Safeguarding public health

Public Assessment Report

Mutual Recognition Procedure

Carboplatin 10mg/ml Solution for Injection

UK/H/879/01/MR

UK licence no: PL 10622/0070

Pliva Pharma Limited

LAY SUMMARY

Germany, Ireland and Italy approved Pliva Pharma Limited a Marketing Authorisation (licence) for the medicinal product Carboplatin 10mg/ml solution for injection. This is a Prescription-only medicine (POM) that is used for the treatment of advanced ovarian carcinoma of epithelial origin in first and second line therapy and for small cell carcinoma of the lung.

Carboplatin is an antineoplastic agent. Its activity has been demonstrated against several murine and human cell lines.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Carboplatin outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Carboplatin 10mg/ml Solution for Injection
Type of Application	Generic, Article 10.1
Active Substance	Carboplatin
Form	Solution for Injection
Strength	10mg/ml
MA Holder	Pliva Pharma Ltd Vision House Bedford Road Petersfield Hampshire GU32 3QB
RMS	UK
CMS	Germany, Ireland, Italy
Procedure Number	UK/H/879/01/MR
Timetable	Day 90 – 18/12/2006

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carboplatin 10mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10mg carboplatin.
Each 5ml vial contains 50mg carboplatin.
Each 15ml vial contains 150mg carboplatin.
Each 45ml vial contains 450mg carboplatin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for infusion.
A colourless to pale yellow, clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carboplatin 10mg/ml Concentrate for Solution for Infusion 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 dosage of carboplatin in previously untreated adult patients with normal kidney function is 400 mg/m² as a single i.v. dose administered by a 15 to 60 minutes infusion. Alternatively, see Calvert formula below:

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

Target AUC	Planned Chemotherapy	Patient treatment status
5-7 mg/ml.min	single agent carboplatin	Previously untreated
4-6 mg/ml.min	single agent carboplatin	Previously treated
4-6 mg/ml.min	Carboplatin plus cyclophosphamide	Previously untreated

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

Calvert's formula should not be used in patients who have received extensive pretreatment with the following therapy regimens:
- Mitomycin C,
- Nitrosourea,
- combination therapy with doxorubicin/cyclophosphamide/cisplatin,
- combination therapy with 5 or more agents,
- radiotherapy ≥ 4500 rad, focussed on a 20 x 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 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/mm^3.

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 developing 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 < 30 ml/min carboplatin should not be administered at all.
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

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

Elderly

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

Dilution & Reconstitution

See 6.6 Instructions for Use / Handling.

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

Carboplatin is contra-indicated in patients with bleeding tumours.

4.4 Special warnings and precautions for use

Warnings
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, 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. 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 evaluations should also be performed on a regular basis.

4.5 Interaction with other medicinal products and other forms of interaction

Patients receiving concomitant therapy with other nephrotoxic agents are likely to experience more severe and prolonged myelotoxicity. The use of carboplatin with aminoglycosides or other nephrotoxic compounds is not recommended.

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

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
Carboplatin is genotoxic. 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.

Lactation

It is unknown whether carboplatin is excreted in human breast milk. Breast feeding should be discontinued during carboplatin therapy.

4.7 Effects on ability to drive and use machines

Carboplatin has no or negligible influence on the ability to drive and use machines. However, Carboplatin may cause nausea and vomiting, indirectly impairing the ability to drive and use machines.

4.8 Undesirable effects

Incidences of adverse reactions reported 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, ≤1/100)
- Rare (≥1/10,000, ≤1/1,000)
- Very rare (≤1/10,000) including isolated reports

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

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 has been observed in 48% of patients with normal base-line values. Anaemia occurs frequently and may be cumulative.

Common: Haemorrhagic complications, usually minor, have also been reported.

Uncommon: Infectious complications have occasionally been reported.

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

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 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.

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.

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 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.

Immune system disorders
Common: Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythema, fever with no apparent cause or pruritus.

Rare: Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria and facial oedema have occurred (See Warnings).

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.

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.

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.

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.

Hepato-biliary 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.

