For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

ACCORD CARBOPLATIN 150/450

Carboplatin Injection BP 150 mg/15 ml & 450 mg/45 ml

Composition:

Each ml contains:
Carboplatin Ph. Eur. 10 mg
Water for Injection Ph. Eur. Q.S.

Product Description

A clear, colourless to slightly pale yellow solution in an amber glass vial. When examined under suitable conditions of visibility it should be practically free from particles.

Pharmacodynamic 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 tumors 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”.
Pediatric patients: safety and efficacy in children have not been established

Pharmacokinetic 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. Following the administration of Carboplatin reported values for the terminal elimination of half-lives of free ultrafilterable platinum and Carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultrafilterable platinum is present as Carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primarily in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

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

Indication/Usage

Carboplatin is indicated in the treatment of advanced stage ovarian cancer of epithelial origin.

Recommended Dose

Dosage and Administration:
Carboplatin should be used by the intravenous route only. Carboplatin is given in doses of 400 mg/m^2 body surface area by intravenous infusion over 15 minutes to 1 hour in previously untreated adults (with normal renal function).

Doses should not be given more frequently than every 4 weeks, and should be reduced in patients at risk of myelosuppression. Lower doses may also be given as part of combination regimens.

Determination of the hematological nadir by weekly blood counts is recommended for adjusting future dose and scheduling of carboplatin therapy.

Renal Impairment: As carboplatin is excreted by the kidney and is nephrotoxic, the optimum dosage should be determined by frequent monitoring of the hematological nadir and renal function.

Safety and effectiveness in pediatric patients have not been established. Clinically significant hearing loss has been reported to occur in pediatric patients when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

Immediately before use each vial of Carboplatin should be diluted to concentrations as low as 0.5 mg/ ml with 5% Dextrose solution or 0.9% Sodium Chloride solution

Dose Modifications

1. In patients with renal failure

Creatinine Clearance (ml/min)	Starting dose (mg/m^2)
>60	no dose reduction
41 - 59	250
16 - 40	200
Creatinine Clearance (ml/min) = N(140 – Age)	Weight (kg)
Serum creatinine (mol/L)	
Where N = 1.04 for females and 1.23 for males	

2. Dose of carboplatin has to reduced

- When it is used along with aminoglycosides as they increase the toxic effects of carboplatin
- In patients having myelosuppression

Route of Administration

Intravenous route
(For IV / IV Infusion after dilution)

Contraindication

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)

Warnings & Precaution

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 and during therapy.

Carboplatin Infusion courses should not be repeated more frequently than monthly under normal circumstances. Thrombocytopenia, leucopenia and anaemia occur after administration of Carboplatin. Frequent monitoring of peripheral blood counts is recommended throughout and following therapy with Carboplatin. 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 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.

Interaction with other medicaments

- Aminoglycosides (eg: amikacin gentamycin, tobramycin) increase the risk of carboplatin induced nephrotoxicity and ototoxicity.
- Carboplatin decreases the serum level of phenytoin by decreased absorption or increased metabolism of phenytoin
- Carboplatin increases the anticoagulant effect of warfarin by decreased protein binding or decreased metabolism of warfarin
- The renal effects of nephrotoxic drugs may be potentiated by Carboplatin
- Bone marrow depression may be more severe when Carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy

Pregnancy and Lactation

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.

File Name : 10 5559 0 6012046-ACCORD CARBOPLATIN(Myanmar)PIL
Size : 170 x 550 (mm) Front Side
Colour : Pantone Black
Date : 11/10/21, 18/10/21, 19/10/21

Fertility
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.

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.

Adverse Reactions

Hematologic toxicity: Bone marrow suppression is the dose limiting toxicity of Carboplatin. The nadir usually occurs about day 21 in patients receiving single agent therapy. Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leucopenia and thrombocytopenia. Anaemia with haemoglobin less than 11g/dl occurs in majority of the patients who start therapy with a baseline above the value. The incidence of anemia increases with increasing exposure to carboplatin.
Transfusions may be required in some patients treated with carboplatin. Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal toxicity: Vomiting occurs in about a quarter of patients receiving carboplatin vomiting has been reported in over half of the patients and about one-third of these suffer severe emesis. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin, usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) anti-emetic medication. A quarter of patients experience no nausea or vomiting. Vomiting that could not be controlled by drugs was observed in only 1% of patients. Vomiting seems to occur more frequently in previously treated patients, particularly in patients pre-treated with cisplatin.

Neurologic toxicity: Peripheral neuropathies have been observed in small number of patients receiving carboplatin with mild paresthesias occurring most frequently. Patients older than 65 years have an increased risk for peripheral neuropathies. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste occur rarely. Central nervous system symptoms have been reported in fewer patients and appear to be most often related to the use of antiemetics. Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment may result in cumulative neurotoxicity

Nephrotoxicity: Development of abnormal renal function test results is uncommon with carboplatin. Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Nephrotoxicity may manifests as reduced creatinine clearance, elevated serum creatinine, blood urea nitrogen and uric acid levels.

Hepatic toxicity: Abnormal liver function tests in patients may be found with normal baseline value. These abnormalities (e.g.: SGOT, total bilirubin and alkaline phosphatase) have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumour in the liver may complicate the assessment in many patients.

Electrolyte changes: Hypocalcaemia, hypomagnesaemia, hypokalemia, hyponatremia, increased blood urea nitrogen, increased uric acid are some of the electrolyte abnormalities occurring with carboplatin Electrolyte supplementation is not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities are rarely associated with symptoms.

Allergic reactions: Hypersensitivity to Carboplatin develops only in a small number of patients and consists of rash, urticaria, erythema, pruritus and rarely bronchospasm and hypotension. These reactions are successfully managed with standard epinephrine, corticosteroid and antihistamine therapy.

Ototoxicity: Ototoxicity may manifests as tinnitus and hearing loss in the higher frequency range. Hearing impairment may worsen with carboplatin therapy.

Others: Pain and asthenia occur most frequently. Alopecia, cardiovascular, respiratory, genitourinary and mucosal side effects occur only in small number of patients. Pre-existing paraesthesia (especially those related to previous cisplatin therapy) may worsen during carboplatin therapy.

Overdosage

There is no known antidote for carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression or hepatic toxicity. The patient may need to be sustained through complications relating to myelosuppression, renal and hepatic impairment. Diarrhoea and alopecia may develop.

Storage

Store below 25°C. Protect from light.
Do not refrigerate or freeze.

Shelf life

Unopened: 2 years

After dilution
In use: Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C and 30 hours at 2-8°C.

From a microbiological point of view, 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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions

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.

Incompatibilities: Aluminium – containing equipment should not be used.

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 1000°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.

Package
Carboplatin Injection BP 150 mg/15 ml & 450 mg/45 ml is packed as one vial per box.

Manufactured by:
INTAS
INTAS PHARMACEUTICALS LTD.
Plot No. 457-458, Village Matoda,
Bavla Road, Dist. – Ahmedabad, India.

10 5559 0 6012046

INP001

Approved
(25/10/2021)

File Name : 10 5559 0 6012046-ACCORD CARBOPLATIN(Myanmar)PIL
Size : 170 x 550 (mm) Back Side
Colour : Pantone Black
Date : 11/10/21, 18/10/21, 19/10/21