Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Carboplat 150mg Injection (Carboplatin 150mg)

Carboplat 450mg Injection (Carboplatin 450mg)

2. Qualitative and quantitative composition

Carboplat 150mg Injection:
Each 15ml Contains: Sterile Carboplatin..... 150mg

Carboplat 450mg Injection:
Each 45ml Contains: Sterile Carboplatin..... 450mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Aqueous solution for Injection

Description: Visual description of the product: A clear colorless sterile solution is filled and sealed in an amber glass Vial USP type – 1

4. Clinical particulars

4.1 Therapeutic indications

As single-drug therapy or in combination with other antineoplastic drugs for the treatment of the following diseases:

Advanced epithelial ovarian cancer
Small-cell lung cancer.

4.2 Posology and method of administration

The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m^2, 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: Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

Target AUC	**Planned Chemotherapy**	**Patient Treatment status**
5-7 mg/ml.mi	single agent carboplatin	previously untreated

n		
4-6 mg/ml.min	single agent carboplatin	previously treated
4-6 mg/ml.min	carboplatin plus cyclophosphamide	previously untreated

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m^2. 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/mm^3 and the platelet count is at least 100,000 cells/mm^3.

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.

Pediatric population

There is insufficient information to support a dosage recommendation in pediatrics

Method of administration

Carboplatin injection should be used by the intravenous route only.

The solution for infusion is given as a short intravenous infusion over 15 – 60 minutes. For instructions on dilution of the medicinal product before administration, see section 6.6.

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or Intravenous 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. Thus, aluminium containing equipment should not be used during preparation and administration of carboplatin.

Carboplatin is a mutagenic and potentially carcinogenic substance. The usual precautions for hazardous substances must be observed during preparation and administration of the drug. The solution must be prepared by suitably trained staff wearing protective gloves, mouth protection and protective clothing.

Note
The average body surface of an adult is 1.73 m^2.

Based on the recommended dosages of 400 mg/m^2 body surface and 300 – 320 mg/m^2, this means mg quantities of 680 mg and 480 – 520 mg carboplatin respectively.

The different pack sizes of this medication must be combined appropriately to make up these quantities. In order to minimize the

amount of solution left over, the pack sizes containing 50 mg and 150 mg carboplatin should be used to achieve exactly the desired dosage.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 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 tumours
- Concomitant use with yellow fever vaccine
- 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.

4.4 Special warnings and precautions for use

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 and the effects carefully monitored through frequent blood counts between courses.

Peripheral blood counts (including platelets, white blood cells and hemoglobin) 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. If any of these events occurs, carboplatin should be discontinued.

Allergic 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.

The vial stopper contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Renal Toxicity

In patients with impaired renal function, the effect of carboplatin on the hematopoietic 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

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 hematological 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/mm^3 or platelets are less than 100,000 cells/mm^3 then postponement of carboplatin therapy until bone barrow 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.

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

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

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

Hemolytic-uremic syndrome (HUS)

Hemolytic-uremic syndrome (HUS) is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of micro-angiopathic hemolytic anemia, such as rapidly falling hemoglobin 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 program 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.

Veno-occlusive liver disease

Cases of hepatic veno-occlusive 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 Cockroft 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, ^{51}Cr-EDTA, ^{99m}Tc-DTPA, ^{125}I-iothalamate or iohexol) should be preferred when feasible.

Others

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 pediatric patients. A long- term audiometric follow-up in this population is recommended.

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.

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.

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 exist (poliomyelitis).
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), 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 minimise the additive myelosuppressive effects.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Carboplatin can cause fetal 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. Women of childbearing potential should be fully informed of the potential hazard to the fetus 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 fetus.

Breast-feeding

It is not known whether carboplatin is excreted in breast milk. To avoid possible harmful effects in the infant, breast-feeding must be stopped during carboplatin therapy.

Fertility

Gonadal suppression resulting in amenorrhea 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.