Skin and subcutaneous tissue disorders
Common: Alopecia.

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

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

Rare: Haemolytic uraemic syndrome.

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

Carboplatin is an antineoplastic agent. Its activity has been demonstrated against several murine and human cell lines. ATC code: L01X A02.

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 that 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 ≥ 60ml/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 of 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.

5.3 Preclinical safety data

Carboplatin has been shown to be embryotoxic and teratogenic in rats. (See 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
Concentrated ammonia solution.

6.2 Incompatibilities

Needles, syringes, catheters 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

Unopened product - 18 months
Diluted product - When dilution is carried out under validated aseptic conditions, and if justified, the product may be stored for a maximum period of 24 hours at 2-8°C or 8 hours at room temperature (15 - 25°C).

6.4 Special precautions for storage

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

Diluted product:
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature (15 - 25°C).

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.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Cardboard carton containing one colourless Type I glass vial with a fluoropolymer coated bromobutyl rubber stopper and aluminium closure with polypropylene top.

Pack sizes:
5 ml vial, containing 50mg of carboplatin, 10mg/ml.
15 ml vial, containing 150 mg of carboplatin, 10mg/ml.
45 ml vial, containing 450 mg carboplatin, 10mg/ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product is for single dose use only.
Discard any unused solution.

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).

Guidelines for the safe handling of anti-neoplastic agents:

1. Trained personnel should reconstitute 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 1,000 °C. Liquid waste may be flushed with copious amounts of water.
7. The work surface should be covered with disposable plastic-backed absorbent paper.
8. Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

7. MARKETING AUTHORISATIN HOLDER

PLIVA Pharma Limited
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
United Kingdom

8. MARKETING AUTHORISATION

PL 10622/0070

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

24th November 2004

10 DATE OF REVISION OF THE TEXT

01/05/2007

Module 3
Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Carboplatin 10mg/ml Concentrate for Solution for Infusion

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

In this leaflet:

1. WHAT CARBOPLATIN INFUSION IS AND WHAT IT IS USED FOR

The name of your medicine is 'Carboplatin 10mg/ml Concentrate for Solution for Infusion' but in the rest of this leaflet it will be called 'Carboplatin Infusion'.

What Carboplatin Infusion is
Carboplatin Infusion contains carboplatin, which belongs to a group of medicines known as platinum co-ordination compounds which are used to treat cancer.
You will normally be given this injection in hospital.

What Carboplatin Infusion is used for
Carboplatin Infusion is used to treat some cancers of the ovary and lung (ovarian cancer of epithelial origin, small-cell lung cancer).

2. BEFORE YOU ARE GIVEN CARBOPLATIN INFUSION

You should not be given Carboplatin Infusion
- if you are allergic (hypersensitive) to carboplatin or any of the other ingredients of Carboplatin Infusion.
- if you are allergic to another drug that belongs to the group of platinum containing compounds
- if you have severe problems with your kidneys (creatinine clearance at or below 20ml/min)
- if you have an imbalance of your blood cells (severe myelosuppression)
- if you have a tumour that bleeds

If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do so as soon as possible and before receiving the injection.

Carboplatin Infusion is usually given to patients in hospital. Normally you should not handle this medicine. Your doctor or nurse will administer the medicine and will carefully and frequently monitor you during and after treatment. You will normally have blood tests before each administration.

Take special care while receiving Carboplatin Infusion
- if you are pregnant or if there is a chance you may be pregnant
- if you are breast-feeding
- if you are likely to drink any alcohol whilst being treated with this injection

- if your kidneys are not working properly the effects of carboplatin on the blood (haematopoietic system) are increased and prolonged compared to patients with normal kidney function. Your doctor will want to monitor you more regularly if your kidneys are not working properly.

If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do so as soon as possible and before receiving the injection.

Your injection may be diluted with another solution before it is administered. You should discuss this with your doctor or nurse and ask for a patient information leaflet to make sure that it is suitable for you.

