Public Assessment Report

Decentralised

Carboplatin 10mg/ml concentrate for solution for infusion

UK/H/1126/01//DC

Accord Healthcare Ltd

LAY SUMMARY

The MHRA granted a market authorisation to Accord Healthcare Ltd for the medicinal product Carboplatin 10mg/ml concentrate for solution for infusion on 09/12/2008. The product is a prescription only medicine used to treat the following cancers

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."

This was an abridged application according to Article 10(1) of 2001/83/EC, as amended, a so called "generic application" for Carboplatin 10mg/ml solution for injection referring to the European reference product Paraplatin 10mg/ml. The active substance is carboplatin.

TABLE OF CONTENTS

Module 1

Product Name	Carboplatin 10mg/ml concentrate for solution for infusion
Type of Application	Standard Abridged Decentralised (Article 10.1)
Active Substance (INN)	Carboplatin
Pharmacotherapeutic Classification (ATC)	L01XA02, Antineoplastic agents
Pharmaceuctical Form and Strength	Concentrate for solution for infusion, 10mg/ml
Procedure Numbers	**UK/H/1126/01/DC**
RMS	UK
CMS	AT, BE, CZ, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, SE and SK.
Start Date	07/11/2007
End Date	05/11/2008
MA Number	PL 20075/0028
Name and address of MA holder	**Accord Healthcare Limited** Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, UK

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

1 ml of concentrate for solution for infusion contains 10mg of Carboplatin
Each 5 ml vial contains 50 mg carboplatin
Each 15 ml vial contains 150 mg carboplatin
Each 45 ml vial contains 450 mg carboplatin
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
A clear, colourless 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.

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, i.e. creatinine clearance > 60 ml/min is 400 mg/m² as a single short term IV dose administered by a 15 to 60 minutes infusion. Alternatively, the Calvert formula shown below may be used to determine dosage:
Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]		
Target AUC	**Planned chemotherapy**	**Patient treatment status**
5-7mg/ml .min	single agent Carboplatin	Previously untreated
4-6 mg/ml .min	single agent Carboplatin	Previously treated
4-6mg/ml .min	Carboplatin plus cyclophosphamide	Previously untreated

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

**Patients are considered heavily pretreated if they have received any of the following:

- Mitomycin C
- Nitrosourea
- Combination therapy with doxorubicin/ cyclophosphamide/cisplatin,
- Combination therapy with 5 or more agents,
- Radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of not tolerable side effects.

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

Reduction of the initial dosage by 20-25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80).

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

Impaired renal function:

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

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

In case of a glomerular filtration rate of ≤ 20 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 and Reconstitution:

The product must be diluted prior to infusion, see section 6.6

4.3 Contraindications

Carboplatin is contraindicated in patients with:

- hypersensitivity to the active substance or to other platinum containing compounds
- breast feeding
- severe myelosuppression
- bleeding tumors
- pre-existing severe renal impairment (with creatinine clearance of ≤ 20 ml per minute)

4.4 Special warnings and precautions for use

Warnings:

Carboplatin should be administered by individuals under the supervision of a qualified physician who is experienced in the use of anti-neoplastic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

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

Carboplatin Infusion 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 ($\geq$ 5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and/or renal function. It is not clear whether an appropriate hydration programme might overcome effects on renal function. Dose reduction or discontinuation of therapy is required in the presence of moderate to severe alteration in renal or hepatic function test. (See Section 4.8).

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is also more likely in patients who have previously experienced nephrotoxicity as a result of Cisplatin therapy. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine Carboplatin with aminoglycosides or other nephrotoxic compounds.
Infrequent allergic reactions to Carboplatin have been reported, e.g. erythematous rash, fever with no apparent cause or pruritus. Rarely anaphylaxis, angio-oedema and anaphylactoid reactions including bronchospasm, urticaria and facial oedema have occurred. These reactions are similar to those observed after administration of other platinum containing compounds and may occur within minutes. The incidence of allergic reactions may increase with previous exposure to platinum therapy; however, allergic reactions have been observed upon initial exposure to Carboplatin. Patients should be observed carefully for possible allergic reactions and managed with appropriate supportive therapy, including antihistamines, adrenaline and/or glucocorticoids.

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

The carcinogenic potential of Carboplatin has not been studied but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic (See section 5.3)

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

Aluminium containing equipment should not be used during preparation and administration of Carboplatin (See section 6.2).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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.

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

4.6 Pregnancy and lactation

Pregnancy

The safe use of Carboplatin during pregnancy has not been established: Studies in animals have shown reproductive toxicity (see 5.3.). Carboplatin has been shown to be an embryo toxin and teratogen in rats and mutagenic in vivo and in vitro. Carboplatin should not be used during pregnancy unless clearly indicated. If Carboplatin is used during pregnancy the patient should be apprised of the potential hazard to the fetus.

