

SUMMARY OF PRODUCT CHARACTERISTIC:

1.Product Description:

Name of Medicinal Product:

CPLATDN (Carboplatin Injection BP 150 mg/15 ml)

2.Qualitative & Quantitative Composition:

Each ml contains

Carboplatin BP..... 10 mg

3.Pharmaceutical Form:

Description:

A clear, colorless solution

Pack Style:

A Clear Colorless solution filled in 15 ml amber molded glass vial USP Type I, stoppered with 20 mm Bromo butyl rubber plug sealed with 20 mm Aluminium Flip off Seal having Red color.

4.Clinical Particulars:

4.1 Therapeutic indications:

Antineoplastic agent indicated in the management of:

- ovarian carcinoma of epithelial origin
- small cell lung carcinoma.

4.2 Posology and method of administration Posology

The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m², given as a single short term intravenous infusion over 15 to 60 minutes. Alternatively, the Calvert formula shown below may be used to determine dosage:

$$\text{Dose (mg)} = \text{target AUC (mg/ml x min)} \times [\text{GFR ml/min} + 25]$$

| 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/m².

Therapy should not be repeated until 4 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.

Initial dosage should be reduced by 20-25% in patients with risk factors such as previous myelosuppressive therapy and/or poor performance status (ECOG-Zubrod 2-4 or Karnofsky below 80).

Determination of hematologic nadir by weekly blood counts during initial courses is recommended for future dosage adjustment and scheduling of carboplatin.

Needles or intravenous sets containing aluminium parts that may come in contact with carboplatin injection should not be used for preparation or administration. Aluminium reacts with carboplatin injection causing precipitate formation and/or loss of potency. The safety measures for dangerous substances are to be complied with preparation and administration. Preparation must be carried out by personnel who have been trained in the safe use while wearing protective gloves, face mask and protective clothes.

Impaired renal function: In patients with impaired renal function, dosage of carboplatin should be reduced (refer to Calvert formula) and hematological nadirs and renal function monitored.

Patients with creatinine clearance values below 60 ml/min are at increased risk of severe myelosuppression. The frequency of severe leukopenia, neutropenia, or thrombocytopenia has been maintained at about 25% with the following dosage recommendations:

| Baseline Creatinine | Clearance Initial Dose (Day 1) |
|---------------------|--------------------------------|
| 41-59 ml/min | 250 mg/m ² I.V. |
| 16-40 ml/min | 200 mg/m ² I.V. |

Insufficient data exist on the use of carboplatin injection 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 carboplatin in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

Elderly population

In patients of more than 65 years of age, adjustment of the carboplatin dose to the general condition is necessary during the first and the subsequent therapeutic courses.

Paediatric population

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

Method of administration

Carboplatin injection should be used by the intravenous route only.

4.3 Contraindications

Carboplatin is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- patients with severe myelosuppression
- patients with pre-existing severe renal impairment (with creatinine clearance of < 30 ml per minute) unless in the judgment of the physician and patient, the possible benefits of treatment outweigh the risks
- patients with bleeding tumors
- concomitant use with yellow fever vaccine (see section 4.5)
- patients with a history of severe allergic reaction to carboplatin or other platinum containing compounds. Dosage adjustment may allow use in the presence of mild renal impairment (see section 4.2).

4.4 Special warnings and precautions for use:

Warnings:

Myelosuppression

Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the drug. Therefore, in patients with abnormal renal function, or who are receiving concomitant therapy with nephrotoxic drugs, myelosuppression, especially thrombocytopenia, may be more severe and prolonged.

The occurrence, severity and protraction of toxicity is likely to be greater in patients who have received extensive prior treatment with the drug for their disease or with cisplatin, have poor performance status and are advanced in years. Renal function parameters should be assessed prior to, during and after carboplatin therapy. Initial carboplatin dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.

Peripheral blood counts (including platelets, white blood cells and haemoglobin) should be followed during and after therapy. Combination therapy with other myelosuppressive drugs may require modification of dosage/timing of schedules in order to minimize additive effects.