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

You should tell your doctor if you are taking any of the following medicines as they may interact with Carboplatin Infusion:

- other medicines that are known to be toxic to your kidneys
- chelating agents
- phenytoin

Pregnancy and breast-feeding
Pregnancy
You must not be treated with Carboplatin Infusion during pregnancy unless clearly indicated by your doctor. If you are being treated with Carboplatin Infusion whilst pregnant, you should discuss with your doctor the possible risk of effects on your unborn child.

Women of childbearing potential must use an effective method of contraception both before and during treatment with Carboplatin Infusion. Since Carboplatin Infusion can cause genetic damage, if pregnancy occurs during treatment with Carboplatin Infusion, genetic counselling is recommended. Genetic counselling is also recommended for patients wishing to have children after treatment with Carboplatin Infusion.

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

Fertility
Carboplatin Infusion can cause genetic damage. Men treated with Carboplatin Infusion are advised not to father a child during and up to 6 months after treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility.

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

Driving and using machines
Carboplatin Infusion should not affect your ability to drive or use machinery. However, you should take extra care when you are first given the injection, especially if you feel dizzy or unsure of yourself.

3. HOW YOU ARE GIVEN CARBOPLATIN INFUSION

Your injection will always be administered by a nurse or doctor. It is usually given in a drip by slow injection (infusion) into a vein (intravenously) and will usually take between 15 to 60 minutes to be administered. If you require any further information, ask your doctor or nurse who will be or who has administered the injection.

Your dose will be dependent on your height and weight, function of your blood (haematopoietic) system and your kidney function. Your doctor will choose the best dose for you. The injection will normally be diluted before use.

Adults
The usual adult dose is 400g/m^2 of your body surface area (calculated from your height and weight).

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

Kidney problems
If you suffer from kidney problems your doctor may reduce the dose and may perform frequent blood tests as well as monitoring your kidney function.

Children
There has not been enough usage of carboplatin in children to allow the recommendation of a specific dose.

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

There will usually be a gap of four weeks between each dose of Carboplatin Infusion. Your doctor will want to perform some blood tests each week after giving you Carboplatin Infusion so that he/ she can decide on the correct next dosage for you.

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

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

If you stop using Carboplatin Infusion
It you have any further questions on the use of this product ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (affecting more than 1 in 10 people)
- changes in your red and white blood cells and platelets (myelosuppression). Your doctor may want to monitor you.
- anaemia (a condition in which there is a decreased number of red blood cells which may lead to tiredness)
- increases in the levels of creatinine and urea in your blood. Your doctor may want to monitor you.
- decreases in the levels of salts in your blood. Your doctor may want to monitor you.
- slight loss of hearing
- abnormal liver enzyme levels. Your doctor may want to monitor you.
- increased uric acid levels in the blood which may lead to gout.
- feeling or being sick
- abdominal pain
- unusual feelings of tiredness or weakness.

Common side effects (affecting less than 1 in 10 people)

- unusual bruising or bleeding (haemorrhagic complications)
- reduced function of your kidneys. Your doctor may want to monitor you.
- diarrhoea, constipation, sore mouth
- allergic reactions including rash, itching, high temperature
- ringing in the ears (tinnitus)
- pins and needles
- hair loss (alopecia)
- feeling unwell.

Uncommon side effects (affecting less than 1 in 100 people)

- secondary malignancies (a tumour that has spread to other parts of the body) have been reported
- infections
- central nervous symptoms often associated with medicine you may be taking to stop you from feeling or being sick
- fever and chills without evidence of infection
- redness, swelling and pain or dead skin around the injection site (injection site reactions).

Rare side effects (affecting less than 1 in 1000 people)

- feeling unwell with a high temperature due to low levels of white blood cells (febrile neutropenia)
- life-threatening infections and bleeding
- taste alteration
- loss of appetite (anorexia)
- severe allergic reactions (anaphylaxis). This type of reaction is most likely to occur within minutes of receiving Carboplatin Infusion. Symptoms of a severe allergic reaction include sudden wheeziness or tightness of the chest, swelling of the eyelids, face or lips, rash, itching, high temperature. If these symptoms occur soon after receiving the injection, tell your doctor or nurse immediately.
- temporary sight loss
- reduced liver function, damage or death of liver cells. Your doctor may want to monitor you.
- haemolytic-uraemic syndrome (a disease characterised by acute renal failure, decreased number of red blood cells [microangiopathic haemolytic anaemia] and a low platelet count).

