SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Carboplatin Injection BP 450 mg/45 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains:
Carboplatin BP 10 mg
Water for Injections BP q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for infusion.

Description: A clear, colourless solution

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Antineoplastic agent indicated in the treatment of:
• ovarian carcinoma of epithelial origin
• small cell lung carcinoma.

4.2 Posology and method of administration Dosage and Administration
The recommended dose of carboplatin in previously untreated adults with normal renal function is 400mg/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.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/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/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.
Determination of haematologic nadir by weekly blood counts during initial courses is recommended for future dosage adjustment and scheduling of carboplatin.

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

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
Dosage adjustment may be necessary in elderly patients.

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

4.3 Contraindications
Carboplatin is contraindicated in patients with severe myelosuppression, pre-existing severe renal impairment (with creatinine clearance of less than 20 ml per minute) and 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 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 for their disease, have poor performance status and are advanced in years. Renal function parameters should be assessed prior to, during and after carboplatin therapy.

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 minimise 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.
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 therapy, including antihistamines, adrenaline and/or glucocorticoids.

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 and renal function tests should be monitored closely. Blood counts should be performed prior to commencement of carboplatin therapy 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/mm^3 or platelets 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.

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.

Neurological evaluation and an assessment of hearing should be performed on a regular basis. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes and ototoxicity are more likely seen in patients previously treated with cisplatin. 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.

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

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

4.6 Pregnancy and Lactation

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.

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.

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

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Myelosuppression is the dose limiting toxic reaction of carboplatin. It is generally reversible and not cumulative when carboplatin is used as a single agent at recommended frequencies of administration. Adverse reactions which have occurred in studies to date can be grouped under the following systems:

Blood and the lymphatic system disorders: Leucopenia (55%), thrombocytopenia (32%) and anaemia (59%) of patients. Transfusion support has been required in about 20% of patients. Haemolytic uraemic syndrome has been reported. Infectious

complications and haemorrhagic complications have also 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: Nausea and vomiting (53%), nausea only in 25%. 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. Diarrhoea occurred in 6% and constipation in 3% of patients. Abdominal pain and cramps have also been reported.

Nervous system disorders: Mild peripheral neuropathy occurred in 6% of patients and dysgeusia in less than 1% of patients. Parasthesias present prior to treatment, especially if caused by cisplatin, may persist or worsen during carboplatin therapy. (See Precautions).
Eye disorders: Transient visual disturbances, sometimes including transient sight loss, have been reported rarely with platinum therapy. This is usually associated with high dose therapy in renally impaired patients.

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. Clinical ototoxicity also manifested itself as tinnitus (1% of patients). 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.

Hepato-biliary disorders*:* Transient increases in liver enzymes have been reported in some patients. Alkaline phosphatase was increased in 30% of patients, with aspartate aminotransferase (15% patients) and elevated serum bilirubin (4% patients) occurring less frequently.

Renal and urinary disorders: Renal toxicity is not usually dose limiting. However, a decrease in creatinine clearance is observed in approximately 25% of patients. A rise in uric acid (25%) and, less frequently, a rise in serum creatinine (7%) and blood urea nitrogen (16%) have also been observed. Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

General disorders*:* Rarely anaphylaxis and anaphylactic-like reactions have been reported including tachycardia, bronchospasm, dyspnoea, hypotension, wheezing, urticaria, facial oedema and facial flushing. Erythematous rash, fever and pruritis have been observed in less than 2% of patients treated. These were reactions similar to those seen after cisplatin therapy but in a few cases no cross-reactivity was present.

Decreased serum levels of magnesium (37% patients), potassium (16% patients) and calcium (5% patients) have occurred although not severe enough to cause clinical symptoms. Decreased serum sodium has also been reported although it is normally insufficient to require treatment. There have also been rare reports of hyponatraemia.
Asthenia is very commonly reported. Rare events have included alopecia (2%), a flu-like syndrome (1%) and reaction at the injection site (<1%). Cases of anorexia have been reported.

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 providers are asked to report any suspected adverse reactions to the

marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*.

4.9 Overdose
No overdosage occurred during clinical trials. If necessary, however, the patient may need supportive treatment relating to myelosuppression, renal and hepatic impairment. Reports of doses
up to 1600mg/m^2 indicate patients feeling extremely ill with diarrhoea and alopecia developing.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC Code: Antineoplastic agent LO1X A02
Carboplatin, like Cisplatin, interferes with DNA intrastrand and interstrand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.
Paediatric patients:
Safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties
After a 1-hour infusion (20-520mg/m^2), 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.

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.

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.

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
arboplatin has been shown to be embryotoxic and teratogenic in rats. It is mutagenic *in vivo* and *in vitro* and although the carcinogenic potential of carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for Injections.

6.2 Incompatibilities
Aluminium-containing equipment should not be used (see Section 4.5).

6.3 Shelf life
2 years

In use:
Carboplatin solution for infusion may be further diluted in Glucose 5% and administered as an intravenous infusion. The infusion solution is chemically stable when stored for 96 hours at both 2- 8ºC and 22ºC. Carboplatin solution for infusion may also be further diluted in Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution is chemically stable for up to 24 hours when stored at 2-8ºC and up to 8 hours when stored at 22ºC.

From a microbiological point of view however, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Do not store above 30°C. Protect from light.

6.5 Nature and contents of container
50 ml clear moulded USP type I glass vials stoppered with rubber plug & sealed with aluminum seal having flip off tops which is finally packed in a unit carton.

6.6 Special precautions for disposal and other 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 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.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE
Venus Remedies Limited
Hill Top Industrial Estate, Jharmajri EPIP, Phase-1 (Extn.), Bhatoli Kalan,
Baddi, Distt. Solan (Himachal Pradesh) 173205,
India.

8. MARKETING AUTHORISATION NUMBER(S)
TAN 20 HM 0536

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/11/2020

10. DATE OF REVISION OF THE TEXT