Carboplatin courses should not, in general, be repeated more frequently than every 4 weeks in order to ensure that the nadir in blood counts has occurred and there has been recovery to a satisfactory level.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patients with severe and persistent myelosuppression are at high risk of infectious complications including fatal outcomes (see section 4.8). If any of these events occurs,

carboplatin should be discontinued.

Hypersensitivity Reactions

As with other platinum-based drugs, allergic reactions appearing most often during administration may occur and necessitate discontinuation of infusion. Patients should be observed carefully and an appropriate symptomatic treatment (including antihistamines, adrenaline and/or glucocorticoids) must also be initiated in such cases. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

Kounis syndrome can develop in patients with and without cardiac risk factors, and may be presented with a combination of cardiac and allergic symptoms, or as standalone. Coronary vasospasm may be eliminated with steroids, antihistamines in addition to spasmolytics treatment.

Renal Toxicity

In patients with impaired renal function, the effect of carboplatin on the haematopoietic system is more pronounced and longer-acting than in patients with normal renal function. In this risk group, therapy with carboplatin must be performed with special caution (see section 4.2).

Precautions:

Carboplatin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Peripheral blood counts, renal and hepatic function tests should be monitored closely. Blood counts should be performed prior to commencement of carboplatin therapy and at weekly intervals thereafter.

The drug should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Hematologic Toxicity

Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood counts should be monitored during carboplatin treatment. This will

monitor toxicity and help determine the nadir and recovery of haematological parameters and assist in subsequent dosage adjustments. Median day of nadir is day 21 in patients receiving single agent carboplatin and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. Lowest levels of platelets are generally seen between days 14 and 21 of initial therapy. A greater reduction is seen in patients who previously received extensive myelosuppressive chemotherapy. Lowest levels of white cells occur generally between days 14 and 28 of initial therapy. If neutrophil levels fall below 2000 cells/mm³ or platelets are less than 100,000 cells/mm³ then postponement of carboplatin therapy until bone marrow recovery is evident, should be considered. This recovery usually takes 5 to 6 weeks. Transfusions may be necessary and dosage reductions recommended for subsequent treatment.

Anaemia is frequent and cumulative, however rarely requires a transfusion.

Haemolytic anaemia, with the presence of serologic drug-induced antibodies, has been reported in patients treated with carboplatin. This event can be fatal.

Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

Haemolytic-uremic syndrome (HUS)

Haemolytic-uremic syndrome (HUS) is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Renal toxicity

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 severe alteration in renal function test. Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

Neurologic Toxicity

Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decreases in osteotendinous reflexes, its frequency is increased in patients older than 65 years and/or in patients previously treated with cisplatin. Monitoring and neurological examinations should be carried out at regular intervals. Visual disturbances, including loss of vision, have been reported after the use of carboplatin in doses higher than those recommended in patients with renal impairment. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) have been reported in patients receiving carboplatin in combination chemotherapy. RPLS is a rare, reversible (after treatment discontinuation), rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Geriatric Use

In studies involving combination therapy with carboplatin and cyclophosphamide, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. Because renal function is often decreased in the elderly, renal function should be considered when determining dosage.

Venoocclusive liver disease

Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases.

Tumor lysis syndrome (TLS)

In post marketing experience tumor lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Carboplatin dosing

Some subgroups of patients (i.e. age 40-59, BMI 20-25) are at particular risk of undertreatment if GFR is estimated using Cockcroft Gault Formula. Being an accurate estimation of GFR crucial for treatment with curative intent, in such cases GFR determination using a measured standard method (inulin, ⁵¹Cr-EDTA, ^{99m}Tc-DTPA, ¹²⁵I-iothalamate or iohexol) should be preferred when feasible.

Hearing Functions

Auditory defects have been reported during carboplatin therapy. Ototoxicity may be more pronounced in children and is more likely seen in patients previously treated with cisplatin. Cases of hearing loss with a delayed onset have been reported in paediatric patients. A long-term audiometric follow-up in this population is recommended. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides) (see Section 4.5).

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including carboplatin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Aluminium-containing equipment should not be used during preparation and administration of carboplatin (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction:

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come into contact with carboplatin, should not be used for the preparation or administration of the drug.

Due to the increase of thrombotic risk in cases of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the possibility of interaction between oral anticoagulants and anticancer chemotherapy, may require an increase in frequency of INR monitoring if a patient is treated with oral anticoagulants.