Very rare side effects (affecting less than 1 in 10 000 people)

- heart failure, blockage in the vessels of your heart, high blood pressure
- bleeding in the brain which may result in a stroke or loss of consiousness.

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

5. HOW TO STORE CARBOPLATIN INFUSION

You will not be asked to store your medicine. It will be brought to you ready to be administered straight away. There are no special storage conditions for this medicine during administration.

Your doctor, nurse or pharmacist should ensure that Carboplatin Infusion is stored out of the reach and sight of children.

Your doctor, nurse or pharmacist will ensure that you do not receive Carboplatin Infusion after the expiry date which is stated on the label after Exp:. The expiry date refers to the last day of that month. Your doctor, nurse or pharmacist should ensure that the vial is kept in the outer carton, in order to protect from light, at below 25°C.

When mixed with other solutions the solution should be used immediately or can be stored for not longer than 24 hours at 2-8°C. It should not be frozen. Your doctor, nurse or pharmacist will ensure that these storage requirements are met.

Medicines should not be disposed of via wastewater or household waste. Your doctor, nurse, or pharmacist will dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Carboplatin Infusion contains
- The active substance is carboplatin.
- The other ingredients are water for injections and concentrated ammonia solution.

What Carboplatin Infusion looks like and contents of pack
Carboplatin Infusion is a colourless to pale yellow, clear concentrate for solution for infusion.

Each ml of solution contains 10mg carboplatin.

Each 5ml vial contains 50mg carboplatin.
Each 15ml vial contains 150mg carboplatin.
Each 45ml vial contains 450mg carboplatin.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB.
Tel: 01730 710900
[To be completed nationally]

Manufacturer:
PLIVA – Lachema a.s., Karasek 1, 621 33 Brno, Czech Republic

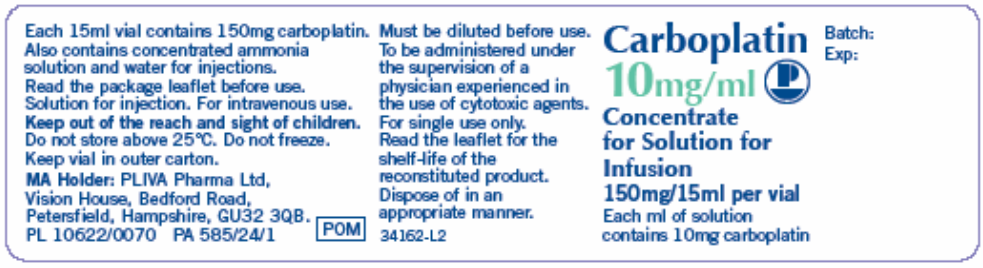
This leaflet was last approved in XX/YYYY.

