IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0585/024/001
Case No: 2045950

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pliva Pharma Limited

Vision House, **Bedford Road**, **Petersfield**, **Hampshire GU32 3QB**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Carboplatin 10 Micromol Solution for Infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/07/2008** until .

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

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 Solution for Injection 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.

Paediatric Patients

There is insufficient information to support a dosage recommendation in the paediatric population.

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 overdosage. The anticipated complications of overdosage 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".

Paediatric patients: safety and efficacy in children have not been established.

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.

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

5.3 Preclinical safety data

Carboplatin has been shown to be embryotoxic and teratogenic in rats. (See 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 and other handling

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:
Trained personnel should reconstitute the drug.
This should be performed in a designated area.
Adequate protective gloves should be worn.
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.
The cytotoxic preparation should not be handled by pregnant staff.
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.
The work surface should be covered with disposable plastic-backed absorbent paper.
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

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8 MARKETING AUTHORISATION NUMBER

PA 585/24/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th April 2007

10 DATE OF REVISION OF THE TEXT

January 2008