Concomitant use contraindicated

Yellow fever vaccine: risk of generalized disease mortal (see section 4.3).

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease.

This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis).

- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug which lead to a decrease in phenytoin serum levels); risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

- Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymph proliferation.

- Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.

- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimize the additive myelosuppressive effects.

4.6 Fertility, pregnancy and lactation Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving carboplatin and to use effective contraception during treatment with carboplatin and for at least 7 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with carboplatin and for at least 4 months after the last dose.

Pregnancy

Carboplatin can cause foetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryo toxic and teratogenic in rats receiving the drug during organogenesis. No controlled studies in pregnant women have been conducted.

Safe use of carboplatin in pregnancy has not been established. Both men and women receiving carboplatin should be informed of the potential risk of adverse effects on reproduction (see section 5.3). Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during carboplatin therapy. Carboplatin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.

Breast-feeding

Carboplatin and its active metabolites have been identified in human milk of treated mothers. To avoid possible harmful effects in the infant, breast-feeding must be stopped

during carboplatin therapy and for 1 month following last dose or discontinue treatment, taking into account the importance of the drug to the mother.

Fertility

Male and female fertility may be impacted by treatment with carboplatin (see section 5.3). Both men and women should seek advice for fertility preservation before treatment with carboplatin.

Gonadal suppression resulting in amenorrhoea or azoospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian functional impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.

Male patients should seek advice about sperm preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, carboplatin may cause nausea, vomiting, vision abnormalities and ototoxicity; therefore, patients should be warned of the potential effect of these events on the ability to drive or to use machines.

4.8 Undesirable effects:

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single agent carboplatin injection and post-marketing experience.

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon, ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data).

| System Organ Class | Frequency | MedDRA Term |
|---|------------------|--|
| Neoplasms, benign and malignant and unspecified (incl cysts and polyps) | Not known | Treatment related secondary malignancy |
| Infections and infestations | Common | Infections* |
| | Not known | Pneumonia |

| | | |
|--------------------------------------|-------------|---|
| Blood and lymphatic system disorders | Very common | Thrombocytopenia, neutropenia, leukopenia, anaemia |
| | Common | Haemorrhage* |
| | Not known | Bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome (HUS), haemolytic anaemia (sometimes fatal) |
| Immune system disorders | Common | Hypersensitivity, anaphylactoid type |

| | | |
|---|-------------|--|
| | | reaction |
| Metabolism and nutrition disorders | Not known | Dehydration, anorexia, hyponatraemia, Tumour lysis syndrome |
| Nervous system disorders | Common | Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia |
| | Not known | Cerebrovascular accident*, encephalopathy, Reversible Posterior Leukoencephalopathy Syndrome (RPLS) |
| Eye disorders | Common | Visual disturbance (incl. rare cases of loss of vision) |
| Ear and labyrinth disorders | Common | Ototoxicity |
| Cardiac disorders | Common | Cardiovascular disorder* |
| | Not known | Cardiac failure*, Kounis syndrome |
| Vascular disorders | Not known | Embolism*, hypertension, hypotension, venoocclusive disease (fatal) |
| Respiratory, thoracic and mediastinal disorders | Common | Respiratory disorder, interstitial lung disease, bronchospasm |
| Gastrointestinal disorders | Very common | Vomiting, nausea, abdominal pain |
| | Common | Diarrhoea, constipation, mucous membrane disorder |

| | | |
|--|-------------|--|
| | Not known | Stomatitis, pancreatitis |
| Skin and subcutaneous tissue disorders | Common | Alopecia, skin disorder |
| | Not known | Urticaria, rash, erythema, pruritus |
| Musculoskeletal and connective tissue disorders | Common | Musculoskeletal disorder |
| Renal and urinary disorders | Common | Urogenital disorder |
| General disorders and administration site conditions | Common | Asthenia |
| | Not known | Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise |
| Investigations | Very Common | Creatinine renal clearance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased. |
| | Common | Blood bilirubin increased, blood creatinine increased, blood uric acid increased |

* Fatal in <1%, fatal cardiovascular events in <1% included cardiac failure, embolism, and cerebrovascular accident combined.