Men of sexually mature age treated with carboplatin are advised

not to father a child during treatment and up to 6 months afterwards. 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 (≥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), 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, haemolytic anaemia
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*
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	Common	Urogenital disorder

disorders		
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/mm^3 occurs in 25% of patients, neutropenia with granulocyte counts below 1,000/mm^3 in 18% of patients, and leukopenia with WBC counts below 2,000/mm^3 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.

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, diarrhea, 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.

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 hypoacusis 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 pediatric 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 hyponatremia 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.

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/m^2 indicate patients feeling extremely ill with diarrhea and alopecia developing. Use of higher than recommended doses of carboplatin has been associated with loss of vision.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agent

ATC code: LO1XA02

Mode of Action

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.

5.2 Pharmacokinetic properties

Absorption

After a 1-hour infusion (20-520mg/m^2), 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. All free platinum is in the form of carboplatin in the first 4 hours after administration.

Distribution

It is not carboplatin itself but its platin-containing degradation products that are bound to plasma proteins. During the first four hours post-infusion the proportion of the platin bound to plasma proteins is 24% and reaches 87% within 24 hours. Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin.

Elimination

After intravenous administration, the peak plasma level and the area under the concentration time curve for unchanged substance, filterable platin and total platin are linear and dependent on the dose of carboplatin administered.

After intravenous administration of carboplatin as a short infusion (< 1 hour) the plasma level falls in a biphasic exponential fashion.

The $t_{1/2}$ α is 90 minutes for unchanged carboplatin and filterable platin, 100 minutes for platin. The $t_{1/2}$ ß is 6 hours for filterable platin and approximately 5 days for total platin in plasma.

No accumulation of platin in plasma is found after multiple administration of carboplatin repeated over 5 days and given as a short intravenous infusion. The pharmacokinetic parameters on the first day of administration are largely identical to those on days 2 – 5.

Carboplatin is excreted primarily in urine. Urinary recovery is 60 – 80% of the platin dose administered after 24 hours.

In the case of carboplatin, total body clearance, renal clearance and excretion of filterable platin in urine correlate with creatinine clearance. The elimination of carboplatin is thus largely dependent on the GFR.

For patients with renal impairment, the carboplatin dose must therefore be reduced, depending on the reduction in clearance. This is because its myelosuppressant effect is dependent on the area of filterable platin under the concentration time curve.

5.3 Preclinical safety data

Carboplatin has been shown to be mutagenic in vitro and in vivo. The carcinogenic potential of carboplatin has not been studied but compounds with a similar mode of action have been reported to be carcinogenic. Carboplatin is embryotoxic and teratogenic in rats. When rats were treated with carboplatin during organogenesis, there was an increased incidence of abnormalities of the skeleton and internal organs.

6. Pharmaceutical particulars

6.1 List of excipients

Water for injection

6.2 Incompatibilities

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

Carboplatin should not be administered with giving sets, syringes and injection needles containing aluminium because, based on theoretical considerations, the possibility that its antineoplastic potency may be reduced cannot be ruled out.

6.3 Shelf life

36 months.

6.4 Special precautions for storage:

Store the vial in original carton below 30°C, away from light. DO NOT REFRIGERATE. Keep out of the reach of the children.

6.5 Nature and contents of container

The primary packaging is an amber glass vial
Secondary packaging: Paper board carton
Pack size: One vial in a box

6.6 Special precautions for disposal and other handling

Store the vial in original carton below 30°C, away from light. DO NOT REFRIGERATE. Keep out of the reach of the children.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Beacon Pharmaceuticals Limited, 9/B/R, Toyenbee circular road, Motejheel Dhaka-1223, Bangladesh.

Manufacturing site address:
Beacon Pharmaceuticals Limited, 9/B/R, Toyenbee circular road, Motejheel Dhaka-1223, Bangladesh.

8. Marketing authorization number

CTD10264: Carboplat 150mg Injection (Carboplatin 150mg)
CTD10265: Carboplat 450mg Injection (Carboplatin 450mg)

9. Date of first registration

CTD10264: Carboplat 150mg Injection (Carboplatin 150mg) – 20/06/2023

CTD10265: Carboplat 450mg Injection (Carboplatin 450mg) - 20/06/2023

10. Date of revision of the text:
17/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable