Applicant: Teva Pharmaceuticals (Pty) Ltd
Product name: CARBOSIN 150 / 450 / 600
Dosage form & strength: Each 15 ml, 45 ml or 60 ml single dose glass vial contains 150 mg, 450 mg or 600 mg carboplatin, respectively.
Registration Numbers: Z/26/260 ; Z/26/261 ; Z/26/262 ; A39/26/0170

SCHEDULING STATUS:

S4

PROPRIETARY NAMES AND DOSAGE FORMS:

CARBOSIN 50 Solution for injection

CARBOSIN 150 Solution for injection

CARBOSIN 450 Solution for injection

CARBOSIN 600 Solution for injection

COMPOSITION:

Active ingredients:

CARBOSIN 50 contains 50 mg carboplatin (10 mg/ml)

CARBOSIN 150 contains 150 mg carboplatin (10 mg/ml)

CARBOSIN 450 contains 450 mg carboplatin (10 mg/ml)

CARBOSIN 600 contains 600 mg carboplatin (10 mg/ml)

Inactive ingredients:

Mannitol and water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Carboplatin [cis-diammine (1,1-cyclobutane-dicarboxylato) platinum] is a platinum co-ordination compound with anti-tumour properties. It is soluble in water at concentrations below 15 mg/ml.

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

Pharmacokinetics:

In patients with creatinine clearances of 60 ml/min or greater given carboplatin at doses of 300 to 500 mg/m^2, the plasma concentrations of carboplatin decay in a biphasic manner with mean alpha and beta half-lives of 1,6 hours and 3,0 hours, respectively. The total body clearance, apparent volume of distribution, and mean residence time for carboplatin are 73 ml/min, 16 L, and 3,5 hours, respectively.

Carboplatin exhibits linear, dose-independent pharmacokinetics in patients with creatinine clearances $\geq$ 60 ml/min. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of about 60 ml/min or greater, excrete 70 % of the dose of carboplatin in the urine, with most of this occurring within 12 to 16 hours.

In patients with creatinine clearances of less than 60 ml/min, carboplatin renal and total body clearances decrease progressively. Doses of carboplatin, therefore, should be reduced in patients with creatinine clearance < 60 ml/min (see **DOSAGE AND DIRECTIONS FOR USE**).

INDICATIONS:

Carboplatin is indicated for the treatment of:

- **Advanced ovarian carcinoma of epithelial origin in:**
  - First line therapy.
  - Second line therapy, after other treatments have failed.
- **Limited evidence in support of the following:**
  - Small cell carcinoma of the lung.
  - The treatment of squamous cell carcinoma of the head and neck.

CONTRAINDICATIONS:

CARBOSIN is contraindicated in patients with a history of severe hypersensitivity reactions to carboplatin or other platinum-containing compounds.

CARBOSIN should not be used in patients with severe pre-existing renal impairment (creatinine clearance at or below 20 ml/min).

CARBOSIN should not be employed in severely myelosuppressed patients and/or in patients with localised tumoral bleeding.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity reactions to CARBOSIN have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is an increased risk of allergic reactions, including anaphylaxis in patients previously exposed to platinum therapy (see **CONTRAINDICATIONS** and **SIDE EFFECTS: Hypersensitivity Reactions**).

CARBOSIN should be used only by a medical practitioner experienced with cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available. Blood counts as well as renal and hepatic function tests must be done regularly and the medicines should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Haematological toxicity:

Myelosuppression (leucopenia, neutropenia and thrombocytopenia) is dose-dependent and dose limiting.

Peripheral blood counts should be monitored frequently and until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent CARBOSIN and day 15 in patients receiving CARBOSIN in combination with other chemotherapeutic agents. Single intermittent courses of CARBOSIN should not be repeated until leucocyte, neutrophil and platelet counts have returned to normal.

Transfusional support is frequently needed during treatment with CARBOSIN, particularly in patients receiving prolonged therapy, since anaemia is cumulative. Myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial CARBOSIN dosages in these groups of patients should be appropriately reduced (see **DOSAGE AND DIRECTIONS FOR USE**) and the effects carefully monitored through frequent blood counts between courses. CARBOSIN combination therapy with other myelosuppressive forms of treatment must be planned very carefully with respect to dosages and timing in order to minimise additive effects.