Blood and lymphatic system disorders:

Myelosuppression is the dose-limiting toxicity of carboplatin injection. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm³ occurs in 25% of patients, neutropenia with granulocyte counts below 1,000/mm³ in 18%

of patients, and leukopenia with WBC counts below 2,000/mm³ in 14% of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin injection with other myelosuppressive compounds or forms of treatment.

Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired kidney function. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia. These effects, although usually reversible, have resulted in infectious and hemorrhagic complications in 4% and 5% of patients given carboplatin injection, respectively. These complications have led to death in less than 1% of patients.

Anaemia with haemoglobin values below 8 g/dL has been observed in 15% of patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to carboplatin injection.

Neoplasms, benign, malignant and unspecified (including cysts and polyps):

Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported.

Respiratory, thoracic and mediastinal disorders:

Pulmonary fibrosis has been reported very rarely, manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see General disorders below).

Gastrointestinal disorders:

Vomiting occurs in 65% of patients, in one-third of whom it is severe. Nausea occurs in an additional 15%. Previously treated patients (in particular patients previously treated with cisplatin) appear to be more prone to vomiting. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin, are readily controlled or prevented with antiemetics and disappear within 24 hours. Vomiting is more likely when carboplatin injection is given in combination with other emetogenic compounds.

The other gastrointestinal complaints corresponded to pain in 8% of patients, diarrhoea, and constipation in 6 % of patients. Cramps have also been reported.

Nervous system disorders:

Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4% of patients administered carboplatin injection. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin injection, appear to be at increased risk.

Clinically significant-sensory disturbances (ie, visual disturbances and taste modifications) have occurred in 1% of patients.

The overall frequency of neurologic side effects seems to be increased in patients

receiving carboplatin injection in combination. This may also be related to longer cumulative exposure. Parasthesias present prior to treatment, especially if caused by cisplatin, may persist or worsen during carboplatin therapy (see section 4.4).

Eye disorders:

Visual disturbances, including sight loss, are usually associated with high dose therapy in renally impaired patients.

Ear and labyrinth disorders:

A subclinical decrease in hearing acuity in the high frequency range (4000-8000 Hz), determined by audiogram, occurred in 15% of patients. Very rare cases of hypoacusia have been reported.

Tinnitus was also commonly reported. Hearing loss as a result of cisplatin therapy may give rise to persistent or worsening symptoms. At higher than recommended doses, in common with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin is administered.

Hepatobiliary disorders:

Modification of liver function in patients with normal baseline values was observed, including elevation of total bilirubin in 5%, SGOT in 15%, and alkaline phosphatase in 24% of patients. These modifications were generally mild and reversible in about one-half the patients.

In a limited series of patients receiving very high dosages of carboplatin injection and autologous bone marrow transplantation, severe elevation of liver function tests has occurred.

Cases of an acute, fulminant liver cell necrosis occurred after high-dose administration of carboplatin.

Renal and urinary disorders:

When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin injection has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6% of patients, elevation of blood urea nitrogen in 14%, and of uric acid in 5% of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven to be the most sensitive renal function measure in patients receiving carboplatin injection. Twenty-seven percent (27%) of patients who have a baseline value of 60 mL/min or greater, experience a reduction in creatinine clearance during carboplatin injection therapy. Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin

therapy.

Immune system disorders:

Anaphylactic-type reactions, sometimes fatal, may occur in the minutes following injection of the product: facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm.

Fever with no apparent cause has also been reported.

Skin and subcutaneous tissue disorders:

Erythematous rash, fever and pruritis have been observed. These were reactions similar to those seen after cisplatin therapy but in a few cases no cross-reactivity was present.

Investigations:

Decreases in serum sodium, potassium, calcium, and magnesium occur in 29%, 20%, 22%, and 29% of patients, respectively. In particular, cases of early hyponatraemia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.

Cardiac disorders:

Isolated cases of cardiovascular incidents (cardiac insufficiency, embolism) as well as isolated cases of cerebrovascular accidents have been reported.

General disorders and administration site conditions:

Reactions at the site of injection (burning, pain, reddening, swelling, urticaria, necrosis in connection with extravasation) have been reported.