Fertility

Women of childbearing potential should be advised to avoid becoming pregnant by using effective contraception during treatment and up to 6 months after therapy. For women who are pregnant or become pregnant during therapy, genetic counseling should be provided.

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

Lactation:

It is not known whether Carboplatin is excreted in human milk.
Because of the possibility of harmful effects in suckling infants, breast-feeding must be discontinued if the mother is treated with carboplatin (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Incidences of adverse reactions reported here under are based on cumulative data obtain in a large group of patients with various pretreatment prognostic features.
The following frequencies have been used:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, ≤1/100)
Rare (≥1/10,000, ≤1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Cardiac disorders

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

Blood and lymphatic system disorders

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

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

Leukopenia has also occurred in approximately 20% of patients but its recovery from the day of nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy. Neutropenia with granulocyte counts below 1 x 10^9/l occurs in approximately one fifth of patients. Haemoglobin values below 9.5 mg/100ml have

been observed in 48% of patients with normal base-line values. Anaemia occurs frequently and may be cumulative. *Common*: Haemorrhagic complications, usually minor, have also been reported.
Uncommon: Infectious complications have occasionally been reported.
Rare: Cases of febrile neutropenia have been reported. Single cases of life-threatening infections and bleeding have occurred.

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

Nervous system disorders
Common: The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in elderly patients and those previously treated with cisplatin. Paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin. (See Precautions).
Uncommon: Central nervous symptoms have been reported, however, they seem to be frequently attributed to concomitant antiemetic therapy.

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

Ear and labyrinth disorders
Very common: Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.
Common: Clinical ototoxicity. Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen.
At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

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

Common: Diarrhoea (6%), constipation (4%), mucositis.
Rare: Taste alteration. Cases of anorexia have been reported.

Renal and urinary disorders
Very common: Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as high volume fluid hydration or forced diuresis. Nevertheless, increasing blood urea and blood urea nitrogen levels or serum creatinine levels can occur.
Common: Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min, may also be observed. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment.
It is not clear whether an appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41-59 ml/min) or severe renal impairment (creatinine clearance 21-40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min.

Skin and subcutaneous tissue disorders
Common: Alopecia.

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

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

General disorders and administration site conditions
Very common: Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allopurinol. Asthenia.
Common: Malaise, urticaria. flu-like syndrome, erythematous rash, pruritis,
Uncommon: Fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis
Rare: Haemolytic uraemic syndrome.

Immune system disorders
Common: Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus. These reactions are similar to those observed after administration of other platinum containing compounds and should be managed with appropriate supportive therapy.
Rare: Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial odema and facial flushing, dyspnoea, hypotension, dizziness, wheezing, and tachycardia have occurred (See section 4.4).

Hepatobiliary disorders

Very common: Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about one-third of the patients with normal baseline values. The alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment.
Rare: Severe hepatic dysfunction (including acute liver necrosis) has been reported after administration of higher than recommended carboplatin dosages.

4.9 Overdose

Symptoms of overdose

Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m^2 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

Pharmacotherapeutic group: Antineoplastic agents, Platinum compounds

ATC code: LO1X A02

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

Carboplatin exhibited comparable activity to cisplatin against a wide range of tumours regardless of implant site.

Alkaline elution techniques and DNA binding studies have demonstrated the qualitatively similar modes of action of Carboplatin and cisplatin. Carboplatin, like cisplatin, induces changes in the superhelical conformation of DNA, which is consistent with a “DNA shortening effect”.

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

5.2 Pharmacokinetic properties

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 ≥ 60 ml/min.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of Carboplatin reported values for the terminal elimination 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. It is mutagenic *in vivo* and *in vitro* and although the carcinogenic potential of Carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal product except those mentioned in section 6.6.

Carboplatin may interact with aluminium to form a black precipitate. 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. Precipitation can lead to a reduction of the antineoplastic activity.

6.3 Shelf life

Unopened:

2 years

After dilution

In use: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 30 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 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

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze
Keep vial in the outer carton in order to protect from light
For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

Carboplatin infusion is supplied in 5 ml/ 15 ml/ 50 ml type I amber tubular glass vial containing 5 ml/ 15 ml/ 45 ml concentrate for solution respectively. Vials are closed using grey chlorobutyl rubber stopper with an aluminium flip off seal.
1 glass vial in one monocarton
5 ml vial, containing 50mg of carboplatin, 10mg/ml.
15 ml vial, containing 150 mg of carboplatin, 10mg/ml.
50 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.

