprehensive review of the published literature on carboplatin by an appropriately qualified physician has been submitted.

### **8. PATIENT INFORMATION LEAFLET (PIL)**

Satisfactory.

### **9. LABELLING**

Medically satisfactory.

## **10. APPLICATION FORM (MAA)**

Medically satisfactory.

## **11. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

Contraindications: Satisfactory

Special warnings: Satisfactory

Interactions: Satisfactory

Pregnancy: Satisfactory

Driving: Satisfactory

Undesirable effects: Satisfactory

Overdose: Satisfactory

Pharmacology and pre-clinical safety: Satisfactory

## **12. MARKETING/POST-MARKETING**

This product is also marketed in Portugal (Carboplatin, 12 March 1993), Austria (Carbosol, 28 September 1993), Greece (Emorzin, 4 October 1993), UK (Carboplatin Concentrate for Infusion 10 mg/ml, 14 Nov 1997), France (Carboplatin-TEVA, 19 Nov 1998), Germany (Carboplatin-GRY, 28 April 1999), Italy (Carboplatino-TEVA, 5 July 1999).

Post-marketing surveillance will be performed in Europe, according to the National and European regulations.

## **13. DISCUSSION**

All clinical aspects of this application are satisfactory.

## **14. MEDICAL CONCLUSION**

A Marketing authorisation was granted

## **Overall Conclusion**

The Pharmaceutical and Medical Assessments resulted in a positive risk/benefit assessment and a Market Authorisation was granted.