Fever, chills and mucositis have occasionally been observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

Pharmacovigilance Electronic Reporting System (PvERS)

<https://pv.pharmacyboardkenya.org/>

4.9 Overdose:

There is no known antidote for carboplatin overdosage. No overdosage occurred during clinical trials. If necessary, however, the patient may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment. Reports of doses up to 1600mg/m² indicate patients feeling extremely ill with diarrhoea and alopecia

developing. Use of higher than recommended doses of carboplatin has been associated with loss of vision (see section 4.4).

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antineoplastic agent, ATC Code: LO1X A02

Carboplatin, like Cisplatin, interferes with DNA intra-strand and inter-strand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.

Paediatric population

Safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties:

Absorption

After a 1-hour infusion (20-520mg/m²), plasma levels of total platinum and free (ultra filterable) platinum decay biphasically following first order kinetics. For free platinum, the initial phase (t alpha) half-life is approximately 90 minutes and the later phase (t beta) half-life approximately 6 hours. Total platinum has the same initial half-life, while the terminal half-life is longer (approx. 5 days). All free platinum is in the form of carboplatin in the first 4 hours after administration.

Distribution

Protein binding of carboplatin reaches 85-89% within 24 hours of administration, although during the first 4 hours, only up to 29% of the dose is protein bound. Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin.

Elimination

Carboplatin is excreted primarily by glomerular filtration in urine, with recovery of 65% of a dose within 24 hours. Most of the drug is excreted within the first 6 hours. Approximately 32% of a given dose of carboplatin is excreted unchanged.

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 embryo toxic 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:

Aluminium-containing equipment should not be used (see section 4.5).

6.3 Shelf life:

24 Months from the date of manufacturing.

6.4 Special precautions for storage:

Clear glass and Onco-Tain® vials;

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

Onco-Vials®;

Store in a refrigerator (2-8°C). Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container:

Glass Container of USP Type I:

Amber colour USP Type I containers were chosen for the filling of products as containers of USP Type I are high resistant borosilicate glass, generally used for packing of acidic parenteral preparations. This glass has high silicon contents and it is the least reactive, which means that the glass is least likely to have a chemical reaction with whatever you place inside it. The glass will not leech into its contents, which can happen with a more reactive glass type. Type I glass containers are highly resistant to temperature changes. They have a low coefficient of expansion.

Since Carboplatin Injection has pH 5.0 to 7.0, so USP Type I containers are most suitable for packing of Carboplatin Injection. Also amber colour glass vial are chosen because the product is light sensitive.

Closure:

20 mm Bromo Butyl Rubber Plug:

20 mm Bromo Butyl rubber Plug are Teflon coated made from suitable compounded and vulcanized rubber, non-porous having smooth finish and free from embedded particles and having self-sealing property, suitable to fit in 20 mm neck of glass vial.

20 mm Aluminium Flip off Seal:

Flip off Seal Made of Aluminium and Nontoxic Polypropylene.

6.6 Special precautions for disposal and other handling:

Parenteral drugs should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particular matter is

observed, shake and re- inspect. Vials with visible particulate matter should not be used.

Handling

Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents.

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.

In the event of a spillage, two operators should put on gloves and mop up the spilled material with a sponge kept for that purpose. In the event of a powder spillage, cover with a cloth and moisten with water before mopping up. Rinse the area twice with water. Put all solutions and sponges in a plastic bag, seal and label with the words 'CYTOTOXIC WASTE' and incinerate.

Disposal

Syringes and ONCO-VIALS®, containers, absorbent materials, solutions and other material which have come into contact with carboplatin should be placed in a thick plastic bag or other impervious container and incinerated at 1000°C.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Directions for use of the ONCO-VIAL®

ONCO-VIALS® should be used with the appropriate Hospira administration device.

7. Marketing Authorization Holder

NATIONAL PHARMACY LTD,
Colchester Park,
P.O Box 17843 - 00500
Nairobi, Kenya.

8. Marketing Authorization Number(s)

CTD12810

9. Date of First Authorization/Renewal of the Authorization

20th January,2025

10. Date of Revision of the Text

20th January,2025