Contamination
In the event of contact of carboplatin with eyes or skin, wash affected area with copious amounts of water or normal saline. A bland cream may be used to treat transient stinging of skin. Medical advice should be sought if the eyes are affected.

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

Dilution
The product must be diluted prior to infusion, with 5 % dextrose solution or 0.9 % sodium chloride solution, to concentrates as low as 0.5 mg/ml.

Guidelines for the safe handling of anti-neoplastic agents:

1 Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents
2 This should be performed in a designated area.
3 Adequate protective gloves should be worn.
4 Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. In the event of contact with the eyes, wash with water and/or saline.
5 The cytotoxic preparation should not be handled by pregnant staff.
6 Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000 °C. Liquid waste may be flushed with copious amounts of water.
7 The work surface should be covered with disposable plastic-backed absorbent paper.
8 Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to Minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/12/2008

10 DATE OF REVISION OF THE TEXT

09/12/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3

Product Information Leaflet

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PATIENT INFORMATION LEAFLET

Carboplatin 10mg/ml Concentrate for Solution for Infusion

Carboplatin

Read all of this leaflet carefully before you starts using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please 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 the 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 coordination compounds, which are used to treat cancer.

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

2. Before you are given Carboplatin Infusion

Do not use Carboplatin Infusion
- If you are allergic (hypersensitive) to Carboplatin or to any of the ingredients of Carboplatin Infusion
- If you are allergic to another drug that belongs to the group of platinum containing compound.
- If you have severe problems with your kidneys (creatinine clearance at or below 20 ml/min)
- If you have an imbalance of your blood cells (sever myelosuppression)
- If you have tumour that bleeds
- If you are pregnant or breast feeding

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

Take special care 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 Infusion

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 Infusion.

Your Infusion may be diluted with another solution before it is administered. You should discuss this with your doctor and make sure that it suitable for you.

Using other medicines:
You should tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without prescription
You should tell your doctor if you are taking any of the following medicines as they may interact with Carboplatin.

- Other medicines that are known to affect blood cell formation in the bone marrow
- Other medicines that are known to be toxic to your kidneys (e.g. aminoglycosides antibiotics)
- Other medicines that are known to damage the hearing or balance functions of the ear (e.g. aminoglycosides antibiotics; furosemide [used to treat heart failure and edema])
- Chelating agents (substances binding to carboplatin thereby decreasing the effect of carboplatin)
- Phenytoin (used to treat various types of convulsions and seizures)
- Warfarin (used to prevent the formation of blood clots)

Using with food and drink
There is no known interaction between Carboplatin and alcohol. However you should check with your doctor as Carboplatin may affect the liver's ability to cope with alcohol.

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

Pregnancy
You must not be treated with carboplatin infusion during pregnancy unless clearly indicated by your doctor. Animal studies have shown at possible risk of abnormalities in the developing fetus. If you are being treated with carboplatin whilst pregnant, you should discuss with your doctor the possible risk of effects on your unborn child.
Women of child bearing potential must use an effective method of contraception both before and during treatment with carboplatin. Since carboplatin can cause genetic damage, if pregnancy occurs during treatment with carboplatin, genetic counseling is recommended. Genetic counseling 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 can cause genetic damage. Women of childbearing potential should be advised avoid becoming pregnant by using effective contraception during treatment. For women who are pregnant or become pregnant during therapy, genetic counseling should be provided.
Men treated with carboplatin are advised not to father a child during and up to 6 months after treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility.

Ask your doctor or pharmacist for advice before using any medicine

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

3. How you are given Carboplatin Infusion

Your Infusion will always be administered by nurse or doctor. It is usually given in a drip by slow injection into a vein and will usually take between 15 and 60 minutes to be administered. If you require any further information, ask your doctor or nurse who will be or who has administered the Infusion.
Your dose will be dependent on your height and weight, function of your blood (haemetopoietic) system and your kidney function. Your doctor will choose the best dose for you. The Infusion will normally be diluted before use

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

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

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

Instructions for use Cytotoxic

Carboplatin should be used by the intravenous route only. The recommended dosage of Carboplatin in previously untreated adult patients with normal kidney function, i.e. creatinine clearance > 60 ml/min is 400 mg/m² as a single short term IV dose administered by a 15 to 60 minutes infusion. Alternatively, the Calvert formula shown below may be used to determine dosage:
Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

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 untreated
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/m². Calvert's formula should not be used in patients who have received extensive pretreatment**

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

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of not tolerable side effects.

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

Combination Therapy:
The optimal use of Carboplatin Infusion 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 and Reconstitution:
The product must be diluted prior to infusion, with 5 % dextrose solution or 0.9 % sodium chloride solution, to concentrates as low as 0.5 mg/ml.