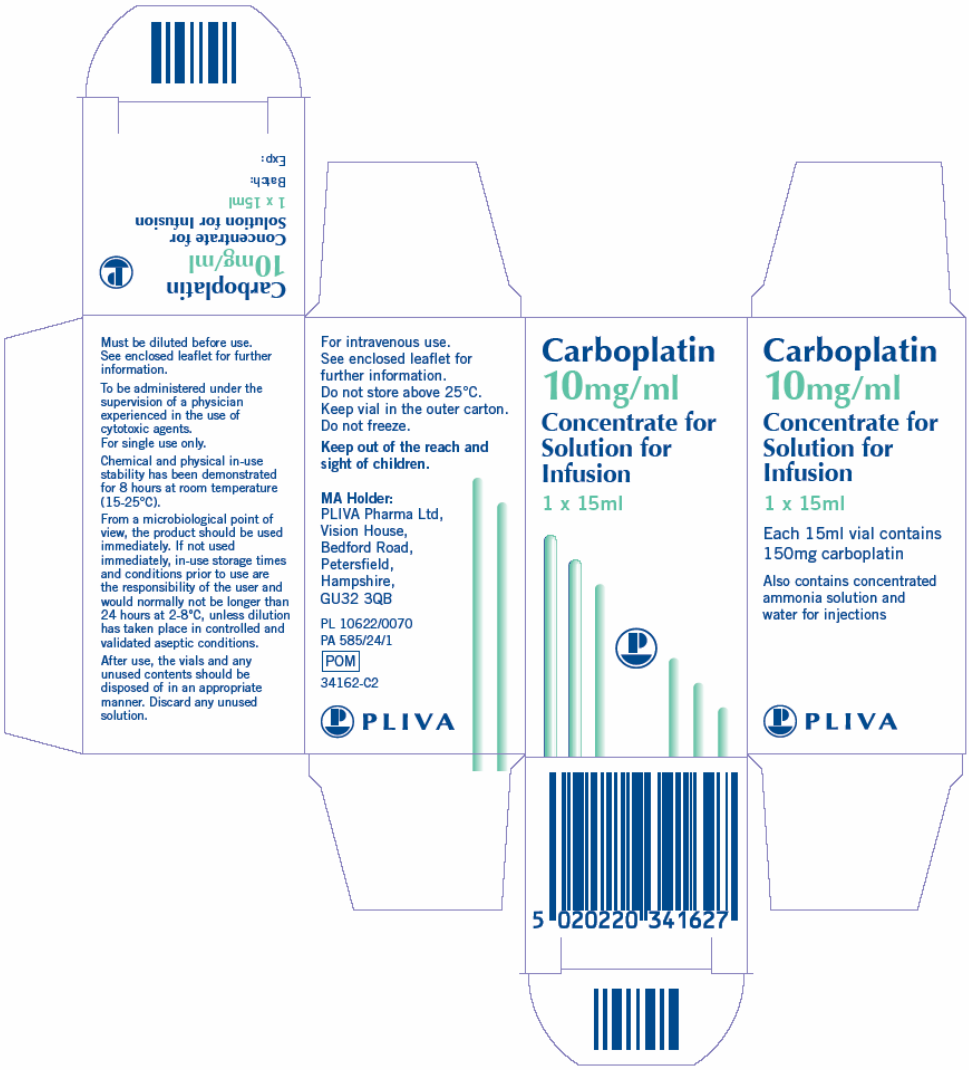
[To be completed nationally]

