Summary of Product Characteristics

1.Name of the Medical Product

Drug Product	**:**	Carboplatin Injection BP (150 mg/ 15.0 mL)
Generic Name	**:**	Carboplatin Injection BP
Strength	**:**	10 mg of Carboplatin BP in Water for Injection USP, Sterile, Pyrogenand preservativefree, aqueous solution as Injection for Intravenous Infusion

2. Quality and Quantitative Composition

Each mL contains

Carboplatin BP	10 mg
Water for Injection USP	qs.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile, Pyrogenand preservativefree, aqueous solution as Injection for Intravenous Infusion.

4. Clinical Particulars

4.1 Therapeutic Indications

Treatment of Ovarian Carcinoma of epithelial origin and small cell of lung carcinoma.

Carboplatin Injection is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agent.

One established combination regimen consist of Carboplatin and Cyclophosphamide.

Two randomized controlled studies conducted by the NCIC and SWOG with carboplatin versus cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups).

There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and long-term survival ($\geq$ 3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor< 2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

Secondary Treatment of Advanced Ovarian Carcinoma

Carboplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.
Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

4.2 Posology and method of administration

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Carboplatin.

Single-Agent Therapy

Carboplatin Injection, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m2 IV on day 1 every 4 weeks . In general, however, single intermittent courses of Carboplatin should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

Combination Therapy with Cyclophosphamide

In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of:
Carboplatin —300 mg/m^2 IV on day 1 every 4 weeks for 6 cycles

Cyclophosphamide—600 mg/m^2 IV on day 1 every 4 weeks for 6 cycles. For directions regarding the use and administration of cyclophosphamide please refer to its package insert.

Intermittent courses of Carboplatin in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

Patients with Impaired Kidney Function

Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single-agent carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

BASELINE CREATININE CLEARANCE	RECOMMENDED DOSE ON DAY 1
41-59 mL/min	250 mg/m2
16-40 mL/min	200 mg/m2

The data available for patients with severely impaired kidney function (creatinine clearance below 15 mL/min) are too limited to permit a recommendation for treatment.

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

Geriatric Dosing

Because renal function is often decreased in elderly patients, formula dosing of Carboplatin based on estimates of GFR should be used in elderly patients to provide predictable plasma carboplatin AUCs and thereby minimize the risk of toxicity.

Preparation of Intravenous Solutions

Carboplatin Injection is a premixed aqueous solution of 10 mg/mL carboplatin.

Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

When prepared as directed, Carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin aqueous solutions be discarded 8 hours after dilution.

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 warning 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, during and after carboplatin 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 and at weekly intervals thereafter. This will monitor toxicity and help determine the nadir and recovery of haematological parameters and assist in subsequent dosage adjustments. 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 levels fall below 2000 cells/mm3 or platelets less than 100,000 cells/mm3 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.
Carboplatin combination therapy with other myelosuppressive compounds must be planned very carefully with respect to dosages and timing in order to minimise additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.

Renal and hepatic function impairment may be encountered with Carboplatin. Very high doses of Carboplatin (≥ 5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and/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.

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

Aluminium containing equipment should not be used during preparation and administration of Carboplatin.

4.5 Interaction with other medicinal products and other form of interactions

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

Contraception in males and females

Pregnancy

The safe use of Carboplatin during pregnancy has not been established: Studies in animals have shown reproductive toxicity. 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

Both men and women receiving carboplatin should be informed of the potential risk of adverse effects on reproduction. 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.

Most forms of chemotherapy have been associated with reduction of oogenesis and spermatogenesis and patients receiving carboplatin should be warned of this potential. Although not reported with carboplatin, this has been reported with other platinum agents. Recovery of fertility after exposure can occur but is not guaranteed.

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

4.7 Effects on ability to drive and use machine

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

Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing; swelling of your face, lips, tongue, or throat.

Call your doctor at once if you have a serious side effect such as:

Pale skin, feeling light-headed or short of breath, rapid heart rate, trouble concentrating;

easy bruising, unusual bleeding (nose, mouth, vagina, or rectum), purple or red pinpoint spots under your skin;

Fever, chills, body aches, flu symptoms, sores in your mouth and throat;

Severe or ongoing vomiting;

Stomach pain, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);

Numbness or tingly feeling in your hands or feet;

Hearing or vision problems;

Skin changes where the medicine was injected; or

Low magnesium (confusion, uneven heart rate, jerking muscle movements, muscle weakness or limp feeling).

Less serious side effects may include:

Nausea, vomiting, loss of appetite;

Tired feeling;

Temporary hair loss; or

Pain, swelling or redness where the medicine was injected.

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 via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdosage

Symptoms of overdose

Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m2 i.v. per course. At this dosage, life-threatening haematological side effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9-25 (median: days 12-17). The granulocytes had reached values of ≥ 500/µl after 8-14 days (median: 11) and the thrombocytes values of ≥ 25.000/µl after 3-8 days (median: 7).

The following non-haematological side effects also occurred: renal function disturbances with a 50% drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, alopesia, 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 Pharmacodynamics 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 Pharmacokinetics 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. After a 1-hour infusion (20-520 mg/m2), plasma levels of total platinum and free (ultrafilterable) 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. 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. Carboplatin is excreted primarily in the urine, with recovery of approximately 65% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Approximately 32% of a given dose of carboplatin is excreted unchanged. Total body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion. Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin.

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

Following excipients used during the manufacturing of Carboplatin Injection BP
Water for Injection USP as vehicle.

6.2 Incompatibilities

Carboplatin can harm your kidneys. This effect is increased when you also use other medicines harmful to the kidneys. You may need dose adjustments or special tests if you have recently used:
Medicines to treat a bowel disorder;

Medication to prevent organ transplant rejection;

Antiviral medications;

Pain or arthritis medicines; or

any injected antibiotics.

6.3 Shelf life

Unopen Vial
24 months

Proposed Shelf life (after reconstitution or dilution)

Carboplatin Injection BP when further diluted with Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP, The physical and chemical stability has been found to be 8 hours at 25º C.

Proposed Shelf Life (After first opening containers)

As the finished product is sterile formulation, from the microbiological point of view, the product should be used immediately, but after further dilution is should not longer than 8 hours at 25º (77ºF).

Proposed Storage Conditions

Store protected from light at a temperature not more than 25º (77°F), excursions permitted between 15º and 30º (59º F and 86º F).

6.4 Special precautions for storage

From microbiological point of view reconstituted solution should be used immediately.

6.5 Nature and contents of container

Glass Container of USP Type I:

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 BP (150 mg/15.0 mL) has pH between 5.0 to 7.0, so USP Type I containers are most suitable for packing of Carboplatin Injection BP (150 mg/15.0 mL). Also Amber colour glass vials 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 Non toxic Polypropylene

6.6 Special precautions for disposal and other handling

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

Beta Drugs Limited
Kharuni-Lodhimajra Road,
Vill: Nandpur, Baddi, Distt. Solan,
Himachal Pradesh, 173205 INDIA

8. Marketing authorisation number(s)

07485/08I27/NMR/2021

9. Date of first authorisation

31May 2022

10. Date of revision of the text

July 2024