Incompatibilities
Needles or intravenous sets containing aluminium parts that may come into contact with Carboplatin Infusion should not be used for preparation or administration of Carboplatin Infusion.

Kidney problems
The amount given may vary, according to how well your kidneys are working. If you suffer from kidney problems your doctor may reduce the dose and may perform frequent blood tests as well as monitoring your kidney function. The Infusion will be given by a doctor experienced in the use of cancer treatment.

Children
There has not been enough usage of carboplatin in children to allow the recommendation of specific dose.
You may feel 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 be usual gap of 4 weeks between each dose of Carboplatin Infusion. Your doctor will want to perform some blood tests each week after giving you Carboplatin Infusion. So 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 carboplatin. However in the event that this occurs you may have some problems with your kidneys. If you are worried that too much has been administered or you have any questions about the dose being given. You should talk to the doctor administering your medicine.

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

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

4. Possible side effects

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

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

Very common side effects (occurring in more than 1 in 10 patients):
- Changes in your red and white blood cells and platelets (myelosuppression) your doctor may wants to monitor you.
- Anaemia (a condition in which there is a decreased number of red blood cells which lead to tiredness)
- Increase in the level of the creatinine and urea 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 and cramp
- Unusual feelings of tiredness or weakness
- Decrease in the level of salts in your blood. Your doctor may want to monitor you
- Damage to the kidneys (renal toxicity)

Common side effects (occurring in more than 1 in 100 and less than 1 in 10 patients):
- Unusual bruising or bleeding (haemorrhagic complications)
- Reduced function of your kidneys.
- Diarrhoea, constipation, sore lips or mouth ulcers (mucositis)
- Allergic reaction including rash, urticaria, skin reddening, itching, high temperature
- Ringing in the ears (tinnitus), hearing impairment and hearing loss
- Pins and needles (peripheral neuropathy)
- Hair loss
- Feeling unwell
- decreased serum levels of calcium
- flu-like syndrome
- Loss or lack of bodily strength
- fever

Uncommon side effects (occurring in more than 1 in 1000 and less than 1 in 100 patients):
- Secondary malignancies
- 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 reaction)
- Infection

Rare side effects (occurring in less than 1 in 1000 patients):
- 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)
- Severely impaired liver function, damage or death of liver cells. You doctor may want to monitor you.
- Temporary visual disturbances including temporary sight loss
- Inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Haemolytic uraemic syndrome (a disease characterized by acute renal failure, decreased number of red blood cells [microangiopathic haemolytic anaemia] and a low platelet count).
- Severe allergic reactions (anaphylaxis/anaphylactoid reactions). Symptoms of a severe allergic reaction include sudden wheeziness or tightness of chest, swelling of the eyelids, face or lips, facial flushing, hypotension, tachycardia, urticaria, dyspnoea, dizziness and anaphylactic shock.

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

If any of 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

Keep out of reach and sight of children.
Do not use carboplatin infusion after expiry date, which is stated on the label
The expiry date refers to the last day of that month.

Store below 25°C. Do not refrigerate or freeze. Keep vial in the outer carton in order to protect from light.

In use: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 30 hours at 2-8C.

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 condition

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

6. Further information

What Carboplatin Infusion contains
The active ingredient in Carboplatin infusion is carboplatin.
The other ingredient is water for injections

What Carboplatin Infusion looks like and content of the pack
Carboplatin infusion is a clear, colourless solution.
Each 1ml of concentrate for solution for infusion contain 10mg of carboplatin
Each 5 ml vial contains 50 mg of carboplatin
Each 15 ml vial contains 150 mg of carboplatin
Each 50 ml vial contains 450 mg of carboplatin

Not all pack size may be marketed.

Marketing Authorization holder and manufacturer:
Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF, UK

The leaflet was last approved in 11/2008.

This medicinal product must not be mixed with other medicinal product except 5% dextrose solution or 0.9% sodium chloride solution.

Carboplatin may interact with aluminium to form a black precipitate. 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.

Shelf life and storage
Carboplatin Infusion is intended for single use only.

Before opening
Store below 25°C. Do not refrigerate or freeze. Keep vial in the outer carton in order to protect from light.

After dilution
In use: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 30 hours at 2-8C.

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 condition

INSTRUCTIONS FOR USE/HANDLING, PREPARATION AND DISPOSAL GUIDE FOR USE WITH CARBOPLATIN

Handling of Carboplatin

As with other antineoplastic agents, Carboplatin must be prepared and handled with caution.
The following protective measures should be taken when handling **Carboplatin**
Personnel should be trained in appropriate techniques for reconstitution and handling
1. Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents. Personnel handling Carboplatin Infusion should wear protective clothing: goggles, gowns and disposable gloves and masks.
2. A designated area should be defined for syringe preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper
3. All items used for reconstitution, administration or cleaning (including gloves) should be placed in high-risk, waste-disposal bags for high temperature incineration.
4. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All contaminated and cleaning materials should be placed in high-risk, waste-disposal bags for incineration. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Medical attention should be sought. Always wash hands after removing gloves.