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

Module 4

Labelling



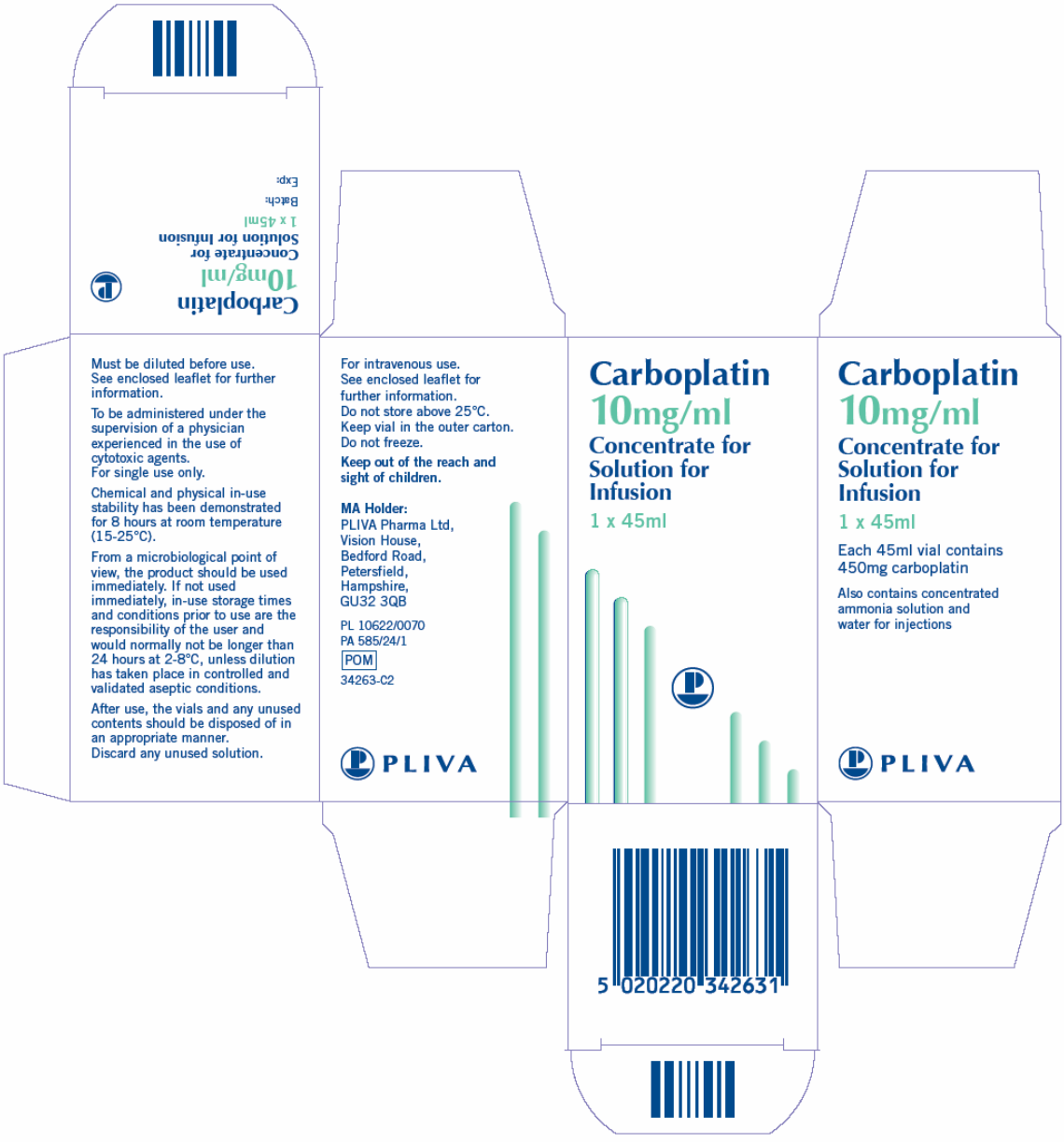

Carboplatin
10mg/ml
Concentrate for
Solution for Infusion
1 x 15ml
Batch:
Exp:
Must be diluted before use.
See enclosed leaflet for further information.
To be administered under the supervision of a physician experienced in the use of cytotoxic agents.
For single use only.
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature (15-25°C).
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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.
After use, the vials and any unused contents should be disposed of in an appropriate manner. Discard any unused solution.
For intravenous use.
See enclosed leaflet for further information.
Do not store above 25°C.
Keep vial in the outer carton.
Do not freeze.
Keep out of the reach and sight of children.
MA Holder:
PLIVA Pharma Ltd,
Vision House,
Bedford Road,
Petersfield,
Hampshire,
GU32 3QB
PL 10622/0070
PA 585/24/1
POM
34162-C2
PLIVA
Carboplatin
10mg/ml
Concentrate for Solution for Infusion
1 x 15ml
5 020220 341627
Carboplatin
10mg/ml
Concentrate for Solution for Infusion
1 x 15ml
Each 15ml vial contains 150mg carboplatin
Also contains concentrated ammonia solution and water for injections
PLIVA

Each 45ml vial contains 450mg carboplatin.
Also contains concentrated ammonia solution and water for injections.
Read the package leaflet before use.
Solution for injection. For intravenous use.
Keep out of the reach and sight of children.
Do not store above 25°C. Do not freeze.
Keep vial in outer carton.
MA Holder: PLIVA Pharma Ltd,
Vision House, Bedford Road,
Petersfield, Hampshire, GU32 3QB.
PL 10622/0070 PA 585/24/1
POM

Must be diluted before use.
To be administered under the supervision of a physician experienced in the use of cytotoxic agents.
For single use only.
Read the leaflet for the shelf-life of the reconstituted product.
Dispose of in an appropriate manner.
34263-L2

Carboplatin
10mg/ml
Concentrate for Solution for Infusion
450mg/45ml per vial
Each ml of solution contains 10mg carboplatin

Batch:
Exp:



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Carboplatin 10mg/ml Solution for Injection in 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

could be approved. A national marketing authorisation was granted on 24th November 2004.