Neurologic toxicity:

Although peripheral neurologic toxicity is generally rare and mild, its incidence is increased in patients older than 65 years and/or in patients previously treated with platinum components.

Visual disturbances, including loss of vision, have been reported less frequently after the use of CARBOSIN in doses higher than those recommended in patients with renal impairment.

Other:

Very high dosages of CARBOSIN (up to five times the single agent recommended dose or more) have resulted in severe abnormalities in hepatic and renal function.

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

NOTE: CARBOSIN interacts with aluminium to form a black precipitate and/or loss of potency. It is important not to use IV sets, needles, catheters or syringes containing aluminium parts while mixing or administering CARBOSIN**.**

Paediatric use:

Safety and effectiveness in paediatric patients have not been systematically studied.

INTERACTIONS:

The use of CARBOSIN with nephrotoxic compounds is not recommended.

Although CARBOSIN has limited nephrotoxic potential, concomitant treatment with aminoglycosides has resulted in episodes of increased renal and audiologic toxicity.

Hearing loss has been reported to occur in paediatric patients when CARBOSIN was administered in combination with other ototoxic agents.

CARBOSIN can induce nausea and vomiting, which can be more severe in previously treated patients (in particular in patients previously pre-treated with cisplatin).

PREGNANCY AND LACTATION:

Pregnancy:

Pregnancy is a contraindication. CARBOSIN has been shown to be an embryotoxin and mutagen (see **CONTRAINDICATIONS**).

Women of childbearing potential:

It is recommended that patients with child-bearing or conceiving potential, who are receiving CARBOSIN**,** exercise adequate contraception control.

Lactation:

Safety in lactation has not been established. It is not known whether this medicine is excreted in human milk (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE:

CARBOSIN should be used by the intravenous route only. The recommended dosage of CARBOSIN in previously untreated adult patients with normal kidney function is 400 mg/m^2 as a single IV dose administered by a short term (15 to 60 minutes) infusion. Therapy should not be repeated until four weeks after the previous CARBOSIN course and/or until the neutrophil count is at least 2 000 cells/mm^3 and the platelet count is at least 100 000 cells/mm^3.

Reduction of the initial dosage by 20 to 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).

For patients aged 65 and over, dosage adjustments, initially or subsequently, may be necessary, depending on the physical condition of the patient. Determination of the haematological nadir by weekly blood counts during the initial courses of treatment with CARBOSIN is recommended for future dosage adjustment.

Impaired renal function:

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

Patients with creatinine clearance values below 60 ml/min are at increased risk of severe myelosuppression.

The frequency of severe leucopenia, neutropenia, or thrombocytopenia has been maintained at about 25 % with the following dosage recommendations:

- CARBOSIN 250 mg/m^2 IV on day 1 in patients with baseline creatinine clearance values between 41 – 59 ml/min.
- CARBOSIN 200 mg/m^2 IV on day 1 in patients with baseline creatinine clearance values between 16 – 40 ml/min.

Insufficient data exist on the use of CARBOSIN in patients with creatinine clearance of 15 ml/min or less to permit a recommendation for treatment.

All of the above dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression.

Combination therapy:

The optimal use of CARBOSIN in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

Paediatrics:

Safety and efficacy in paediatrics have not been established.

Elderly:

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

Preparation of IV solution:

Note above warning regarding interaction of CARBOSIN with aluminium.

CARBOSIN solution may be further diluted with sufficient volumes of dextrose 5 % in water or 0,9 % sodium chloride, to concentrations as low as 0,5 mg/ml.

When reconstituted as directed, CARBOSIN solutions are stable for eight hours at room temperature (25 ºC).

NOTE: Single dose vials, discard any unused portions. The infusion bags must be covered with aluminium foil to protect the solution from light.