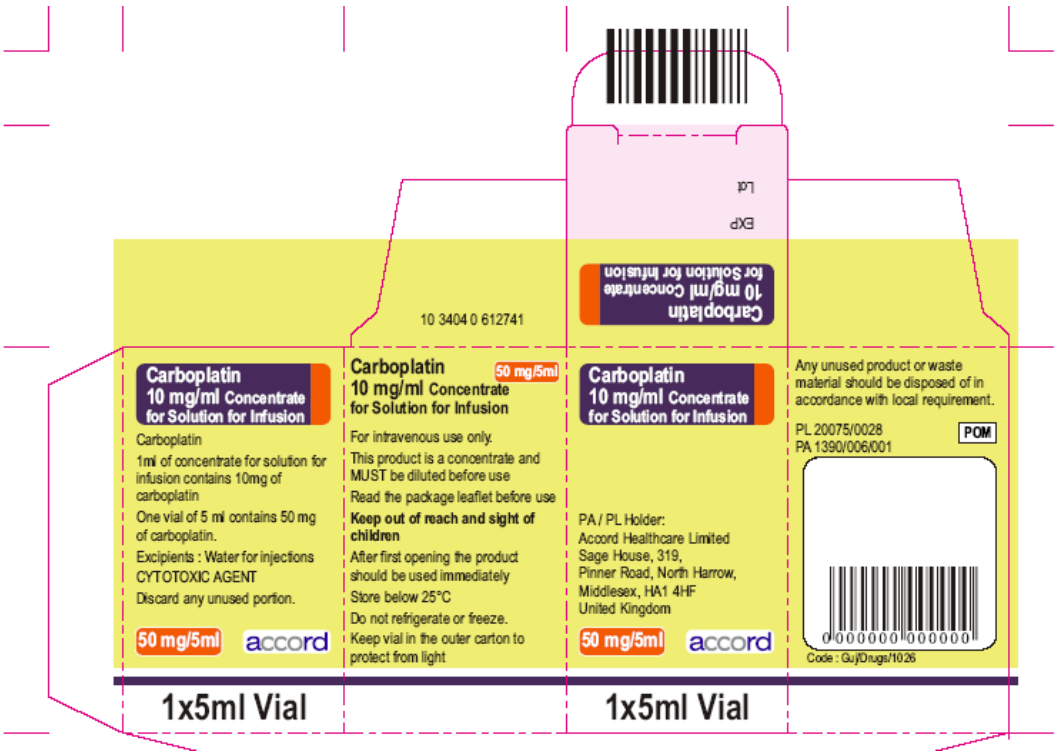
Preparation of infusion solution
The product must be diluted before use. It may be diluted with dextrose or Sodium Chloride, to concentrations as low as 0.5 mg/ml (500 micrograms/ml).

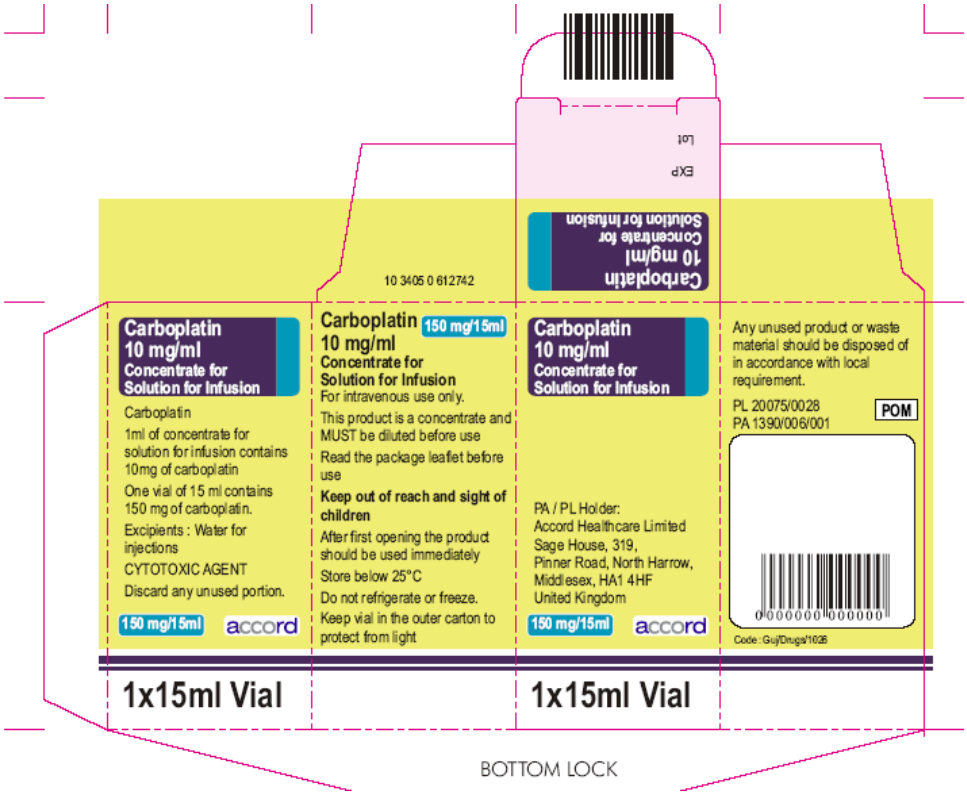
Disposal
Medicines should not be disposed of via wastewater or household waste. All material used for preparation, administration or otherwise coming into contact with carboplatin should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