II EXECUTIVE SUMMARY

II.1 Problem statement

This mutual recognition application concerns a generic version of carboplatin.

The originator product is Paraplatin Solution PL 00125/0201 granted 27/02/199l to Bristol Myers Pharmaceuticals.

About the product

Carboplatin is an anti-neoplastic 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".

II.2 The development programme

The objective of the development programme was to develop a stable solution for injection dosage form of carboplatin comparable to Paraplatin Solution licensed to Bristol Myers Pharmaceuticals.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

No new preclinical studies were conducted, which is acceptable given that the application was a generic medicinal product to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was a generic medicinal product to a product that has been licensed for over 10 years.

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.

For manufacturing sites within the community, 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

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

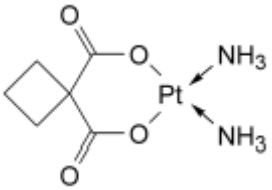
DRUG SUBSTANCE

Nomenclature

USP/USAN/Ph.Eur: Carboplatin

Chemical Name: cis-diammine-1, 1-cyclobutane dicarboxylate platinum (II)

Structure



Molecular Formula: $C_6H_{12}N_2O_4.Pt$.

Molecular Weight: 371.25

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

A letter of access has been provided by the active ingredient manufacturer.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active carboplatin is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Acceptable justification of the proposed specifications are provided.

Satisfactory certificates of analysis have been provided by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been provided supporting a 24 month re-test period, when stored below 25^{o}C in the original package. A commitment is also given that one production batch would be placed on stability every year. The batches would be stored at 25°C/60%RH for up to 36 months. This is satisfactory.

DRUG PRODUCT

Other Ingredients
Other ingredients consist of pharmaceutical excipients, namely water for injection and concentration ammonia solution.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

There were no novel excipients used and no overages.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

No excipients of human or animal origin are used in the preparation of the finished product.

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. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Product is packaged in colourless, clear, Type I glass vials. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging comply with EU legislation regarding contact with solutions for parenteral and ophthalmic use Directive 2002/72/EC (as amended).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. A shelf-life of 18 months with storage conditions “Do not store above 25 degree C” and “Keep vial in the outer carton” have been set. These are satisfactory.

Conclusion
It is recommended that Marketing Authorisation is granted for this application.

V PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are necessary. A non-clinical overview summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

VI CLINICAL ASSESSMENT

1. INTRODUCTION

This abridged application is a generic medicinal product of Paraplatin. Marketing authorisation was first granted to Bristol Myers Squibb under PL 0125/0201 on 27th February 1991.

2. BACKGROUND

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

3. INDICATIONS

Satisfactory

4. DOSE & DOSE SCHEDULE

Satisfactory

5. TOXICOLOGY

No new data submitted and none are required for this application

6. CLINICAL PHARMACOLOGY

No new data submitted and none are required for this application.

7. EFFICACY

No new data submitted

8. SAFETY

No new data submitted

9. EXPERT REPORTS

The applicant has submitted a clinical expert report by an appropriately qualified physician

10. PATIENT INFORMATION LEAFLET (PIL)

Satisfactory

11. LABELLING

Satisfactory

12. APPLICATION FORM (MAA)

Satisfactory

13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory

14. MEDICAL CONCLUSION

Marketing authorisation is recommended

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
13/02/2007	Type II	To update the SPC following the successful conclusion of MRP and to implement the harmonised labelling and leaflet texts agreed between the RMS and CMS during this MRP	Approved 01/05/2007