SIDE EFFECTS:

Central nervous system disorders:

*Less frequent***:** Peripheral neuropathies have been observed, mild paraesthesiae occurring most frequently. The incidence and severity may be increased in patients previously treated with cisplatin. Clinical ototoxicity and other sensory disturbances (including visual disturbances and taste modifications) have been reported.

Gastrointestinal disorders:

Frequent: Nausea and vomiting are commonly seen. Nausea and vomiting usually cease within 24 hours after treatment. Emesis during carboplatin treatment can be effectively reduced by appropriate anti-emetic medication. Alternatively, emesis may be reduced by sustained administration schedules e.g. by dividing the total dose over 5 days, or over a 24 hour IV infusion.

Pain, diarrhoea, constipation and anorexia have been reported.

Haematological system disorders:

Frequent: Myelosuppression is the major dose-limiting toxicity of carboplatin. Thrombocytopenia (platelets< 50,000/mm^3) is seen in most of the patients, with a nadir at about 3 weeks and full recovery at 4 – 5 weeks. Leucopenia (< 2,00/mm^3) is usually less pronounced, with a nadir at about 3 weeks and a somewhat slower recovery at 5 weeks.

Neutropenia and anaemia (haemoglobin < 2 mg/dl) is commonly seen.

Haemorrhagic complications, usually minor, have also been reported.

Myelosuppression is more severe in patients with impaired renal function, patients with an inadequate bone marrow reserve, or patients with poor performance status.

Hepatic system disorders:

Less frequent: The alkaline phosphatase level is increased more frequently than ALT, AST or total bilirubin.

Hypersensitivity reactions:

Less frequent: Anaphylaxis, angioedema, and anaphylactoid reactions, including rash, urticaria, erythema, pruritus, bronchospasm, hypotension and facial oedema may occur within minutes of administration and should be managed with appropriate supportive therapy.

Renal system disorders:

Frequent: Elevation of serum creatinine, elevation of blood urea, and of uric acid has been reported.

Other:

Second malignancies have been reported in association with multi-drug therapy; however the relationship to CARBOSIN is unclear. Respiratory, cardiovascular, mucosal, genito-urinary, cutaneous and musculoskeletal side-effects have occurred.

Although death occurred because of cardiovascular events (cardiac failure, embolism, cerebrovascular accident) it is unclear whether this was related to chemotherapy rather than general patient conditions.

Hypertension has been reported.

Among miscellaneous side effects, asthenia and alopecia are the most frequent. Haemolytic-uremic syndrome has been reported less frequently.

Malaise has also been reported.

Serum electrolytes:

Decreases in serum electrolytes (sodium, potassium, magnesium and calcium) have been reported after treatment with CARBOSIN. Several cases of hyponatremia have been reported.

Carcinogenesis, mutagenesis, impairment of fertility:

The carcinogenic potential of CARBOSIN has not been studied, but compounds with a similar mechanism of action and mutagenicity have been reported to be carcinogenic. CARBOSIN has been shown to be mutagenic both *in vitro* and *in vivo*. CARBOSIN can cause foetal harm when administered to a pregnant woman (see **PREGNANCY AND LACTATION**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no known antidote for CARBOSIN overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal function.

Use of higher than recommended doses of CARBOSIN has been associated with loss of vision.

IDENTIFICATION:

A clear, colourless to faintly yellow solution, free from fibres and particles of foreign matter.

PRESENTATION:

Amber, 5 ml, 15 ml, 45 ml or 60 ml, single dose glass vials containing 50 mg, 150 mg, 450 mg or 600 mg carboplatin respectively.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC and protect from light. Discard any unused portion.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CARBOSIN 50: Z/26/260

CARBOSIN 150: Z/26/261

CARBOSIN 450: Z/26/262

CARBOSIN 600: A39/26/0170

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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2090

DATE OF PUBLICATION OF THE PACKAGE INSERT:

05 February 2016

Botswana	**Namibia**
CARBOSIN 150: BOT0400614	CARBOSIN 150: 04/26/1206
CARBOSIN 450: BOT0400615	CARBOSIN 450: 04/26/1207
S2	NS2