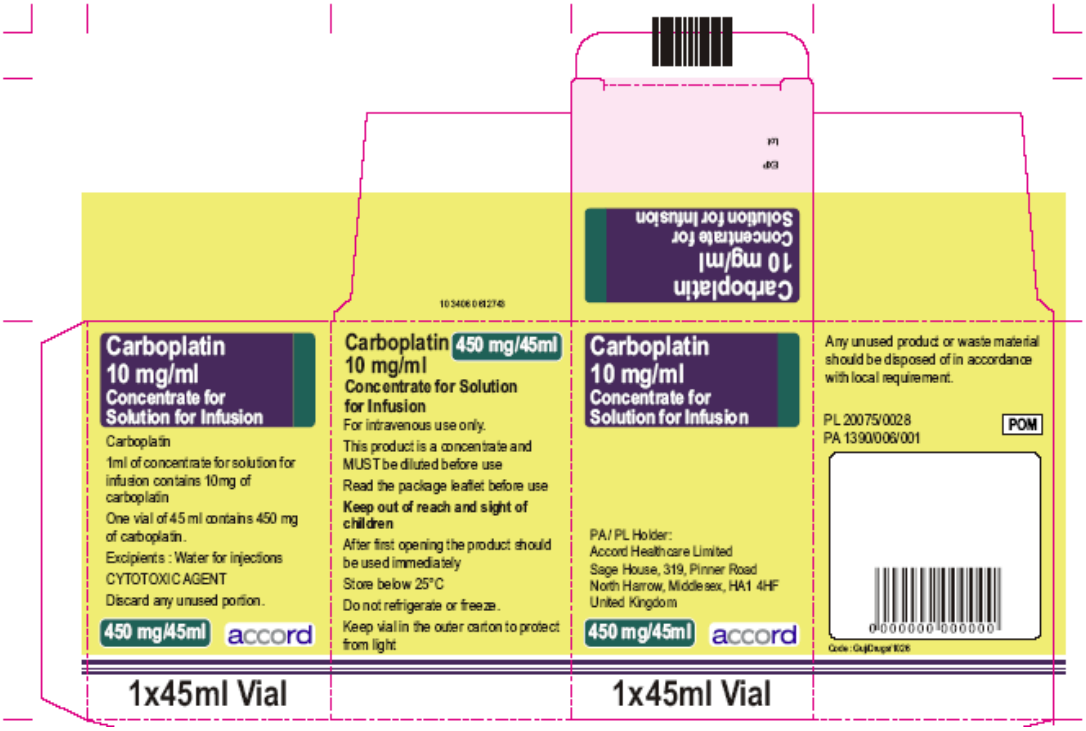
10 3070 0 611949

Module 4

Labelling




10 3405 0 612742
Carboplatin 10 mg/ml Concentrate for Solution for Infusion
Carboplatin 10 mg/ml Concentrate for Solution for Infusion
Carboplatin 150 mg/15ml 10 mg/ml Concentrate for Solution for Infusion
For intravenous use only.
This product is a concentrate and MUST be diluted before use
Read the package leaflet before use
Keep out of reach and sight of children
After first opening the product should be used immediately
Store below 25°C
Do not refrigerate or freeze.
Keep vial in the outer carton to protect from light
150 mg/15ml accord
Carboplatin 10 mg/ml Concentrate for Solution for Infusion
PA / PL Holder:
Accord Healthcare Limited
Sage House, 319,
Pinner Road, North Harrow,
Middlesex, HA1 4HF
United Kingdom
150 mg/15ml accord
Any unused product or waste material should be disposed of in accordance with local requirement.
PL 20075/0028
PA 1390/006/001
POM
Code : Guj/Drugs/1026
1x15ml Vial
1x15ml Vial
BOTTOM LOCK


Carboplatin 10 mg/ml Concentrate for Solution for Infusion
Carboplatin 10 mg/ml Concentrate for Solution for Infusion
Carboplatin 450 mg/45ml 10 mg/ml Concentrate for Solution for Infusion
For intravenous use only.
This product is a concentrate and MUST be diluted before use
Read the package leaflet before use
Keep out of reach and sight of children
After first opening the product should be used immediately
Store below 25°C
Do not refrigerate or freeze.
Keep vial in the outer carton to protect from light
450 mg/45ml accord
Carboplatin 10 mg/ml Concentrate for Solution for Infusion
PA/ PL Holder:
Accord Healthcare Limited
Sage House, 319, Pinner Road
North Harrow, Middlesex, HA1 4HF
United Kingdom
450 mg/45ml accord
Any unused product or waste material should be disposed of in accordance with local requirement.
PL 20075/0028
PA 1390/006/001
POM
1x45ml Vial
1x45ml Vial


Carboplatin 10 mg/ml
Concentrate for Solution for Infusion
Carboplatin
Intravenous route
This product is a concentrate and MUST be diluted before use
Read the package leaflet before use
50 mg/5ml
POM
PL 20075/0028
PA 1390/006/001
accord
1x5ml Vial
Varnish Free Area
EXP


Carboplatin 10 mg/ml
Concentrate for Solution for Infusion
Carboplatin
Intravenous route
This product is a concentrate and MUST be diluted before use
Read the package leaflet before use
150 mg/15ml
POM
PL 20075/0028
PA 1390/006/001
accord
1x15ml Vial
Varnish Free Area
EXP


Carboplatin 10 mg/ml
Concentrate for Solution for Infusion
Carboplatin
1ml of concentrate for solution for infusion contains 10mg of carboplatin
One vial of 45 ml contains 450 mg of carboplatin.
Excipients : Water for injections
For intravenous use only.
This product is a concentrate and MUST be diluted before use
Read the package leaflet before use
Keep out of reach and sight of children
After first opening the product should be used immediately
Store below 25°C.
Do not refrigerate or freeze.
Keep vial in the outer carton to protect from light
Discard any unused portion.
CYTOTOXIC AGENT
Any unused product or waste material should be disposed of in accordance with local requirement.
450 mg/45ml
PA / PL Holder:
Accord Healthcare Limited
Sage House, 319, Pinner Road
North Harrow, Middlesex, HA1 4HF
United Kingdom
POM
PL 20075/0028
PA 1390/006/001
accord
1x45ml Vial
Varnish Free Area
EXP

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for a Marketing Authorisation for the medicinal product Carboplatin 10mg/ml concentrate for solution for infusion is approvable.

Carboplatin 10mg/ml concentrate solution for infusion is used 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."

About the product

Carboplatin is an analogue of cisplatin which is more stable and has less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis than cisplatin. Platinum compounds are among the most active group of cytotoxic agents against epithelial ovarian cancer and have been the main drug used either alone or in combination since the 1970s. Platinum based chemotherapy produced improvement in survival for women, regardless of cancer stage of age of the patient.

Carboplatin was introduced in the late 1980s and has since been used in clinical treatment due to its reduced side-effects compared to its parent compound cisplatin. Carboplatin is classified as DNA alkylating agent. It has similar activity in lung cancer but exhibits a more favourable toxicity profile and is easier to administer than cisplatin. The dose-limiting toxicity for Carboplatin is myelosuppression, particularly thrombocytopenia.

Ovarian cancer is a major cause of morbidity and death for women around the world. Approximately 14, 300 U.S women died because of ovarian cancer in 2003, which makes this tumour is leading cause of gynaecologic cancer death. Overall, ovarian cancer accounts for 4% of all cancer diagnosis and 5% of all cancer deaths. The lifetime risk of developing ovarian cancer is approximately 1.7% and approximately 1 in 60 women will die of the disease. The vast majority of epithelial ovarian carcinomas are diagnosed in postmenopausal women, and the median age at diagnosis is 63 years. The age specific incidence increases from 15 to 16 per 100 000 in the 40 to 44 year old age group to a peak rate of 57 per 100 000 in the 70 to 74 year old age group.

Lung cancer is also the leading cause of death due to cancer in the entire world. Of new lung cancer cases, small cell lung cancer (SCLC) accounts for approximately 20%-25% of them. Most cases of SCLC, present with extensive disease, are due to the aggressive nature of SCLC.

The proposed Indications for this application are in line with the reference product Paraplatin.

"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."

General comments on the submitted dossier

This is an abridged application according to Article 10(1) of 2001/83/EC, as amended, a so called "generic application" for Carboplatin 10mg/ml solution for injection referring to the European reference product Paraplatin 10mg/ml. The active substance is carboplatin. The reference product is Paraplatin, 10 mg/ml, concentrate for solution for infusion registered in Europe since February 1991. The UK reference product is Paraplatin 10mg/ml solution for injection (PL 00125/0201) granted to Bristol Myers Squibb

With the United Kingdom as the Reference Member State in the Decentralised Procedure UK/H/1185/001/DC, Accord Healthcare Limited, United Kingdom is applying for marketing authorization in the following Concerned Member States: AT, BE, CZ, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, SE and SK.

No scientific advice has been given for the proposed medicinal product. The proposed product will be a prescription only medicine (POM). There is no proposed paediatric development plan for this product.

Pharmacotherapeutic group:

ATC Code: L01X A02

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

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. 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. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance

There is a Ph Eur monograph for carboplatin and the control tests and specifications for drug substance are adequately drawn up and in accordance with the Ph Eur. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches of each fill sizes. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 2 years with a storage condition of below 25°C, protected from light and do not refrigerate or freeze for the drug product is considered acceptable.

NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of carboplatin are well known. As carboplatin is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. An overview based on a literature review is, thus, appropriate. A satisfactory overview written by a suitably qualified expert was provided.

CLINICAL ASPECTS

Pharmacokinetics
As the product is a solution for injection, a bioequivalence study has not been carried out.

Carboplatin is poorly absorbed by the oral route. It is widely distributed and crosses the blood-brain barrier and enters the cerebro-spinal fluid. It does not bind to plasma proteins and has an apparent volume of distribution of 16 L. At 98.6°F (37°C) the retention half-life of Carboplatin in blood plasma is 30 hours, whereas that for cisplatin is only 1.5-3.6 hours. Following administration of Carboplatin injection in man, linear relationships exist 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 when creatinine clearance $\geq$ 60 mL/min.

Carboplatin does not undergo significant metabolism. As observed with cisplatin, Carboplatin undergoes an aquation reaction in the presence of low concentrations of chloride. This reaction is 100-fold slower with Carboplatin when compared with cisplatin. The kidneys extensively clear Carboplatin, with about 60%–70% of the drug excreted in urine within 24 hours. The elimination of Carboplatin is slower than that of cisplatin, with a terminal elimination half-life in man is approximately 6 hours. The terminal half-life for total plasma platinum is 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of platinum correlate with the rate of glomerular filtration but not tubular secretion.

Pharmacodynamics
Carboplatin is an established drug therefore only an overview will be presented here.

Carboplatin is an analogue of cisplatin. Like cisplatin, it contains a platinum atom surrounded in a plane by two ammonia groups and two other ligands in the cis position. The other two ligands in Carboplatin are present in a ring structure rather than as two chloride atoms in cisplatin. This difference makes Carboplatin more stable and it has less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis. The exact mechanism of action of Carboplatin is not known. Carboplatin undergoes intracellular activation to form reactive platinum

complexes, which are believed to inhibit DNA synthesis, by forming interstrand and intrastrand cross-linking of DNA molecules. Carboplatin is a radiation-sensitising agent. It is cell cycle-phase nonspecific.

The use of carboplatin in conjunction with anti-angiogenesis products has been discussed, as has the role of p53 in apoptosis following DNA damage, as induced by chemotherapeutic agents.

Carboplatin was active in the treatment of transgenic murine retinoblastoma, in S-180 lung neoplasm models when incorporated in to non-phospholipid vesicles and in a malignant glioma model in rats when applied using a convection-enhanced delivery system.

Clinical efficacy
Carboplatin has an established efficacy and has proved to be a feasible alternative to cisplatin for the treatment of many solid tumors, especially ovarian cancer and lung cancer. As a second generation analog of cisplatin, Carboplatin shares many structural and pharmacologic features with cisplatin, yet it has an improved toxicity profile. These characteristics have made Carboplatin a feasible candidate for not only dose-intensive chemotherapy but also combination therapy with newer agents such as paclitaxel. No new data were presented for this application and none were required.

Clinical safety
No new data were presented for this application and none were required.

Summary of Product Characteristics, Patient Information Leaflet and Labelling
These were satisfactory.

Conclusion
A market authorisation may be granted.

Module 6

Steps taken after procedure

No non-confidential alterations have been made to the market authorisation.